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Assessment Of The Semantic Knowledge Network In Older Adults With Familial History Of Alzheimer's Disease

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ASSESSMENT OF THE SEMANTIC KNOWLEDGE NETWORK IN OLDER ADULTS WITH FAMILIAL HISTORY OF ALZHEIMER'S DISEASE

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Disruption of the Semantic Knowledge Network in Older Adults with Familial Risk for Alzheimer's Disease

INTRODUCTION

Alzheimer's disease (AD) currently affects over 4.5 million Americans, and projections suggest that the prevalence will increase to 15 million affected persons in the United States alone by 2050. In order to deal with this major public health menace, strategies for delaying the onset or slowing the progression of AD are ongoing (Thies & Bleiler, 2011). Development of new approaches for the early detection of AD have been coupled with the development of prevention strategies, as any new intervention strategy should be initiated as early as possible in order to have a meaningful impact on the disease course. In addition to a variety of imaging, serum, and cerebrospinal fluid markers of early risk for AD, neuropsychological testing has shown promise for predicting future cognitive impairment. Because episodic memory is one of the earliest cognitive domains affected by AD (Braak & Braak, 1991) episodic memory tasks are frequently used in preclinical detection studies of dementia risk (Bondi, Salmon, & Butters, 1994; Estevez-Gonzalez, Kulisevsky, Boltes, Otermin, & Garcia-Sanchez, 2003; Howieson et al., 1997). However, these tasks may have several limitations that could reduce their effectiveness for predicting preclinical AD risk. Episodic memory performance declines with normal aging as well as with AD (Nilsson, 2003), thus, it may be difficult to distinguish between typical and pathological episodic memory impairment. Furthermore, episodic memory tasks can be especially difficult for older adults, and performance may be susceptible to variable levels of motivation. In contrast, semantic memory tasks, which assess the ability to access previously stored knowledge pertaining to general facts about the world, may provide a viable alternative to episodic tasks. Semantic memory impairment is typically observed in persons with AD but is

relatively unaffected in healthy aging (Nebes, 1989; Nilsson, 2003). Furthermore, semantic memory tasks tend to be more engaging and less effortful than episodic memory tasks (Howieson, et al., 1997). Additionally, deterioration of the semantic memory system has been proposed as a clinical marker for tracking the rate of progression of cognitive changes in AD (Chan, Salmon, Butters, & Johnson, 1995). Finally, functional magnetic resonance imaging (fMRI) activation observed while performing a famous name discrimination task requiring semantic processing ability has successfully predicted cognitive decline after 18 months in healthy older adults (Woodard et al., 2010) Thus, changes in semantic memory functioning may reflect early neuropathological changes associated with preclinical AD.

The semantic memory system is composed of multiple levels. In addition to the simple familiarity with or recognition of a concept, deeper semantic processing also manifests knowledge of attribute and categorical information pertaining to a concept that may contain perceptual and abstract knowledge (Nebes, 1989). This more detailed semantic information may be especially susceptible to loss in individuals with AD, and this loss may result in impairments in language functioning (Bayles, Kaszniak, & Tomoeda, 1987) and episodic memory (Weingartner et al., 1981). Attributional knowledge appears to be most vulnerable in AD, while the categorization and familiarity/recognition systems are relatively intact (Nebes, 1989).

One method for observing gradual changes within the semantic memory network involves the examination of the temporal gradient (TG), in which recent memories are more vulnerable to the effects of neuropathological changes than older, remote memories (Ribot, 1881). Recent studies (Bizzozero, Lucchelli, Saetti, & Spinnler, 2009; Seidenberg, Guidotti, Nielson, Woodard, Durgerian, Antuono, et al., 2009a) have suggested that the TG for semantic knowledge can help predict cognitive decline and distinguish between groups at differential risk

for AD. One way to operationalize risk for AD is to contrast persons with a first-degree family history of AD with individuals who have no AD family history, as a first-degree family history of AD is strongly associated with late-onset AD (Fratiglioni, Ahlbom, Viitanen, & Winblad, 1993; Johnson et al., 2006). Contrasting semantic memory performance and the nature of the TG in cognitively intact older adults with and without a first-degree family history could reveal subtle semantic memory changes that may signal the earliest stages of memory decline. Such a study could also provide valuable insights into the nature and temporal course of age-related memory changes as well as memory changes that are associated with familial risk for AD.

BACKGROUND AND SIGNIFICANCE

Early Detection & Risk Factors

Alzheimer's disease (AD) is the most common form of dementia, affecting approximately 13% of individuals aged 65 years and older. In absence of disease modifying treatments, the cumulative costs of care for people with AD will exceed $20 trillion annually from 2010 to 2050, as the number of older adults suffering from the disease is projected to rise to over 13.5 million within the United States alone (Thies & Bleiler, 2011). While there are currently no effective treatments for altering the course of AD, several early intervention strategies have been proposed for delaying the onset or preventing the progression of the disease (Daviglus et al., 2010). AD-related neuropathology is detectable decades prior to the onset of cognitive symptoms (Kok et al., 2009), making the identification of preclinical markers essential for effective treatment of the disease. Interventions initiated in the preclinical stages of AD, prior to the accumulation of irreversible neuronal damage, might have the greatest meaningful impact on the disease course.

The need for reliable and valid methods to predict the onset of AD has led to extensive research dedicated to the identification of risk factors and preclinical markers. Several preclinical biomarkers of AD have shown promise for the detection of risk for cognitive decline in asymptomatic older adults (de Leon et al., 2007; Hampel et al., 2004; Wolk & Klunk, 2009). For example, measurements of specific proteins in cerebrospinal fluid (de Leon, et al., 2007; Wolk & Klunk, 2009) and positron emission tomography using fluorodeoxyglucose (Chetelat et al., 2003; Chetelat et al., 2005) or amyloid imaging (Jack et al., 2009; Rowe et al., 2007) have been identified as promising biomarkers. In addition, genetic risk factors, such as the presence of the angiotensin I-converting enzyme (ACE alu repeat insertion (I)/deletion (D) polymorphism) (Lehmann et al., 2005), the CST3 gene (Balbin & Abrahamson, 1991) and one or more apolipoprotein E (APOE) ε4 alleles (Roses, 1996; Yip et al., 2005) have all been associated with an increased risk for late-onset AD.

However, these methods cannot predict onset of AD and associated cognitive decline with 100% accuracy, and several of these techniques are invasive and/or expensive. Cost and practicality limit the implementation of these screening approaches on a widespread basis. Therefore, recent studies have focused on easily measurable and less invasive risk factors for AD. For example, lifestyle factors such as diet (Scarmeas, Stern, Tang, Mayeux, & Luchsinger, 2006) and participation in social (Saczynski et al., 2006), cognitive (Wilson, Scherr, Schneider, Tang, & Bennett, 2007), and physical activity (Rolland, Abellan van Kan, & Vellas, 2008) have been linked to AD risk. Additionally, studies have focused on identifying subtle aspects of cognitive performance that may suggest early disease-related changes in at-risk individuals (Bondi et al., 2008), and have combined with other biomarkers for enhanced accuracy (Woodard, et al., 2010). These approaches have considerable promise, as they are non-invasive,

inexpensive, and easily implemented. However, continued exploration into the efficacy of non-invasive, easily quantified risk factors is needed to optimize prediction accuracy and promote assessment of risk across large populations of older adults.

Family History as a Risk Factor

The association between a first-degree family history of AD and risk for developing AD is well established in the literature (Cupples et al., 2004; Fratiglioni, et al., 1993; Johnson, et al., 2006). Assessment of family history is non-invasive and easily accessible compared to other risk factors such as genotyping and neuroimaging biomarkers. The link has been established through several longitudinal epidemiological studies. One such study observed 379 first-degree relatives of 79 probands, and found that the cumulative incidence of AD among relatives increased significantly with age to 49% by age 87 in comparison to <10% of healthy controls (Breitner, Silverman, Mohs, & Davis, 1988). In another study, 70 families with one or more AD subjects were examined using survival analysis, and it was determined that subjects had an estimated lifetime risk of 86% for late-onset AD (Farrer et al., 1990). More recent longitudinal familial aggregation studies using much larger databases have replicated these preliminary findings. For example, as part of the Multi-Institutional Research in Alzheimer Genetic Epidemiology (MIRAGE) project, a study was conducted to estimate the risk of 12,971 first-degree relatives of 1,694 probands. They found this risk to be 39% by age 96 years, which is approximately twice the estimated incidence in the general population (Lautenschlager et al., 1996). Further analysis of the MIRAGE data (Green et al., 2002) assessing risk to first-degree relatives in African-Americans compared to European Americans indicated that the risk attributable to familial aggregation was similar in the two ethnic groups. In these studies, presence of an APOE ε4 allele in the proband increased AD susceptibility in the relatives. However, there was also increased

AD risk to relatives of patients without an APOE ε4 allele, suggesting that family history may carry risk for AD independent of the APOE gene.

Within first-degree relatives, presence of a biological *parental* history of AD has also been examined. The presence of a parental history has been associated with both cognitive (Debette et al., 2009) and biological (Debette, et al., 2009; Xu et al., 2009) risk factors for AD in asymptomatic older adults. For example, one study examined 717 offspring of the original participants enrolled in the Framingham Aging Study. In comparing older adults with and without verified parental dementia, the authors found that parental history was significantly related to declines in verbal memory, visuospatial memory, executive functioning and total brain volume, as measured by structural MRI (Debette, et al., 2009). Similarly, asymptomatic participants with maternal history of AD have shown high rates of biological and cognitive correlates of AD. Specifically, participants with maternal family history of Alzheimer's disease show reduced glucose metabolism with positron emission tomography in brain areas associated with memory functioning that are most susceptible to the disease pathology, when compared with subjects with paternal or no family history (Mosconi et al., 2007). Additional longitudinal investigation revealed that maternal family history of Alzheimer's disease was also associated with more rapid metabolic decline in these same brain areas (Mosconi et al., 2009).

These patterns of impairment suggest that there are detectable differences in the neural substrates supporting memory functioning in asymptomatic individuals at familial risk for AD. However, an overwhelming majority of the research has focused on the effects of parental family history of AD on episodic memory. Relatively little research has investigated the effects of AD family history on memory functioning in other domains, such as semantic memory functioning. Understanding the effects of parental history of AD on cognitive functioning beyond traditional

episodic memory tasks have the capacity to greatly inform our understanding of how memory functioning may be impacted by early neuropathological changes.

Episodic and Semantic Memory Distinction in AD

It has long been established that memory is not a unitary construct, but rather is a complex network of multiple systems, each with its own unique subsystems. One such distinction in systems is made between procedural and declarative memory. Declarative memory, as a major system, involves the explicit and conscious encoding, storage and recollection of information. Two subsystems within declarative memory have been identified. The first, semantic memory, consists of an organized body of knowledge involving words and concepts, as well as their meanings and associations. Specifically, semantic memory represents only a conceptual knowledge base independent of context. In contrast, the second subsystem, episodic memory, includes memory for specific events defined by a spatial and temporal context (i.e. memories for specific experiences that occurred at a particular time and place) (Tulving, 1972).

Episodic memory impairment is generally the earliest symptom of AD and continues to progress over the course of the disease (Braak & Braak, 1991). These episodic memory impairments are well-established in the literature across different types of memory tasks, sensory modalities (i.e. visual & verbal) and encoding strategies (Corkin, Davis, Growden, Usdin, & Wurtman, 1982; Delis et al., 1991; Weingartner, et al., 1981; Welsh, Butters, Hughes, Mohs, & Heyman, 1991; Wilson, Kaszniak, Bacon, Fox, & Kelly, 1982). The hippocampus (HC) and medial temporal lobe (MTL) participate in episodic memory processes (Eichenbaum, 1992; Squire, 1992). According to one theory, it is believed that these structures are responsible for consolidation of information into long-term memory processes. In contrast, semantic memory is thought to be linked to a more widely distributed neocortical network and may be less dependent

on MTL structures (Schmolck, Kensinger, Corkin, & Squire, 2002; Squire, L. R. & P. Alvarez, 1995). AD is characterized by MTL atrophy, which is thought to underlie the cardinal feature of this disorder: episodic memory impairment. Thus, episodic memory impairment has become the most widely studied feature of AD (Braak & Braak, 1991; Deweer et al., 1995; Köhler, Moscovitch, Winocur, Houle, & McIntosh, 1998). However, episodic memory deficits are also observed in normal aging and may not be entirely unique to AD (Nebes, 1989). MTL atrophy may also occur during normal aging (Jack et al., 1998). In contrast, semantic memory appears to remain stable across the lifespan (Salthouse & Prill, 1987; Salthouse & Somberg, 1982) and access to semantic information appears to be performed just as effectively and rapidly as in younger adults (Mueller, Kausler, & Faherty, 1980). However, semantic memory deficits can be observed in AD patients, suggesting that semantic memory tasks may be more useful in differentiating between typical and pathological aging than episodic memory tasks (Nebes, 1989).

Models of Semantic Memory

Given the overwhelming evidence supporting disruption in the semantic memory network during the course of the disease process, examination of specific components of semantic memory affected by AD is likely to further our understanding of the neurobiological underpinnings of the disease. Additionally, this exploration is expected to reveal whether or to what extent specific aspects of semantic memory are particularly susceptible to AD pathology. Appreciation for theories regarding the organization and structure of the semantic memory network has informed our current understanding of AD-related deficits. The most prominent theoretical models of semantic memory are: 1) network spreading/activation, 2) feature comparison and 3) connectionist/parallel processing distributed models.

Collins and Quallian (1969) proposed that semantic memory could be described as an intersecting network in which concepts are represented as nodes and interconnections among concepts are based on relationships between the nodes. The individual concept networks form hierarchies with subordinate and superordinate nodes. This early model provided the first approach to understanding semantic memory organization and subsequently led to the spreading/activation model (Collins & Loftus, 1975). The spreading activation theory of semantic memory organization rejected ideas of hierarchy, and it instead conceptualized the semantic memory network in terms of interconnections whose weights differ by association strength between the two nodes. This model is usually represented visually by a matrix of word associations similar to that of a spider web, whereby the distance between the nodes indicates the relatedness of the concepts. Additionally, in this model, interconnections are determined by personal experiences rather than logical hierarchies. With respect to semantic memory recall, the time that it takes to access connecting nodes will vary as a function of the distance and weight (association between nodes) and activation of one of the interconnections that leads to activation of other nodes that are similarly related in the semantic network.

The feature comparison model (Smith, Rips, & Shoben, 1974) presents an alternative conceptualization of the semantic memory system. This model emphasizes that a set of features defines each concept, and a two-stage decision-making process is involved in drawing conclusions about a concept. The features related to a concept are divided into two broad categories: defining features and characteristic features. For the decision-making process, in the first stage, all features are compared to make quick judgments based on overlap between two concepts. Only when there is a moderate amount of overlap between concepts does the second stage occur, in which the defining features are compared. The feature comparison model

indicates that the more similar two concepts are, the greater the connection and the faster the judgments regarding the concept can be made.

The most recent model was developed by McClelland, Rumelhart, and Hinton (1990). In their connectionist model/ parallel distributing model, they attempt to incorporate current knowledge about neural processing. Semantic knowledge is represented by a network of connections where each unit is a hypothetical neuron linked to other neurons. Instead of knowledge being stored in each node, knowledge is composed of distributed connections. Processing occurs through these connections, which send either excitatory or inhibitory messages to other units, and these messages are sent simultaneously. When a concept is retrieved, all units related to that concept are activated, including all of the associated attributes related to the concept.

Concept Knowledge Specificity in Semantic Memory

Though the specific models of semantic memory differ in their general conceptualization of the organization and activation of the semantic knowledge network, they all contain information concerning different levels of specificity for each concept as a crucial component of their respective model. For example, knowledge regarding the semantic category (such as whether a famous name is a musician or an actor) to which a concept belongs reflects more general knowledge about the concept, whereas judgments made about the specific attributes of a particular concept (such as a specific piece of work associated with a famous name) reflect a greater specificity of knowledge about the concept of interest.

The most common theory surrounding the organization of semantic knowledge specificity is that of superordinate-subordinate concept knowledge (Warrington, 1975). Both early and relatively recent cognitive research suggest that semantic memory is organized in a

superordinate-subordinate structure and that preferential processing for superordinate propositions occurs during the processes of comprehension, encoding and recall (Chertkow & Bub, 1990; Waters, 1978). This hypothesis has been supported by findings that higher-order concepts in prose (e.g. general categories) showed greater recall probability than lower order concepts (e.g. attributes) across different age groups (Kintsch & Keenan, 1973; Waters, 1978). However, the distinction between superordinate and subordinate concepts may not be entirely clear. Some studies have demonstrated that object recognition most commonly occurs at the intermediate level between superordinate and subordinate levels (Rosch, 1977). For example, when shown a picture of a "Beagle," individuals are likely to answer "dog" before "animal" or "Beagle." However, this pattern of performance was demonstrated with a set of stimuli where the intermediate level of specificity has a frequency of use that equals or exceeds that of the superordinate category. For example, if shown a picture of "beans," individuals are not more likely to say "legume" over "beans" or "vegetable."

The basis for the assumption that superordinate knowledge is more easily accessible compared to subordinate information in semantic memory can also be explained by the aforementioned models of semantic memory organization. For example, the hierarchical network model explicitly states that higher-order knowledge is accessed before lower-order specific information; thus, degradation of the semantic memory system will affect the subordinate information first (Collins, 1969; Shallice, 1989; Warrington, 1975). The spreading activation model is also consistent with preferential processing of superordinate information because these nodes have more interconnections that are shared and weighted than subordinate nodes (Collins & Loftus, 1975; Hodges, Graham, & Patterson, 1995; Rogers et al., 2004). Finally, the model offered by McClelland and colleagues (1986) suggests that subordinate information is more

likely to be affected by cortical degeneration because it is activated by smaller networks that cover relatively fewer nodes distributed across the cortex. In comparison, superordinate information would be accessible via wider networks covering a broader area across the cortex. That is, the wider, broader network activation would make processing of superordinate information not only preferred, but less susceptible to disease processes.

Semantic Memory in Healthy Aging

There is considerable evidence that memory functioning declines with normal aging (Kausler & Wiley, 1991; Salthouse, 1991). Although episodic memory functioning is the most frequently studied memory domain in aging, studies focusing on semantic memory in healthy aging demonstrate some, but relatively less severe changes to the semantic knowledge system. For example, Nilsson (2003), in a cross-sectional analysis, demonstrated a relatively intact semantic memory performance, in comparison to episodic memory across the lifespan. For this study, Nilsson used data from the sample 1 participants (S1) of the Betula project, a large-scale, longitudinal study exploring the development of memory in adulthood and old age. The sample consisted of 1,000 Swedish adults aged 35, 40, 45…80 years. Examination of standardized mean performance across the age cohorts revealed that performance on episodic memory tasks was stable from 35-45 years and then consecutively decreased for each age group thereafter. In contrast, mean performance for semantic memory tasks (vocabulary and general knowledge) revealed a much more stable performance over time. Specifically, performance increased until around the age of 65 and then decreased, only slightly, from 65 to 80 years. The authors concluded that there are clearly demonstrated deficits for episodic memory; however, the same deficits do not exist for semantic memory.

These results are consistent with work supporting theories of stable crystalized

intelligence in health older adults utilizing similar semantic memory tasks (Birren & Morrison, 1961; Lindenberger & Baltes, 1994; Schaie & Willis, 1993). However, comparable results have been found for performance on remembering proper names (Crook & West, 1990), object naming (Au et al., 1995), word fluency (Nyberg, Backman, Erngrund, Olofsson, & Nilsson, 1996) and producing words from definition (Backman & NIlsson, 1996). In a recent study, Small, Dixon, & McArdle (2011) compared changes in performance on fact recall and vocabulary tasks in health older adults aged 55 to 95 years, using an accelerated longitudinal design. Results exhibited that both tasks remain relatively stable up until 75 years of age and then steadily decreased with each consecutive cohort thereafter. In comparing the tasks, the fact recall task had a significantly greater decline in performance form 55 to 95 years than the vocabulary task, suggesting some possible differential effects of aging on specific aspects of the semantic memory system. Further, in comparing the semantic to episodic memory performance they replicated the earlier mentioned results of Nilsson (2003), such that episodic memory performance exhibited a substantially greater decline in performance with increasing age compared to semantic memory tasks.

Other research comparing the performance of healthy older adults to younger adult samples (18-30 years) has demonstrated detectable differences between the groups even in the absence of impairment within the older adult sample (Bowels & Poon, 1985; Loacano et al., 2011; Small, et al., 2011). For example, Loacano and colleagues (2011) examined semantic memory processing in a group of healthy older adults compared to college students. Specifically, they examined differences in specific and general knowledge about famous names from different time epochs: a) remote (individuals became famous between 1960-1980 and are no longer in the public eye), b) enduring (individuals who became famous between 1960-1980 and are still

popular today) and c) recent (individuals who reached fame between 2000 and 2010). Their results revealed a different temporal gradient (TG) between the two groups. Older adults demonstrated a traditional TG, such that accuracy for semantic knowledge about the famous names was highest for the enduring time epoch followed by remote and then recent. However, the younger adult sample exhibited a reversed TG, with the most semantic knowledge for recent names, suggesting that more frequent and recent exposure to famous names may override age of acquisition in younger adults.

Overall, the evidence suggests that generally, there are some observable, yet relatively mild changes to the semantic memory system in healthy aging. However, these changes are not comparable to the deficits observed for episodic memory performance. Yet, there are still questions to be answered regarding how the aging process might differentially affect distinct components of the semantic memory system (Nyberg, et al., 1996). Investigation into the differences in semantic memory performance between healthy older adults and at-risk and patient populations, such as AD may continue to answer some of these questions.

Semantic Memory Impairment in AD

One of the earliest experimental studies directly investigating the disruption of semantic memory in AD concluded that semantic and episodic memory impairments were equally prominent (Martin & Fedio, 1983). The researchers demonstrated that AD patients had considerable impairment in confrontation naming, verbal fluency and judgment of word meanings and that the overwhelming majority of errors made by AD patients were semantic rather than phonemic in nature. Furthermore, a review conducted by Nebes (1989) provides an extensive documentation of the semantic memory impairments observed amongst individuals with AD across a wide variety of domains including, verbal fluency (Butters, Grandholm,

Salmon, Grant, & Wolfe, 1987; Martin & Fedio, 1983; Ober, Koss, Friedland, & Delis, 1985), object naming (Kirshner, Webb, & Kelly, 1984; Rochford, 1971), concept knowledge (Grober, Buschke, Kawas, & Fuld, 1985; Nebes & Brady, 1988) and sentence completion (Moscovitch, 1982; Nebes, R. D., R. Boller, & A. Holland, 1986).

Tests of verbal fluency are sensitive measures of semantic memory deficits in AD and tend to show a steady decline as the disease progresses. An early and comprehensive examination of verbal fluency in AD patients found that AD patients produced only half as many items as healthy controls and generated more inappropriate responses (Ober, 1986). However, they also concluded that low-frequency words were just as accessible in AD patients and healthy controls. That is, the mean word frequency of the responses made by AD patients did not differ from that of normal controls.

Despite the similarities in word frequency between AD and control groups, results from the above mentioned studies suggest a disruption in the organization of the semantic memory network. In order to demonstrate this point, researchers implemented a novel semantic category task whereby participants are required to name as many items as possible that can be found in the supermarket within a 60 second time limit (Martin & Fedio, 1983; Ober, 1986). The healthy subjects typically named three to four items from each of a number of different subcategories, such as meats, produce or toiletries. In contrast, AD patients not only named fewer items overall, but they also tended to produce only a single item from each subcategory or gave the subcategory name itself (e.g. vegetables), rather than specific items. The researchers argued that if the AD patients' decreased fluency was due merely to a slowing in the rate at which they searched their memory, then they should have reported fewer subcategories but would have still averaged the same number of items per subcategory as healthy controls. The patterns observed,

however, suggest that there is a disruption in the organization of semantic memory structure, as indicated by the seemingly random search methods.

Another specific semantic memory deficit observed in AD is object naming. Difficulty in naming objects is considered to be a sensitive marker for language impairment due to neurological insult (Benson, 1979), as deficits in this domain do not typically occur with normal aging (Albert, Heller, & Milberg, 1988; LaBarge, Edwards, & Knesevich, 1986; Nicholas, Obler, Albert, & Goodglass, 1985). AD patients are impaired when naming objects, and object naming performance is strongly correlated with the severity of the dementia (Kirshner, et al., 1984). However, it has also been argued that the deficits observed in object naming could be due to the deterioration of cognitive processes other than semantic memory, including perceptual misidentification (Rochford, 1971) and impaired lexical access (Albert, Heller, & Milberg 1988). Several research studies support the notion that the object naming deficits are indeed a product of semantic memory impairment. The naming mistakes made by AD patients tend to be semantically related words (Huff, F.J., S. Corkin, & J.H. Growdon, 1986). Additionally, the hypothesis that a perceptual deficit contributes to naming errors has fallen out of favor as research suggests that although processing of visual input is intact (i.e. lack of perceptual deficit), the patient's knowledge of the semantic features associated with the presented concept is impaired (Huff, F. J., S. Corkin, & J. H. Growdon, 1986). That is, the patient has trouble matching the derived attributes to those of the semantic concept because that semantic information has been lost or is inaccessible. Further evidence suggests that impairments in object naming are also derived from disruptions in semantic memory. For example, one study demonstrated that dementia patients have more difficulty relative to controls with recognizing the name of an object when the distractor words provided belong to the same semantic category

(Skelton-Robinson & Jones, 1984).

Semantic memory impairment appears to be present during the early phases of AD, and deficits increase with dementia severity. With respect to the relationship between severity of dementia and semantic memory impairment, research has demonstrated that patients with only minimal symptoms of AD demonstrated impairments on various semantic measures (Hodges & Patterson, 1995). In a study comparing minimal, mild and moderate AD patients and aged-matched healthy control subjects, minimal AD patients showed significant semantic impairment on category fluency, confrontational object naming, naming verbal descriptions, semantic feature questions, and matching pictures according to semantic categories. Further, the magnitude of these deficits increased as the dementia became more severe (Hodges & Patterson, 1995).

Concept Knowledge Specificity in AD

A number of researchers (Huff, F. J., et al., 1986; Martin & Fedio, 1983; Nebes, 1989; Warrington, 1975) have suggested that although demented patients may retain general semantic information about a concept (i.e. its superordinate category), they progressively lose knowledge of the specific semantic attributes (subordinate information) over time. As these attributes are believed to help differentiate between two closely related concepts, the loss of specific concept knowledge can account for the impairments that AD patients have in naming (Huff, F. J., et al., 1986) and in encoding words to memory (Weingartner, et al., 1981).

The original hypothesis that subordinate information is more susceptible to disease pathology comes from Warrington's (1975) study of three patients with progressive dementia. These patients could answer questions about the category to which objects belonged, but they were significantly impaired when asked questions about their physical features. They could also sort objects by category, but could not sort objects by physical features or functions. Similarly,

Martin and Fedio (1983) found that AD patients could sort objects by category and answer yes/no questions about an objects category (e.g. “Is it alive?”), but could not answer similar yes/no questions about the object’s physical features.

Intact performance compared to controls on tasks examining superordinate categorical knowledge with deficits in subordinate knowledge in AD have been consistently reported (Funnell, 1983; Hodges, 1994; Rapp & Carramaza, 1993; Shallice, 1989). The reported ability of AD patients to make accurate decisions regarding the category membership of concepts dates back to several experiments conducted in the 1980s. In one study, when AD patients were shown a picture and asked whether the object belonged to a specific category (e.g. “Is this a fruit?”), their accuracy was comparable to that of healthy controls (Huff, F. J., et al., 1986). Similar results were also found in a study examining reaction time (Nebes, R. D., F. Boller, & A. Holland, 1986).

In another study (Chertkow & Bub, 1990), participants with probable AD were presented with pictures of common objects and asked questions varying in specificity of knowledge required for the answer. The questions focused on specific knowledge, such as perceptual attributes or contextual features (e.g. “Is the tip made of metal or wood?”). This experiment found that AD patients committed significantly more errors when answering questions probing specific semantic knowledge, but they performed at the same level as normal controls when the questions involved superordinate information.

Anterograde Memory, Retrograde Memory and the Temporal Gradient

All memories can further be conceptualized in terms of how recently the information was acquired and stored. A common distinction based on retention time is between anterograde and retrograde memory. Anterograde memory refers to the acquisition and retention of newly learned

information while retrograde memory refers to the ability to recall information that was previously acquired and has been stored in memory.

Scoville and Milner's (1957) classic work with the famous patient H.M. provides a powerful example of dissociations between both episodic and semantic knowledge and anterograde and retrograde memory. H.M. underwent surgery to remove bilateral hippocampus and surrounding MTL structures. After surgery, H.M. demonstrated severe anterograde amnesia, as he was unable to learn new information and consolidate it to long-term memory. For example, it is often noted that he read the same mechanics magazine everyday for years, each time believing it was his first experience with the magazine (Scoville & Milner, 1957).

In addition to substantial anterograde amnesia he exhibited noticeable retrograde amnesia as well, such that events that took place closer to the time of surgery were remembered more poorly than more remote memories. The observed deficits in H.M. are consistent with Ribot's Law (1881), which postulates that pre-morbid memory is disrupted in the inverse order of its formation. That is, older memories appear to have greater permanence than recently acquired memories and are organized in a "first-in, last-out" fashion. That is, memories acquired early in life are the most resistant to loss due to brain injury or neurodegenerative disease. This concept is commonly referred to as the Temporal Gradient (TG). Understanding the nature of the temporal gradient and the neuroanatomical structures involved is of both theoretical and clinical importance. First, the specific pattern of temporally graded remote memory impairment can help differentiate between certain patient groups, with a stronger gradient being observed in those with dementia or brain damage (Beatty, Salmon, Butters, Heindel, & Granholm, 1988a; Sadek et al., 2004). Additionally, the nature of the observed temporal gradient has implications for specifying the cognitive mechanisms and neural systems supporting long-term memory

consolidation and retrieval (Moscovitch et al., 2005; Squire, L.R. & P. Alvarez, 1995; Winocur, Moscovitch, & Bontempi, 2010).

Research indicates that the TG is variable, depending upon the size and location of the brain lesion. For example, a time-limited remote memory impairment is associated with damage localized to the hippocampus. Damage beyond the hippocampus in neocortical networks is associated with further memory impairment for older, progressively more remotely learned information. In contrast, individuals with semantic dementia, which is characterized by focal damage to the anterior regions of the temporal lobe (sparing the MTL), have better recall of recent events than remote events (Hodges & Graham, 1998). Lastly, lesions in frontal or subcortical regions have been shown to produce retrograde memory loss that is not temporally graded (Cermak & O'Connor, 1983; Sanders & Warrington, 1971).

The Temporal Gradient in AD

The stronger permanence of remote memory compared to more recent memory has been an important source of information concerning the relative roles of the hippocampus, adjacent MTL regions and neocortex in the consolidation, storage and retrieval of long-term memories (Moscovitch, et al., 2005; Squire, L. R. & P. Alvarez, 1995) As these areas are progressively affected throughout the disease course (Fennema-Notestine et al., 2009), investigation into the nature of the temporal gradient within AD patients and at-risk populations has been used to further understand the characteristics of long-term memory impairments in AD.

Studies of the TG are generally associated with one of two categories: autobiographical episodic memory or semantic memory. Autobiographical episodic memory is conceptualized as a mental representation of personal events and facts that allows retrieval of both personal semantic information (e.g. one's birth date) and episodic memories (e.g. what one did on a specific

birthday). Impairment of long-term autobiographical memories is consistently observed in AD (Kopelman, 1989). However, findings regarding the nature of the TG associated with autobiographical remote memory in AD have not been consistent. Some studies have demonstrated a clear time-limited TG (Hou, Miller, & Kramer, 2005; Ivanoiu, Cooper, Shanks, & Venneri, 2004; Kopelman, 1989; Leyhe, Muller, Milian, Eschweiler, & Saur, 2009) and other studies have not observed a TG (Dall'Ora, Della Sala, & Spinnler, 1989; Greene, Hodges, & Baddeley, 1995; Meeter, Eijsackers, & Mulder, 2006).

For example, using the Autobiographical Memory Interview (AMI), researchers have found significant deficits in patients with AD. These deficits were more pronounced for recent memories than for remote ones (Kopelman, 1989). Other groups have reported similar results (Hou, et al., 2005; Snowden, Griffiths, & Neary, 1996). However, other research examining autobiographical memory in patients with early AD and found a slight TG in the incident component of the AMI, but not in the personal semantic component of the AMI (Greene, et al., 1995). Ivanoiu, Cooper, Shanks, and Venneri (2004) compared episodic and semantic autobiographical memory in AD patients and healthy controls, and the AD patients did not show a clear TG for episodic autobiographical memory. They did, however, demonstrate a modest gradient for semantic autobiographical memory.

Studies of recent and remote semantic memory (e.g. famous faces, famous names, historical events) in AD often find a modest TG (Beatty, Goodkin, Monson, Beatty, & Hertsgaard, 1988b; Hodges, Salmon, & Butters, 1993; Sagar, Cohen, Sullivan, Corkin, & Growdon, 1988). For example, one study reported a mild TG for famous faces and names, such that there was relatively greater memory impairment for the identification of recent famous faces and names compared to remote ones compared to controls (Greene, J. D. W. & J. R. Hodges,

1996). Furthermore, Beatty, Salmon, Butters, Heindel, and Granholm (1988b) used a Famous Faces and Public Events Recall Questionnaire to compare retrograde amnesia in patients with AD. The Famous Faces portion consisted of photographs of persons who were best known during the five decades from the 1940s to the 1980s. The Public Events Recall Questionnaire inquired about knowledge of events during the same time frame. AD patients performed more poorly than controls overall, and they showed a time-limited TG with better recall of famous faces and events from 1940s and 1950s than famous faces from 1960s through 1980s.

Use of Semantic Memory Tasks in Early Detection of Cognitive Decline and AD

Recently, the nature of the TG within semantic memory has been used in to predict cognitive decline in older adults. For example, Seidenberg et al. (2009b) suggested that investigation of the TG pattern for semantic information may provide a useful approach for examining the transition from normal aging to Amnestic Mild Cognitive Impairment (aMCI) and AD. Using a famous name discrimination task, in which participants are asked to respond via button press as to whether a name presented on a computer screen is famous or not, they found that aMCI subjects recognized remote famous names as well as healthy controls, but they recognized significantly fewer recent famous names. Additionally, participants were asked to complete (in writing) information about the famous names that they correctly recognized. Semantic knowledge was determined by having subjects provide information in response to four distinct probes: (1) Reason this person is well known (e.g., occupation), (2) Known works/accomplishments of this individual, (3) Names of specific individuals or events associated with this individual, (4) History and background (e.g., family life, health status). Each of these four probes was scored on a 0-3 point scale. A total specific semantic knowledge score (range 0-12) was derived for each item by adding scores from the four probes. Analysis of the specific

semantic knowledge score revealed that the control group provided more semantic information overall compared to the aMCI group and exhibited a significantly steeper TG (enduring > remote > recent) than the control group.

Similarly, other researchers utilized the Media-mediated Memory Task (Bizzozero, Capitani, Saetti, Spinnler, & Lucchelli, 2005) to assess semantic knowledge for public events in aMCI patients and controls (Bizzozero, et al., 2009). The Media-mediated Memory Test consists of 65 questions concerning famous public events that had occurred from 1976 to 2000, subdivided into five 5-year periods, each including 13 events. Participants were evaluated in a free-recall format and scores were based on the number of details provided. Overall, controls were able to provide significantly more details regarding the public events compared to aMCI individuals. Additionally, they reported that 47% of aMCI participants exhibited what they termed a "pathological temporal gradient" (i.e. remote > recent in excess of a control group), which then increased to 80% of at an 18-month follow-up.

Furthermore, functional magnetic resonance imaging (fMRI) activation during semantic memory tasks has been utilized to discriminate between at-risk groups as well as to successfully predict cognitive decline in healthy older adults (Seidenberg, et al., 2009a, Seidenberg et al., 2009b; Smith et al., 2011; Woodard et al., 2009; Woodard, et al., 2010). Woodard and colleagues (2009) examined functional activation during a famous name discrimination task, with results suggesting compensatory recruitment during semantic memory retrieval in those with aMCI. In this study, 57 older adults completed a famous name discrimination task during fMRI. Participants included 19 cognitively intact at-risk older adults with at least one APOE ε4 allele and a family history of dementia, 19 patients diagnosed with amnestic MCI according to Petersen criteria (Petersen, R. C. et al., 2001), and 19 cognitively intact controls without the

APOE ε4 allele or a family history of dementia. Importantly, the three groups did not differ on task performance, although there were non-significant trends towards lower accuracy and longer reaction times in the MCI patients. Results revealed that at-risk and MCI participants displayed an overall greater extent and magnitude of activation than controls for famous relative to unfamiliar names in several MTL and neocortical regions.

In a subsequent longitudinal study (Woodard, et al., 2010), 78 healthy, cognitively intact adults aged 65 years of age and older completed neuropsychological testing at baseline and 18-month follow-up. In addition, participants performed a famous name discrimination during task-activated fMRI at baseline. At the 18-month follow-up, 27 participants exhibited cognitive decline, defined as a decrease of at least one SD on one or more of three neuropsychological outcome measures (only two participants met Petersen criteria for MCI (Petersen, R.C. et al., 2001)) at the 18-month follow-up). While stable and declining participants had equivalent famous name discrimination task performance at baseline, participants with greater activation at baseline were *less* likely to have exhibited cognitive decline at follow-up (Woodard, et al., 2010).

Present Study Summary

There is clear evidence that semantic memory networks are disrupted during the course of AD, and research has suggested that semantic knowledge is affected in a systematic way. Specifically, the breakdown of semantic knowledge first occurs for specific information about a concept, while more general semantic information is less vulnerable. In addition, the extent of the TG for remote memory has been demonstrated to worsen throughout the progression of Alzheimer's disease. Very little research, however, has focused on changes to both systematic processes in tandem. This study sought to determine whether cognitively intact older adult children of persons with AD exhibit differences in both of these characteristics of semantic

knowledge disruption as compared to older individuals whose parents have not been diagnosed with AD. The long-term goal of this research was to assess for potential early cognitive changes that occur in older adults who are already at elevated risk for AD. Individuals demonstrating semantic inefficiencies can then be followed over time to determine whether they subsequently develop cognitive decline, MCI, or AD.

Ancillary investigation involved exploration of the TG at varying levels of conceptual knowledge specificity in order to determine their potentially interactive and reciprocally dynamic effects on semantic network organization. These theories were tested within two separate conceptual knowledge domains with expectation that new information could be gathered regarding long-term memory encoding and consolidation. These theories were assessed through examination of performance variables (Reaction time and Accuracy) for parental history positive and negative older adults on a computer-generated, semantic memory tasks for famous person and general word knowledge. We proposed to accomplish the following aims in analysis of listed hypotheses:

Specific aims and predictions

Specific Aim 1. To determine the relative contributions of familial risk for AD, the age of memory acquisition (enduring vs. remote vs. recent), and specificity of conceptual knowledge (familiarity/recognition vs. categorization vs. specific attributes) on behavioral performance for semantic tasks associated with famous individuals from different eras. It was predicted that cognitively intact older individuals with a parental history of AD will demonstrate performance differences relative to persons without a family history of AD that will be suggestive of a faster degradation of both specific and recently acquired semantic knowledge, as measured by

differences in reaction times and/or accuracy. In addition, lower order comparisons were planned to assess the following specific hypotheses:

Specific Hypotheses 1. Generally, we expected that the magnitude of the TG for the RT (enduring < remote < recent) and accuracy (enduring > remote > recent) data in the at-risk group would demonstrate a relationship with specificity of the semantic knowledge tasks (Recognition vs. Categorization vs. Attribute). That is, poorer performances (lower accuracy and slower RTs) will be observed for more recent specific semantic knowledge relative to general enduring semantic knowledge. While we anticipated this pattern would be observed in individuals without a parental history, the magnitude of the effects of age of acquisition and specificity of knowledge was predicted to be less pronounced.

Specific Hypotheses 2. For all time epochs, we expected slower RTs and lower accuracy for the Attributes task compared to the Categorical and Recognition tasks. The magnitude of the difference in performance was not expected to be as pronounced in the non-risk group.

Specific Hypotheses 3. We predicted that regardless of task (Recognition vs. Category vs. Attributes) the TG would be more pronounced in the at-risk group.

Specific Aim 2. To explore the concurrent effects of age of memory and specificity of conceptual knowledge on semantic network organization. It was generally predicted that both constructs would have a significant influence behavioral performance in an interactive manner. The following specific hypotheses were explored:

Specific Hypotheses 4. We expected that the TG for the accuracy (enduring > remote > recent) and RT (enduring < remote < recent) would be more pronounced for the attributes task than for the categorical and recognition tasks. Specifically, the relationship described above is expected to be present in both groups such that the poorest performances (lowest accuracy and

slowest RTs) will be observed for the recent name stimuli in the Attributes Task while the best performances will be observed for the enduring name stimuli within the Recognition Task.

Specific Hypotheses 5. It is also expected that a main effect of Time Epoch will be observed, such that participants will produce the fastest RTs and greatest accuracy for enduring famous names followed by remote famous names with the slowest RTs and lowest accuracy for recent names.

Specific Hypotheses 6. Additionally, it is expected that a main effect for task specificity will be observed, such that RTs for Attribute > Categorical > Recognition and Accuracy for Recognition ≥ Categorical > Attribute across time epochs.

Specific Aim 3. To determine if the TG patterns observed for semantic networks for at-risk and non-at-risk groups are stable across different domains of semantic knowledge. Specifically, we examined the nature of the temporal gradient for knowledge associated with names of famous public personalities as well as with word stimuli from different decades. It was expected that the same general pattern of semantic knowledge disruption will be observed across both stimuli lists and reaction time and accuracy differences between groups will be greatest for recent stimuli.

Specific Hypotheses.

It was predicted that behavioral patterns (i.e., RT and accuracy) observed for the word conceptual knowledge tasks would support the above-mentioned theories regarding disruption of the semantic memory network in at-risk older adults as well as the interactive effects of age of memory and knowledge specificity on semantic network organization.

METHOD

Participants

Ninety, non-adopted adults recruited through local senior centers and communities of faith participated in the study. The Wayne State University Institutional Review Board (IRB) approved the project and all participants provided informed consent. Participants were compensated $25 dollars for their participation. All participants were between the ages of 60 and 90 years, were native English speaking, right-handed, had at least 20/20 or corrected to 20/20 vision, had intact hearing, and were absent of any motor difficulties that would affect their ability to press computer buttons. Interested participants were screened for appropriateness for the study over the phone and were excluded based on history of adoption, major medical illness (e.g., cancer, diabetes), history of major neurological illness (e.g. stroke, head trauma with loss of consciousness for greater than 30 minutes, seizure disorder), the presence of a current DSM-IV-TR Axis I disorder, or current use of psychoactive medications. Medical and psychiatric history was confirmed during time of testing by completion of a demographics information form (Appendix 1). In addition to completion of the subject demographics form, participants underwent a brief neuropsychological battery. Participants who performed lower than 1.5 standard deviations below the mean, for their standardization group, on one or more of the neuropsychological testing scores listed in Table 1 were excluded.

Overall, two participants were excluded on the basis of a significant neurological history, one due to current DSM-IV-TR Axis diagnosis/high Geriatric Depression Scale score, two due to refusal to complete over half the measures, one due to low reading achievement based on WRAT-IV grade-equivalent estimate, and three individuals were excluded from final analyses due to performance outside of the predetermined cutoffs on neuropsychological testing. After

applying exclusion criteria, the final sample consisted of 81 healthy community dwelling adults between the ages of 60 and 90 years of age. Participants were then grouped by presence (PH+) or absence of a history of AD in a biological parent (PH-) based on completion of a detailed family history questionnaire (Appendix 2). Forty-one individuals were included in the PH+ groups and 40 in the PH- group prior to data screening.

Instruments

Neuropsychological battery. The following neuropsychological battery was used to determine inclusion of participant data in final analyses as described above.

General cognitive ability. The Dementia Rating Scale (DRS-2) (Mattis, 1988) was used to assess general cognitive ability. The DRS-2 assesses cognitive functioning on five subscales: Attention (ATT, 8 items); Initiation/Perseveration (I/P, 11 items); Construction (CONST, 6 items); Conceptualization (CONCEPT, 6 items); and Memory (MEM, 5 items). The DRS-2 has been demonstrated to be particularly useful in differentiating dementia patients from healthy controls (Monsch et al., 1995), which was important our this study interested in examining individuals absent of clinically significant symptoms. Age-corrected Mayo Older American Normative Studies (MOANS) (Lucas et al., 1998) scaled scores for each domain as well as for total performance were calculated for each participant.

Memory. The Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1958) was used to assess episodic memory in high-load list format. For administration, the experimenter read a 15-item word list and asked the participants to repeat back as many words as they can remember in any order, five times. They were then presented with a distractor list, which they are asked to recall, and then they were asked to recall the original list (immediate recall). Following a 20-minute delay, participants were again asked to repeat aloud any words they can remember from

the original list (delayed recall). Then, participants are presented with a 30-item word list and are instructed to indicate whether each word was present on the original list (Recognition Trial). The Mayo's Older American Normative Studies (Ivnik et al., 1990), age-adjusted scaled scores were calculated for previously proposed variables (Trial 1, Trial 1-5 total and Delayed Recall).

The Wechsler Memory Scale Fourth Edition (WMS-R) Logical Memory subtest (Wechsler, 1987) was used to assess narrative, episodic memory in both immediate and delayed conditions. During the task, a brief narrative story was read aloud to participants, and they were asked to repeat back aloud the story in as much detail as they can remember. This procedure was repeated for a second narrative story. Following a 20-to-30 minute delay, participants were asked to recall as many details from the stories as they can. Scaled scores were calculated using the age-adjusted MOANS norms (Smith, Wong, Ivnik, & Malec, 1997).

Processing Speed. The Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV) Coding and Symbol Search subtests (Wechsler, 2008) were used to assess participants' ability to quickly perceive and process visual stimuli. For the Coding subtest, participants were presented with rows of blanks squares with numbers (1-9) printed above. A key is presented at the top of the page pairing each number with a simple symbol. The participant was given 120 seconds to fill in the blank squares with the symbol that matches the number above it, as quickly as possible without making mistakes. For the Symbol Search task, the participant was instructed to scan a group of five symbols and indicate whether either of two target symbols appears in the search group. Participants were given 120 seconds to complete as many items as possible. The interpretive and technical manual for the WAIS-IV (Wechsler, 2008) provides age-corrected normative data for adults aged 18-89 that were used to calculate participants' scaled scores.

Reading ability and vocabulary. The Word Reading subtest of the Wide Range Achievement Test – Fourth Edition (Wilkinson & Robertson, 2006) assessed reading ability in order to assure participants' ability to accurately read stimulus words presented during computer tasks. In this task, participants were asked to read aloud a list of English words. The WRAT-IV manual (Wilkinson & Robertson, 2006) provides normative data for individuals between 65 and 94 years old, and reports its scores to have high internal consistency (α = .96) among the standardization sample. Age-corrected scaled scores and estimated grade equivalents were calculated for each participant. Participants were required to have an 8th grade reading level to complete the computer tasks.

Mood. The Geriatric Depression Scale, Short From (GDS-SF) (Sheikh & Yesavage, 1986) was used to assess for the presence of mood disturbance. The Geriatric Depression Scale (GDS), first created by Yesavage and colleagues (1983) has been tested and used extensively with the older population. The GDS Long Form is a 30-item questionnaire in which participants are asked to respond to each question by answering yes or no to indicate how they felt over the past week. The Short Form GDS consists of 15 questions from the Long Form GDS that had the highest correlation with depressive symptoms in validation studies. The GDS-SF focuses on the behavioral and cognitive aspects of depression, while minimizing assessment of neuro-vegetative symptoms that may be related to causes other than depression (e.g. medical problems). In a validation study comparing scores from the Long and Short Forms of the GDS for self-rating of symptoms of depression, both were successful in differentiating depressed from non-depressed older adults with a high correlation (r = .84) (Sheikh & Yesavage, 1986). Individuals scoring above the raw score cutoff for moderate level of depressive symptoms ($\geq$ 9) were excluded from the study.

The Positive and Negative Affect Schedule (PANAS) (Watson, Clark, & Tellegen, 1988) was utilized as an additional mood measure. This instrument is a self-report measure consisting of 20 adjectives. Participants were asked to rate the extent to which they felt each adjective during the past week, ranging from 1 = "very slightly or not at all" to 5 = "extremely." The measure consists of 10 positive affect adjectives (e.g., interested, excited) and 10 negative affect adjectives (e.g., irritable, distressed). Scores from the PANAS have exhibited good internal consistency (PA α = .88, NA α = .85) and convergent and discriminant validity in a samples of healthy older adults those with Generalized Anxiety Disorder (Beck et al., 2003). Individuals who scored lower than 1.5 SDs (raw of 22) on the positive affect scale, and those who scored above 1.5 SDs (raw of 27) on the negative affect score were considered for exclusion from the study.

Inhibition. The Stroop Color and Word Test (Golden, 2002) assessed participants' ability to inhibit responses, as low inhibition may influence performance on the experimental tasks by producing low accuracy and short RT due to impulsive responding. The Stroop Test is a test of mental flexibility that involves attention and ability to inhibit a dominant response tendency. Specifically, participants were presented with names of colors that are not congruent with the ink color in which the word is printed. Participants were asked to identify the color in which each word is printed while ignoring the printed word. Performance on this task is compared with the participant's ability to read color names that are printed in black ink and ability to name the ink color in which several X's is printed. The Stroop Color and Word Test yields four basic scores. For the present study, the interference score was the primary index of interest. Previous use of the Stroop with older adults has found the measure to produce scores with good internal consistency ($\alpha \geq .89$) (Salthouse, 1996; Salthouse & Meinz, 1995). Additionally, the Stroop has

been reported to be a valid measure of inhibition in older adult samples (Verhaeghen, Vandenbroucke, & Dierckx, 1998). Raw interference scores were normed using the MOANS normative data tables (Ivnik, Malec, Smith, Tangalos, & Petersen, 1996).

Computer Stimuli and Task Descriptions. The following tasks were used to assess semantic knowledge for famous persons and words. After empirically deriving stimulus lists tasks were generated for presentation on the computer.

Famous Names Stimuli. Famous and non-famous names were standardized in a pilot study (Woodard, 2010) following the same methodology as Douville and colleagues (2005). The pilot study examined recognition of 200 names by 25 older (age range 65-90 years) and 25 younger (age range 20-30 years) adults. Famous names were categorized according to the time period in which the individual achieved prominence and the recognizability of each stimulus by older and younger participants. These categories included recently famous individuals who achieved prominence between 2000 and 2010 (e.g. Justin Bieber) and were correctly recognized by 70% of older and younger pilot participants (Recent category), individuals with enduring fame who became famous between 1960 and 1980 and still well known today (e.g., Paul McCartney) who were identified by at least 70% of older and younger participants (Enduring category), and individuals who achieved a brief but intense period of fame between 1960 and 1980 and were correctly recognized by at least 70% of older pilot participants and by less than 30% of younger participants (Remote category). Non-famous names were randomly selected from a local telephone directory and were correctly identified as non-famous by at least 90% of older and younger pilot participants. Twenty Recent, 20 Enduring, 20 and 60 non-famous names were used in this study. See Appendix 3 for the famous names in the recent time epoch, Appendix 4 for the famous names in the enduring epoch and Appendix 5 for famous names in

the remote time epoch.

Famous Names Semantic Knowledge Tasks. Three tasks were used to assess the TG (remote vs. enduring vs. recent) for general (recognition and categorization) and specific (concept attributes) semantic knowledge about famous individuals: a) *famous name discrimination task*, b) *occupation categorization task* and, c) *attribute knowledge task*.

1. Famous Name Discrimination Task (FNDT). Participants were first asked to decide whether each of the 120 names is famous or non-famous. Name stimuli were presented in the middle of the computer screen with two response choices (i.e., famous and non-famous) in the lower left and right hand corners. Using an RB-834 response pad (Cedrus, 2011), participants made a button press with either their right index or ring finger to indicate their choice of either "famous" or "non-famous" in response to the presented name. Presentation of name stimuli was randomized for each participant, as was side of presentation for response choices. A total of 60 famous names were shown, with 20 from each of the recent, enduring and remote time epochs. In addition, 60 unfamiliar names were presented. Famous and non-famous names were randomly interspersed. See Figure 1 for an example.

2. Famous Name Categorization Task. Each of the previously presented famous names was used in a categorization task. Each name was presented at the top of the screen with two of five occupational categories (e.g., Politics, Movies, Sports, Television, Music) presented at the bottom left and right corners of the screen. Participants were asked to choose the occupational category most closely associated with the target, famous name (e.g., Angelina Jolie: politics vs. **movies**). Again, participants responded via button press. Order of stimulus presentation and side of correct response were randomized for this task as well. See Figure 2 for an example.

3. Famous Name Attributes Knowledge Task. Each of the previously presented famous names was then used in an attribute knowledge task. Each name was, again, presented at the top of the screen, with two attributes, details, or bodies of work that could be associated with the target name at the bottom left and right corners of the screen. Participants were asked to select the attribute that is most closely associated with the target famous name (e.g., Angelina Jolie: The Blind Side vs. **Million Dollar Baby**). Participants pressed either the right or left response pad button corresponding to the side of the selected attribute, which was randomized as was the order of stimulus presentation. See Figure 3 for an example.

Word Semantic Knowledge Stimuli. Using a strategy similar to Kopelman and colleagues (2009), a list of words that came into common usage across a 50-year period (1960-2011) was constructed. The words were grouped by decade in which they entered the English language based on the Timeline database provided by *Oxford English Dictionary* (OED) (Simpson & Weiner, 1989). The OED database keeps detailed records of when words entered into the English language based on frequency of use and the number of times quoted in English literature (See http://www.oed.com for specific criteria). For the decades 1960-2010, words were considered for inclusion in the stimulus list based on the year that their primary definition was officially entered the English language based on OED guidelines, and if a secondary definition for the word had not been recognized by the OED within the same 50-year period. Additionally, words were excluded if they were also a brand name, abbreviation, or acronym.

In addition to recognition by a major scholastic dictionary, words originating between 1960 and 2000 were examined for frequency of use utilizing the Google Ngram database (Jean-Baptiste et al., 2010). The Ngram database examines the frequency of use based on the number of times it is quoted in the corpus of books contained in the Google Books Library. A frequency

percentage is then calculated by dividing the number of times the word is used by the number of words in the Google Books library. Words were eligible for inclusion if their frequency percentage reached < .00001% (1/10,000,000) during the decade of entry in to the English language. See Figure 4 for an example of the Google Ngram frequency calculator.

Words that entered the OED after 2000 were not available for analysis by the Ngram database. Thus, they were considered for the stimulus list based on the year that they were officially included as entries in the OED. The criteria for inclusion in the OED, also employs requirements for frequency of use, which should help ensure that frequency is greater than or equal to 1/10,000,000 of printed words. See Appendix 6 for the Words stimulus list by decade.

Words Semantic Knowledge Tasks. The semantic knowledge tasks utilized with the famous name stimuli were paralleled within the Word Stimuli: a) *word recognition task*, b) *categorization task,* and c) *attribute knowledge task*.

Word Recognition Task. Participants were first asked to decide whether individually-presented groupings of letters represent a true word or a nonsense word. Nonsense words were created by altering a single phonemic segment of a legal English word (i.e. *burple*, *meam*, *flid*). Similar to the famous names tasks, participants made a button press with either their right index or ring finger to indicate their choice of either "word" or "non-word." Similarly, presentation of word stimuli was randomized for each participant, as was side of presentation for response choices. A total of 50 words (10 from each decade) and 50 nonsense words will be shown. True words and nonsense words will be randomly interspersed. See Figure 5 for an example.

Word Categorization Task. Each of the previously presented words was also used in a categorization task. Each word was presented at the top of the screen, with two of six subject categories (e.g., Technology, Science & Medicine, Sports & Leisure, Fashion, Arts, and Food &

Drink) presented at the bottom left and right corners of the screen. Participants were asked to choose the subject category most closely associated with the target word (e.g., Canola: **Food** vs. Fashion). Participants pressed either the right or left response pad button corresponding to the side of the selected subject category. Order of stimulus presentation and side of response were randomized. An example is presented in Figure 6.

Word Attributes Knowledge Task. Each of the previously presented words was used in an attribute knowledge task as well. Each word was, again, presented at the top of the screen, with two attributes or details at the bottom left and right of the screen that could be associated with the target word. Participants selected the attribute that is most closely associated with the target word (e.g., Canola: **edible** vs. metal). Participants, again, indicated their response via button press and presentation of stimulus and choice was randomized. Figure 7 provides an example.

Procedure

After being contacted via telephone and initial eligibility for inclusion in the study was established, participants were tested in single 1.5-2 hour sessions at local IRB-approved testing sites. Individuals worked one-on-one with either the PI or trained research assistants to complete the tasks. After providing informed consent, participants were administered the tasks in the following order: 1) Subject Information Form, 2) Family History Questionnaire, 3) Neuropsychological Battery and 4) Computer presentation of the Semantic Knowledge Tasks. In order to increase the probability of correct completion and to help establish rapport, in some instances participants were offered the option to fill out the family history questionnaire with the help of the research assistant in a structured interview format.

E-prime v2.0 (Schneider, A., & Zuccolotto, 2002) was used to program the presentation of computer stimuli and record accuracy and reaction time (RT) for each response. During

completion of computer tasks, participants were positioned approximately 40 cm from the computer. Instructions for each task were presented on the screen and clarified verbally by research assistants. Following instructions the participant completed 10 practice trials to ensure understanding of directions and further clarification was provided if needed. Presentation of famous name and word tasks were counterbalanced amongst participants. Within a stimulus category (i.e. names vs. words), tasks were always presented in the same order: 1) discrimination, 2) categorization, and 3) attributes. For each task, stimuli were presented until participants entered a response, and there was a 1000ms interval between stimuli. Participants were instructed to respond as fast as possible without making mistakes.

Data Analyses

Mean accuracy and RT for each participant were calculated using the E-Data Aid software provided as part of the E-prime v2.0 software package (Schneider, et al., 2002). Accuracy was calculated for each individual by determining the percentage of correct responses within each condition of the six computer tasks (e.g., Accuracy for enduring names on the discrimination task; accuracy for enduring names on the categorization task etc.). Mean RTs for the correct decisions of each participant were calculated after removal of outliers (i.e. those scores that fell two standard deviations above or below the mean for the sample's correct responses within that condition). Again, mean RTs were calculated within each condition of the six computer tasks (e.g. mean RT for enduring names on the FNDT, mean RT for the remote names on the FNDT etc.).

Before specific aims of the study were evaluated, data were screened. Specifically, the variables were examined for missing data and potential patterns of missing data were explored. Data was also screened for potential univariate outliers and extreme values determined to have

high leverage were deleted. Normality of the data was assessed through examination of histograms, skewness and kurtosis statistics, as well as Q-Q plots. Homoscedasticity, homogeneity of variance and multicolinearity were also assessed. Next, in order to determine the comparability between groups on predetermined demographic variables, descriptive statistics and frequencies were calculated for each group and then compared using independent samples t-tests and chi-square tests of independence where appropriate.

Specific Aims 1 & 2 were examined using two separate 2 (Group) x 3 (Time Epoch) x 3 (Level of Semantic Knowledge) Split Plot Analyses of Variance (ANOVA) conducted for the RT and accuracy data. Interactions and individual main effects were examined in the context of the following specific hypotheses:

Specific Hypothesis 1**:** The expectation that the magnitude of the TG will demonstrate an increasing relationship with knowledge specificity and will differ in magnitude between the groups (PH+ and PH-) was examined via the 3-way interaction between Group, Time Epoch, and Level of Semantic Knowledge with subsequent post hoc analyses when appropriate.

Specific Hypothesis 2**:** The 2-way interaction between Group and Level of Semantic Knowledge variables was used to assess the prediction that lower accuracy/slower reaction times would be observed for attribute task relative to categorical and recognition tasks with a greater magnitude of difference for the PH+ group.

Specific Hypothesis 3: We expected that the TG would be more pronounced in the at-risk group, which was examined via the 2-way interaction between Group and Time Epoch.

Specific Hypothesis 4: For both groups, we expected that the TG would be more pronounced for the Attributes task relative to the Category and Recognition tasks.

Specifically, we expected the relationship between age of memory (Time Epoch) and specificity of knowledge (Task) such that the poorest performances (lowest accuracy and slowest RTs) will be observed for the recent name stimuli in the Attributes Task, while the best performances will be observed for the enduring name stimuli within the Recognition Task. This hypothesis was examined through the 2-way interaction between Time Epoch and Specificity. Subsequent simple main effects analyses were conducted to examine the TG within each task. Comparisons between each task (enduring vs. remote vs. recent) within each time epoch were also examined.

Specific Hypothesis 5: The fastest RTs and greatest accuracy were predicted for enduring famous names, followed by intermediate RTs and accuracy for remote famous names, and the slowest RTs and lowest accuracy were predicted for recently famous individuals. This hypothesis was examined by assessing the significance of the main effect for Time Epoch. Because the Time Epoch variable has more than two levels, pre-planned t-tests were used to determine where significant differences existed following a significant main effect.

Specific Hypothesis 6: Finally, it was expected that the main effect for Level of Semantic Knowledge would be significant. Pre-planned t-tests were used to examine the expectation that RTs would be longest for the Attribute Task, intermediate for the Categorical Task, and fastest for the Recognition Task. Pre-planned t-tests were also used to determine whether the accuracy for the Recognition task was highest, intermediate for the Categorical task, and lowest for the Attribute task.

To examine Specific Aim 3 (and to supplement Specific Aim 2), two separate 2 (Group) x 5 (Decade) x 3 (Level of Semantic Knowledge) Split Plot ANOVAs were conducted for the RT and accuracy data from the Word Tasks. Interactions, simple main effects, overall main effects

and pre-planned t-tests were examined in the same manner outlined above for the Famous Names Tasks.

For each ANOVA, Mauchly's Test of Sphericity was used to assess possible violation of homogeneity of variance given the repeated measures design and size of the sample (Raykov & Marcoulides, 2008). The significance of Mauchly's Test at $p < .05$ was used to determine if the assumption had been violated. Further, a cutoff of $\varepsilon < .75$ was used to establish the appropriate adjustment method for violations of homogeneity of variance when they existed (Collier, Baker, Mandeville, & Hayes, 1967; Raykov & Marcoulides, 2008). Finally, simple main effects analyses following significant interaction terms and pre-planned t-tests following significant overall main effects resulted in a high number of pairwise comparisons. Because false positive errors (type I error rate) was of greatest concern, the Bonferroni correction was utilized to adjust the critical value, as it is often regarded to be the most conservative (Tabachnick & Fidell, 2001).

RESULTS

Data Screening

Before examination of specific aims, the accuracy of the data file was checked and missing data were analyzed. Unfortunate glitches in the computer program when converting participants' performance to the database resulted in occasional corruption of files. Thus, a few instances of missing accuracy and RT data for individual participants were observed within a single task. For example, participant 26 was missing the Word Categorization Task data, but all other computer variables were available. Nevertheless, all computer variables had less than 5% missing data, and because participants otherwise met criteria and provided accurate data, they were not removed from final analyses. None of the demographic and neuropsychological testing variables exhibited missing data above 2%.

Data were also examined for the presence of outliers within each group. For the PH- group, examination of residual scores and graphic representation of the variable distribution revealed five computer variables (Names Categorization Enduring Accuracy; Names Categorization Remote Accuracy; Word Categorization 1970s Accuracy; Word Attributes 1980s Accuracy; Word Attributes 1990s Accuracy) each with a single outlier (determined through examination of residual scores), and the FNDT Enduring Accuracy variable evidenced two outliers. Each of these scores was deleted for final analyses examining specific aims. Outlier detection within the PH+ group revealed a single subject (subject 39) who produced significant outliers on all but one of the RT variables and 1/3 of the accuracy variables. Given the extreme nature on the majority of the participant's scores, it was decided to delete the participant's data from final analyses. The PH+ group also produced a single outlier on three additional variables (Word Categorization 1960s Accuracy; Word Attributes Knowledge 2000s Accuracy; Word Discrimination 1990s RT), which were deleted from further analyses.

The normality of the data within each group was assessed though examination of skewness and kurtosis statistics and formation of Q-Q plots. Comprehensive evaluation and interpretation of these statistics revealed that a majority of the accuracy variables were negatively skewed, such that clear ceiling effects were observed for both groups. Because the tasks were intended to be relatively easy (average accuracy was expected to be 80% to 90%), such skew is expected within the sample. On the FNDT, in particular, healthy, at-risk, and even individuals with impaired episodic memory performance often perform well and produce similar distributions as those observed in our data (Douville, K. L. et al., 2005; Seidenberg, et al., 2009a; Seidenberg, et al., 2009b). Examination of normality among RT variables revealed a moderate degree of positive skew for several of the low-specificity tasks in both groups. Subsequent

analyses involved several Split Plot ANOVA designs that are reported to be robust in the presence of similar deviations from the normal distributions. Research examining the robustness of such techniques has utilized simulation and Monte Carlo methods with a variety of non-normal distributions to demonstrate that the false positive rate is not significantly affected by violation of the normality assumption (Glass, Peckham, & Sanders, 1972; Harwell, Rubinstein, Hayes, & Olds, 1992). Type I error rate was of primary concern during analyses and further studies indicate that greater false positive rates result from violation of the homogeneity of variance assumption than deviation from normality for individual variables (Lix, Keselman, & Keselman, 1996). Thus, transformation of the RT variables was not performed, given the increased difficulty with interpretation and general robustness of ANOVA analyses in the presence of non-normal data. A conservative approach was taken during the following ANOVAs to assess homogeneity of variance and to protect against false positive errors as described in the data analyses section above.

Group Characteristics

After deletion of the participant identified during outlier detection (i.e., Participant 39), descriptive statistics and frequencies were generated for demographic variables within each group (PH+ N = 40; PH- N= 40) and are presented in Table 2. The PH- group was 77.5% female with a mean age of 68.4 years (*SD* = 6. 9 years, range = 60-90 years) and mean education of 15.1 years (*SD* = 2.4 years, range = 12-20 years). In regards to self-reported ethnicity, the PH- group was 97.5% Caucasian, with one Asian participant. Overall, the group of participants reported leading active lifestyles. Ninety percent of the group reported engaging in physical activity or exercise at least once weekly, while two participants reported engaging in physical activities 1-4 times per month, and two participants reported no regular engagement in physical activity.

Twenty-seven individuals were retired, 7 individuals worked part time, and 6 individuals continued to hold full-time positions. None of the PH- participants reported problem drinking, and 16 individuals abstained from alcohol consumption. Two individuals smoked at an average of less than one pack of cigarettes per day. One individual reported use of medical marijuana within the past year, but had not used within one week of being tested for the study.

Similarly, the PH+ group was 65% female with a mean age of 68.9 years (*SD* = 7.3 years, range – 60-85 years) and mean education of 16.1 years (*SD* = 2.1 years, range = 11-20 years). Self-reported ethnicity resulted in an 87.5% Caucasian and 12.5% African American sample. Again, the group reported leading active lifestyles with 77.5% of participants reporting at least weekly exercise, seven individuals reported engaging in physical activity/exercise on a monthly basis, and two individuals reported no engagement in physical activity. Twenty-four individuals were retired, ten individuals worked part time, and 6 individuals continued to hold full-time positions. Again, none of the PH+ participants reported problem drinking, and 14 individuals abstained from alcohol consumption. Two individuals smoked an average of less than a pack of cigarettes per day. One individual within the PH+ also reported use of medical marijuana within the past year, but had not used within one week of being tested for the study.

Independent sample t-tests confirmed that the PH+ and PH- groups did not significantly differ in terms of age ($t_{(77.90)} = -.350$ $p = .727$). Total years of education was slightly higher in the PH+ group than the PH- group ($t_{(76.94)} = -2.07$ $p = .041$). The difference between means, however, was less than half a standard deviation and represented only a one-year difference between groups. Chi-square tests of independence determined that the relative proportions of males versus females ($\chi^2_{(df=1)} = 1.53$ $p = .217$) and self-reported race ($\chi^2_{(df=2)} = 7.21$ $p = .050$) did not differ significantly between groups. Additional chi-square tests of independence confirmed

that the groups did not significantly differ in terms of engagement in physical activity ($\chi^2_{(df=2)}$ = 7.15 p = .067), occupation status ($\chi^2_{(df=2)}$ = .706 p = .703), Tobacco use ($\chi^2_{(df=1)}$ = .001 p = .999), or cannabis use ($\chi^2_{(df=1)}$ = .001 p = .999). Two more individuals abstained from alcohol use in the PH- group than in the PH+ group ($\chi^2_{(df=1)}$ = 5.01 p = .043).

Statistics specific to the diagnosis of AD in a biological parent within the PH+ group are presented in Table 3. Of the 40 participants, 77.5% reported a maternal family history of AD and 22.5% reported a paternal AD family history. No participant reported an AD diagnosis for both parents. AD diagnosis was determined via assessment within a specialized geriatric clinic or by the parent's primary care physician for the majority of individuals. Other sources of confirmed AD diagnosis were obtained from neurologists, neuropsychologists, and in one case, a geriatric psychiatrist. Two participants reported autopsy-confirmed AD diagnosis resulting from their parent's participation in another research study.

No participants reported diagnosis of another neurological disorder or dementia (e.g. Parkinson's Disease) in the parent diagnosed with AD. For the PH+ group, among the non-AD affected parents, 13 suffered a stroke. Within the PH- group, one individual had a parent with a Parkinson's disease diagnosis and 13 persons reported at least one parent suffering a stroke. In regards to further first-degree family history, two PH+ participants reported an AD diagnosis in a one sibling, and another participant had a sibling diagnosed with Parkinson's disease. Within the PH- group, one participant reported a possible AD diagnosis in a sibling and one confirmed Parkinson's diagnosis in a sibling.

Mean neuropsychological testing performance for each group is presented in Table 4. As would be expected, after deleting individuals with impairment on neuropsychological variables, the groups generally performed well, with mean standardized scores falling at or above the

"average" classification level based on normative data. Importantly, the two groups did not significantly differ on any of the predetermined neuropsychological testing scores based on independent-samples t-tests, with all p-values falling well above an alpha level of 05.

Famous Names Semantic Knowledge Specificity

Accuracy. Mean accuracy for each group within each condition of the Famous Names Semantic Knowledge Tasks is presented in Table 5. A 2 (Group) x 3 (Time Epoch) x 3 (Level of Semantic Knowledge) Split Plot ANOVA comparing PH+ and PH- participants was examined for significant differences in accuracy across each of the within subjects variables (Specific Hypotheses 1, 2, and 3); separate main effects and lower order interactions were also examined in order to characterize the effects of knowledge specificity and epoch on accuracy performance, regardless of parental history (Specific Hypotheses 4, 5, and 6). Prior to interpretation of results, it was found that Mauchly's Test of Sphericity was significant and that the assumption of homogeneity of variance had been violated for each of the within subject variables: Time Epoch $\chi^2(2) = 6.8$, $p = .033$ and Level of Semantic Knowledge $\chi^2(2) = 10.06$, $p = .007$, as well as for their interaction term $\chi^2(9) = 26.41$, $p = .002$. Given that for all estimates of sphericity, $\varepsilon \geq .75$, the Huynh-Feldt correction was chosen for adjustment for Type I error rate and applied to all comparisons within the ANOVA (Collier, et al., 1967) . The overall results of the ANOVA are presented in Table 6, with alpha levels reflecting the Huynh-Feldt correction.

In general, group differences were not observed amongst the accuracy data for the Famous Names Semantic Knowledge Tests. The three-way interaction between Group, Time Epoch, and Level of Semantic Knowledge was non-significant, $F_{(3.3, 237.5)} = 1.707$, $p = .160$. In other words, the relative contributions of age of acquisition (Enduring vs. Remote vs. Recent) and level of specificity (Recognition vs. Categorization vs. Attributes) to accuracy performance

did not differ between PH+ and PH- groups as predicted. Examination of lower-order comparisons also revealed that the groups did not differ on the within subject factors independently. The Group by Level of Semantic Knowledge interaction term was non-significant, $F_{(1.8,\ 129.9)} = .036$, $p = .956$ as was the Group by Time Epoch interaction term $F_{(1.9,\ 135.1)} = .485$, $p = .607$.

Although group differences were not observed for the accuracy data, a significant two-way interaction was found between the effects of Level of Semantic Knowledge and Time Epoch on accuracy $F_{(3.3,\ 237.5)} = 6.20$, $p = .026$ e-2; $\eta^2_p = .080$ (See Figure 8). After obtaining an adjusted critical value of $p < .041$ e-1 using the Bonferroni correction for multiple comparisons, simple main effects analysis was used to identify potential differences in the nature of the TG at each level of specificity (i.e., for each task). Results of the pairwise comparisons for simple main effects are presented in Table 7. Findings revealed significant differences between all time epochs for both the Recognition and Categorization Tasks such that accuracy for enduring names was greater than accuracy for remote names, which was greater than accuracy for recent names (all $p < .041$ e-1). As expected, a traditional temporal gradient was observed amongst both the Recognition and Categorization Tasks. Within the Attributes Task, however, there was not a significant difference in accuracy between the enduring and remote famous name stimuli $t_{(76)} = 2.20$, $p = .031$, although accuracy for the remote names was significantly higher than accuracy for the recent names as expected $t_{(77)} = -4.62$, $p = .015$ e-3.

The simple main effects for Level of Semantic Knowledge at each time epoch were also examined (Table 7). As expected, for enduring names, significant differences were observed between all tasks such that recognition accuracy was significantly grater than Categorization accuracy $t_{(73)} = 3.67$, $p = .460$ e-3 and Categorization Task accuracy was greater than the

Attributes task $t_{(74)} = 6.93$, $p < .041$ e-1. For the recent names, however, categorization decisions resulted in significantly higher accuracy than recognition decisions $t_{(74)} = -4.92$, $p = .053$ e-3, which were significantly more accurate than attributes decisions $t_{(76)} = 3.92$, p .189 e-3. For the remote famous names stimuli, the Categorization Task again produced the highest accuracy; however, it was not significantly greater than accuracy for the Recognition Task $t_{(75)} = -1.11$, $p = .270$. Recognition decisions, however, were found to be more accurate than Attribute decisions $t_{(76)} = 4.74$, $p = .010$ e-3.

Though the effects of semantic knowledge level and age of memory acquisition on accuracy performance are best understood in terms of their significant interaction and corresponding simple main effects, overall main effects of each variable were examined in the interest of specific hypotheses 5 & 6. Expectedly, there was a significant main effect of Time Epoch on accuracy performance, $F_{(1.9, 135.9)} = 71.30$, $p < .01$ e-3; $\eta^2_p = .50$. Utilizing a Bonferroni adjusted critical value of 1.6 e-2 during interpretation of pre-planned t-tests, accuracy for enduring names was significantly greater than remote names $t_{(72)} = 5.51$, $p = .01$ e-4 which was significantly greater than accuracy for recent names $t_{(74)} = 7.31$, $p = .015$ e-3. That is, for the Famous Names Semantic Knowledge Tests the overall accuracy pattern is Enduring > Remote > Recent. Additionally, there was a significant main effect of Level of Semantic Knowledge, $F_{(1.8, 129.9)} = 67.70$, $p < .001$ e-2; $\eta^2_p = .48$. Post hoc comparisons indicate that the Attributes Task produced the lowest accuracy: Recognition > Attributes $t_{(73)} = 8.25$, $p < .015$ e-3, and after considering the Bonferroni adjusted critical value ($p = 1.6$ e-2) there was not a significant difference between Recognition and Categorization accuracy performance $t_{(73)} = -2.08$, $p = .041$. However, the overall mean accuracy for the Categorization Task was greater than the

Recognition Task, such that final results more closely resembled: Categorization ≥ Recognition > Attributes.

Reaction Time. Mean RTs for each condition of the Famous Names Semantic Knowledge Tasks are presented in Table 8. A 2 (Group) x 3 (Time Epoch) x 3 (Level of Semantic Knowledge) Split Plot ANOVA was used to compare PH+ and PH- participants for significant differences in RT across each of the within subjects variables (Specific Hypotheses 1, 2, and 3). Separate lower order interactions and main effects were again examined in order to characterize the effects of knowledge specificity and age of memory on RT (Specific Hypotheses 4, 5, and 6). Before further interpretation of results, Mauchly's Test of Sphericity was found to be significant for the Level of Semantic Knowledge variable χ^2 (2) = 65.5, p < .001 e-3 and the Level of Semantic Knowledge by Time Epoch interaction term χ^2 (9) = 23.0, p = .006, indicating a violation of the assumption of homogeneity of variance. Given that for the estimate of sphericity ε ≥ .75, the Huynh-Feldt correction, again, was used in comparisons utilizing the Level of Semantic Knowledge variable. The results of the ANOVA are presented in Table 9 with p-values reflecting the Huynh-Feldt adjustment for Type I error where appropriate.

Again, no group differences were observed in RT across each of the within subject variables. The three-way interaction between Group, Time Epoch, and Level of Semantic Knowledge was non-significant $F_{(3.7, 278.3)}$ = .427, p = .777, as were the two-way interactions between Group and Time Epoch $F_{(2, 148)}$ = 1.81, p = .167, and between Group and Level of Semantic Knowledge $F_{(1.3, 95)}$ = .223, p = .691. These results, again, indicate that there is not a greater influence of age of memory and specificity of knowledge on the performance of PH+ participants relative to PH- participants.

Similarly to the accuracy data, a significant two-way interaction was observed for Level of Semantic Knowledge by Time Epoch, $F_{(3.7, 278.0)} = 15.67$, $p < .01$ e-3; $\eta^2_p = .18$ (See Figure 9). Simple main effects analyses were conducted in order to examine the nature of the TG for each task, again utilizing a Bonferroni adjusted critical value of $p < .041$ e-1. All pairwise comparisons for simple main effects are presented in Table 10. For the FNDT, mean RT for the enduring name stimuli was significantly faster than for the remote name stimuli $t_{(75)} = -5.43$, $p = .01$ e-4, which was significantly faster than the recent names $t_{(76)} = -6.95$, $p < .001$ e-3. The same pattern of RTs (i.e., Enduring < Remote < Recent) was observed for the Categorization and Attributes Tasks as well with all comparisons yielding $p < .027$ e-1. That is, the expected and traditional TG was observed for each task. The simple main effects for Level of Semantic Knowledge at each time epoch were also examined (Table 10). Specifically, for the enduring names, the FNDT produced significantly faster RTs than the Categorization Task $t_{(75)} = -26.84$, $p < .001$ e-3 which produced significantly faster RTs than the Attributes Task $t_{(77)} = -15.27$, $p < .001$ e-3. This same pattern (i.e., Recognition < Categorization < Attributes) was observed for the remote and recent names as well (all $p < .041$ e-1). In this case, the simple main effects of the Level of Semantic Knowledge by Time Epoch interaction support an increasing effect of both factors on RTs such that the fastest RTs were observed for the FNDT enduring names condition and the slowest RTs were observed for the Attributes Task recent names condition.

Finally, overall main effects of each variable were examined in the interest of Specific Hypotheses 5 & 6. Again, there was a significant main effect of Time Epoch on RT $F_{(2.0, 148.0)} = 114.029$, $p < .001$ e-3; $\eta^2_p = .61$. A Bonferroni adjusted critical value of 1.6 e-2 for multiple comparisons was again considered in post hoc comparisons between each level of the variable. Not surprisingly, a typical TG was observed such that enduring names produced faster reaction

times than remote names $t_{(73)} = 6.51$, $p < .001$ e-3, which produced significantly faster reaction times than recent names $t_{(74)} = 7.71$, $p < .001$ e-3 (i.e., Enduring < Remote < Recent). Additionally, there was a significant main effect of Level of Semantic Knowledge, $F_{(1.2, 95.1)} = 554.66$, $p < .001$ e-3; $\eta^2_p = .88$ with the Recognition Task producing shorter reaction times compared to the Categorization Task $t_{(74)} = 9.51$, $p < .001$ e-3 which were faster than the Attributes Task $t_{(74)} = 10.24$, $p < .001$ e-3 (i.e., Recognition < Categorization < Attributes).

Word Semantic Knowledge Specificity

Accuracy. Mean accuracy for each condition of the Word Semantic Knowledge Tasks are presented in Table 11. A 2 (Group) x 5 (Decade) x 3 (Semantic Knowledge Specificity) Split Plot ANOVA comparing PH+ and PH- participants was examined for significant differences in accuracy across epoch (decade) and task (Specific Hypotheses 1, 2, and 3); separate main effects and lower order interactions were also examined in order to characterize the effects of Level of Semantic Knowledge and Decade on accuracy performance regardless of group membership (Specific Hypotheses 4, 5, and 6). Prior to interpretation of results, it was found that Mauchly's Test of Sphericity was significant for the Level of Semantic Knowledge variable $\chi^2(2) = 15.63$, $p = .403$ e-3. Given that the estimate of sphericity $\varepsilon \geq .75$, the Huynh-Feldt correction was again used in comparisons employing the Level of Semantic Knowledge variable. The results of the ANOVA are presented in Table 12, with p-values reflecting the Huynh-Feldt adjustment for Type I error where appropriate.

Similarly to the Famous Names Semantic Knowledge Tests, no group differences were observed across each of the within subject variables for the Word Semantic Knowledge Tasks. The three-way interaction between Group, Decade, and Level of Semantic Knowledge was non-significant $F_{(8,544)} = 1.023$, $p = .417$, as were the two-way interactions between Group and

Decade $F_{(4, 272)} = .351$, $p = .843$ and Group by Level of Semantic Knowledge $F_{(1.71, 116.72)} = 2.09$, $p = .136$. There was not a greater influence of age of memory and knowledge specificity on the performance of PH+ participants relative to the PH- participants during the Word Semantic Knowledge Tasks.

A significant two-way interaction was observed between the effects of Level of Semantic Knowledge and Decade on accuracy $F_{(8,544)} = 9.39$, $p < .001$; $\eta^2_p = .12$ (See Figure 10). A Bonferroni adjusted critical value of 2.27 e-3 was used for interpretation of simple main effects analyses. Results of all pairwise comparisons for simple main effects are presented in Table 13. Unlike the famous names stimuli, relatively less pronounced and disorderly trends were observed between decades for each task. Specifically, for the Word Recognition Task there was not a significant difference in accuracy between the 1960s and 1970s word stimuli $t_{(75)} = -2.36$, $p = .021$; however, accuracy for 1980s words was significantly greater than for 1970 words $t_{(75)} = -4.53$, $p = .02$ e-3 and 1990s words $t_{(75)} = 5.45$, $p < .001$ e-3, which was significantly higher than accuracy for words from the 2000s $t_{(75)} = 4.13$, $p = .009$ e-3. That is, a trend resembling an inverse V was observed for accuracy across decades with the best performance for 1980s words. For the Word Categorization Task no significant differences in accuracy were observed between successive pairs of the first four decades (i.e., 1960-1990s; all $p \geq .300$); however, accuracy for 1990s stimulus words was significantly greater than for the 2000s stimulus words $t_{(73)} = 3.88$, $p = .023$ e-3. That is, for categorization decisions a relatively flat TG exists between words from the first four decades, but then drops significantly for words from the 2000s stimulus list. For the Word Attributes Task, no significant differences in accuracy were found between successive decades of word stimuli (all $p \geq .056$).

Evaluation of simple main effects for differences between tasks within each decade also provided mixed results (Table 13). For 1960s words, accuracy for the Recognition Task was significantly lower than for the Categorization Task $t_{(72)} = -6.24$, $p < .001$ e-3 and Attributes Task $t_{(74)} = -4.08$, $p = .011$ e-2. No significant difference in accuracy was observed between categorization and attribute decisions $t_{(75)} = 1.70$, $p = .094$. That is, accuracy for 1960s words resembled the following pattern: Recognition < Attributes = Categorization. The same relationship was observed for the 1970s stimulus words: Recognition < Attributes $t_{(75)} = 4.20$, $p = .076$ e-3 and Attributes = Categorization $t_{(72)} = .435$, $p = .665$. No significant differences in accuracy between tasks were observed for the 1980s stimulus words with all $p \geq .369$. Similarly to the accuracy patterns for the 1960s and 1970s words, the 1990s stimulus words produced greater accuracy for the Categorization Task than for the Recognition Task $t_{(73)} = -5.23$, $p < .001$ and no significant difference was observed between categorization and attribute decisions $t_{(71)} = -.341$, $p = .734$ (i.e., Recognition < Categorization = Attributes). Finally, for the 2000s word stimuli Recognition accuracy was significantly lower than Categorization accuracy $t_{(73)} = -4.84$, $p = .07$ e-4 which was significantly lower than attributes decision accuracy $t_{(75)} = -3.84$, $p = .269$ e-3 (i.e. Attributes > Category > Recognition). In general, when compared to a priori predictions, a nearly opposite pattern of accuracy performance was produced between tasks within each decade. Specifically, for most word stimulus lists (i.e., decades) recognition decisions were found to produce the lowest accuracy as compared to categorization and attribute decisions.

In the interest of Specific Hypotheses 5 and 6, overall main effects for Decade and Level of Semantic Knowledge were assessed. As was expected, a significant main effect of both Decade $F_{(4,68)} = 8.41$, $p = .03$ e-4; $\eta^2_p = .11$ and Level of Semantic Knowledge $F_{(2,68)} = 48.14$, $p < .001$; $\eta^2_p = .42$ was observed with respect to accuracy. For Level of Semantic Knowledge, post

hoc analyses with a Bonferroni adjusted critical value of 1.6 e-2 revealed that accuracy for categorization decisions was not significantly different than accuracy for attribute decisions $t_{(69)}$ = 1.09, p = .278, which was significantly greater than accuracy for recognition decisions $t_{(71)}$ = -5.32, p = .01 e-4 (i.e. Categorization = Attributes > Recognition). Examination of the main effect of Decade, with an adjusted critical value of .05 e-1, also revealed unexpected results. Specifically, the 2000s stimulus words produced the lowest mean accuracy followed by stimulus words from the 1960s, 1970s, 1990s, and 1980s, respectively. Statistically speaking, performance for the 2000s stimulus words was significantly less accurate compared to 1960s stimulus words $t_{(71)}$ = 2.96, p = .04 e-1; however, examination of the following successive pairs of decades by ascending order of accuracy performance did not reveal any further significant differences. That is, the overall temporal gradient for the Words Semantic Knowledge Task accuracy data was relatively flat, though the 2000s stimulus words produced significantly lower accuracy compared to other decades.

Reaction Time. Mean RTs for each condition of the Word Semantic Knowledge Tasks are presented in Table 14. A 2 (Group) x 5 (Decade) x 3 (Semantic Knowledge Specificity) Split Plot ANOVA comparing PH+ and PH- participants was examined for significant differences in RT across age of memory (decade) and task (Specific Hypotheses 1, 2, and 3). Separate main effects and lower order interactions were again examined in order to characterize potential effects of task (Recognition vs. Categorization vs. Attribute) and Decade on RT performance regardless of group membership (Specific Hypotheses 4, 5, and 6). Mauchly's Test of Sphericity was significant for the Level of Semantic Knowledge variable $\chi^2(2) = 37.15$, $p < .001$ e-3 and Decade by Level of Semantic Knowledge Interaction $\chi^2(2) = 58.13$, p =.008, with estimates of

sphericity $\varepsilon \geq .75$. Results of the ANOVA are presented in Table 15 with Huynh-Feldt corrected critical values for violations of the assumption of homogeneity of variance where appropriate.

Final examination of participants' performances on the Semantic Knowledge Tests did not reveal any significant group differences. The three-way interaction between Group, Decade, and Level of Semantic Knowledge was non-significant $F_{(7.47, 523.47)} = .860$, $p = .544$, as were the two-way interactions between Group and Decade $F_{(4,280)} = 951$, $p = .435$ and between Group and Level of Semantic Knowledge $F_{(1.43,101.72)} = 2.184$, $p = .132$. Similarly to performances on the Famous Name Semantic Knowledge Tests, there is not a greater influence of age of memory and specificity of knowledge on the reaction times of individuals with parental history of AD compared to those without a parental history.

Consistent with previous findings, a significant two-way interaction was observed between the effects of Level of Semantic Knowledge and Decade on RT for the words stimuli data $F_{(7.4, 527.47)} = 15.81$, $p < .001$; $\eta^2_p = .18$ (See Figure 11). With a Bonferroni adjusted critical value of 2.27 e-3 for multiple comparisons, simple main effects were analyzed for differences in the TG across tasks (Table 16). Mixed results were obtained for examination of the TG within each task, with no task producing an expected TG. For the Recognition Task, the 1970s stimulus words produced significantly slower reaction times compared to 1960s words $t_{(75)} = -7.58$, $p < .001$ and 1980s words $t_{(74)} = 5.32$, $p = .01$ e-4. The latter stimulus category did not produce a significant difference in mean reaction time from 1990s stimulus words ($t_{(74)} = 2.50$, $p = .015$), which were generally equivalent to RTs for 2000s stimulus words $t_{(75)} = -.710$, $p = .456$. Namely, RTs by decade for the Words Recognition Task resembled the following pattern: 1960s < 1970s >1980s = 1990s = 2000s. Variable patterns of RTs were also observed for the categorization decisions such that responses to 1960s words were significantly slower than 1970s words $t_{(73)} =$

3.95, $p = .018$ e-2; speed of responses to 1970s were not significantly different from responses to 1980s words $t_{(73)} = -1.31$, $p = .193$ which were significantly slower than responses to 1990s words $t_{(73)} = 5.35$, $p = .01$ e-4; and responses to 1990s were significantly faster than responses to 2000s words $t_{(73)} = -7.31$, $p < .001$ (i.e., 1960s > 1970s = 1980s > 1990s < 2000s). Finally the Attributes Task did not produce any significant differences in RT between successive decades with all $p \leq .108$. On the other hand, when assessing the simple main effects of knowledge specificity at each decade, the expected pattern was observed. That is, RTs slowed as specificity of knowledge increased between tasks. (i.e., Recognition < Categorization < Attributes with all $p < 2.27$ e-3; See Table 16).

Finally, overall main effects for Decade $F_{(4,280)} = 5.00$, $p = .001$; $\eta^2_p = .07$ and Level of Semantic Knowledge $F_{(1.45,\ 101.72)} = 751.74$, $p < .001$; $\eta^2_p = .91$ were found to be significant (Specific Hypotheses 5 & 6). In regards to Level of Semantic Knowledge, recognition decisions were significantly faster than categorization decisions $t_{(72)} = -30.18$, $p < .01$ e-4 which were significantly faster than attribute decisions $t_{(72)} = -13.78$, $p < .01$ e-4 (i.e., Recognition < Categorization < Attributes). When collapsing across tasks, the expected TG pattern was still not observed within the RT data. Specifically, the slowest mean RTs were observed for the 2000s followed by the 1970s, 1960s, 1980s, and 1990s RTs, respectively. The only significant differences in successive mean RTs was observed between the 1980s and 1990s word stimuli $t_{(71)} = 3.92$, $p = .02$ e-3.

DISCUSSION

For several decades, research has documented clear disruptions of semantic memory networks throughout the course of AD (Hodges & Patterson, 1995; Martin & Fedio, 1983; Nebes, 1989). Investigation into this phenomenon has also concluded that the breakdown of

semantic knowledge networks occurs in a systematic way such that degradation of conceptual knowledge first occurs for specific information, while general knowledge remains intact until the late stages of disease (Huff, et al., 1986; Warrington, 1975). One viable means for investigating disruption of the semantic knowledge network is examination of the existence and extent of a TG for remote versus recent knowledge (Douville et al., 2005; Seidenberg et al., 2009a; Seidenberg et al., 2009b; Woodard et al., 2007). While an exaggerated TG (with dramatic loss of recently acquired memories) and systematic disruption in semantic memory are common in AD, their assessment in combination, has rarely been utilized to examine aspects of memory functioning during the preclinical period. Investigations exploring temporally graded impairment for semantic memory often focuses on samples where memory deficits have already reached a clinically detectable level (Douville et al., 2005; Seidenberg, et al., 2009a; Seidenberg et al., 2009b; Sugarman et al., 2012). Assessment of the integrity of the TG across semantic knowledge structures in at-risk, but otherwise healthy, individuals may hasten early identification of those most likely to experience cognitive decline (Woodard et al., 2010).

This study set out to examine the effects of familial risk for AD, age of memory acquisition, and specificity of conceptual knowledge on semantic memory integrity by examining behavioral performance for semantic knowledge tasks amongst older adults with and without a parental history of AD. Performance variables (i.e., reaction time and accuracy) for parental history positive and parental history negative older adults were evaluated while performing semantic memory tasks for famous persons and common word knowledge from different eras. An exaggerated TG (with the greatest difficulty for recent stimuli) and reduced specificity of semantic knowledge was expected in parental history positive participants compared to parental history negative participants. Two supplementary aims were examined as

well: 1) The potential combined effects of age of memory and specificity of knowledge on semantic network organization for person knowledge in older adults, and 2) whether the proposed combined organizational structure could be extended to conceptual word knowledge.

Specific Aim 1: Semantic network disruption in older adults with parental history of Alzheimer's Disease

The proposed disruption of the semantic knowledge network in PH+ individuals was examined through assessment of potential accuracy or RT differences in the relationship between age of memory and specificity of knowledge in our two participant groups. No group differences were observed in either accuracy or RT on any of the within subject variables for either of the computer tasks. Research suggesting that subtle difference in cognitive processes exist for individuals with familial risk for AD (Johnson, et al., 2006; La Rue, O'Hara, Matsuyama, & Jarvik, 1995; Sager, Hermann, & La Rue, 2005) in addition to empirical support for neuroanatomical and brain activation changes in asymptomatic first- degree relatives (Johnson et al., 2006; Small et al., 2000; Small et al., 1995) made this finding unexpected. While it may be tempting to conclude that this pattern of results suggests no differences in the efficiency of semantic memory networks in individuals at risk for AD, there are several possible explanations for why we did not observe significant differences. Further, subtle performance differences reflecting the integrity of semantic memory circuits might have been observed using an alternative strategy.

First, the lack of group differences in our study could have resulted from an inadvertently low overall level of risk for development of AD within the PH+ group. The potential for considerable variability in level of risk across participants could have resulted from a variety of factors, including modest sensitivity of the parental AD history risk factor to early cognitive

changes. While family history has been clearly identified in the research literature as a significant risk factor for AD (Ballard et al., 2011; Cupples, et al., 2004), other increasingly sensitive genetic markers have been proposed (Ertekin-Taner, 2007). For example, ApoE (Breitner, 1996; Corbo & Scacchi, 1999; Slooter, Breteler, Ott, Van Broeckhoven, & van Duijn, 1996), GSK3β (Hernandez et al., 2009; Kwok et al., 2008), and TOMM40 (Roses, 2010) have all received relatively recent attention in the literature as potential risk genes. The most consistently studied risk gene, the ApoE4 allele, has been associated with a 3-10 times increase in risk (Ballard, et al., 2011; Corder et al., 1993), while risk associated with family history alone has often been observed to be lower (Breitner, et al., 1988; Farrer, O'Sulluvan, Cupples, Growdon, & Myers, 1989). It is possible that given a more sensitive risk factor, we would have been able to identify a group of older adults with even more potential to exhibit lower behavioral performances compared to our control group. It is important to note that samples of individuals with a familial history of AD - like ours - have higher rates of risk genes (Breitner, Murphy, & Folstein, 1986), and would likely have an increased risk as a group compared to the family history negative control group. Unfortunately, genetic testing was not available for the purposes of this study in order to satisfy these assumptions; however, in future studies, genetic testing would be expected to increase sensitivity when estimating level of risk. Genetic risk assessment would be an especially important added feature of future research given that most data regarding the genetics of AD risk suggests that the additive effects of AD family history and the presence of the ApoE 4 allele are the among the best genetic predictors of AD available at the present time (Cupples, et al., 2004; Payami et al., 1994).

In addition, the simple determination of parental history of AD may have varied amongst PH+ participants. In other words, it is possible that for some individuals in the PH+ group the

cognitive problems observed in the identified parent may have been unrelated to AD, and/or the parent may not have had AD at all. At present, AD can only be definitively diagnosed post mortem or through an antemortem brain biopsy, and clinically, only a probable diagnosis of AD can be proffered (Ballard, et al., 2011). In our study, parental history was based on self-report, and only two participants indicated that their parent's diagnosis had been confirmed following autopsy. The remaining participants indicated a variety sources for diagnosis provided antemortem. It is possible that several of our PH+ participants had parents diagnosed with AD, though the true underlying etiology could have differed. For example, AD and chronic cerebrovascular disease share similar risk factors, overlap in some degree in clinical presentation, and can be difficult to distinguish during differential diagnosis (Kalaria, 2010; Kalaria, Akinyemi, & Ihara, 2012). Additionally, most autopsy studies have found that very rarely do AD patients present with pure neurodegenerative pathology. A large majority of individuals with confirmed AD pathology have cerebrovascular pathology consisting of microangiopathy, cerebral infarcts, and occasional intracerebral hemorrhage (Yip, et al., 2005). Operationalized diagnostic criteria, such as the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA; Loewenstein & Rubert, 1992) has increased sensitivity (e.g., > 80%) for distinguishing between persons with AD and healthy older adults, but the ability to distinguish between other dementias and AD has varied widely (23-88%; Ballard & Bannister, 2005). Within our PH+ sample, a majority of individuals were unaware if standardized criteria for diagnosis were used with their parents, and even so, the possibility of a misdiagnosis would remain.

There are also some seemingly obvious characteristics of participant groups that could affect the potential to observe group differences. For example, groups were matched on

neuropsychological testing performance in order to exclude individuals who were already demonstrating clinical signs of decline. Because we required intact cognitive functioning for all participants as an inclusion criterion, it may have made it more difficult to observe differences between groups. However, some research has demonstrated that adult first-degree relatives of Alzheimer's probands exhibit subtle, pre-clinical deficits in verbal learning and recall (La Rue et al., 2008; Levy et al., 2004), divided attention (Rosen, Bergeson, Putnam, Harwell, & Sunderland, 2002), and other subtle visual attention and working memory processes (Greenwood, Lambert, Sunderland, & Parasuraman, 2005), indicating that subtle cognitive process are observable in first-degree relatives. Other strict inclusion criteria for our two participant samples may have resulted in the creation of two very equally healthy and well-functioning groups and minimization of the likelihood that our risk group was in the early stages of preclinical AD. That is, various modifiable environmental and life-style characteristics, which have been identified as risk factors for AD and late-life cognitive change, were controlled for within our groups. This requirement may also have artificially deflated the chance of observing cognitive change within the PH+ group. Specifically, mid-life hypertension (Qiu, Winblad, & Fratiglioni, 2005), diabetes (Luchsinger, Tang, Stern, Shea, & Mayeux, 2001), smoking (Lee et al., 2010), alcohol consumption (Lee, et al., 2010), and physical activity (Hamer & Chida, 2009) have been linked to late-life cognitive change and AD specifically (Ballard, et al., 2011). Excluding participants with some of these characteristics and equating these risk factors between our two groups may have caused the level of risk for cognitive change in our PH+ to be artificially low. Further, both groups were reasonably well-educated and reported leading active and stimulating lifestyles. Systematic reviews of the literature provide robust evidence that cognitive reserve (i.e., a combination of education, occupation and participation in stimulating mental activities;

(Valenzuela & Sachdev, 2006) is also an important modifiable risk factor that was nearly equal between our two groups. In fact, both groups were very healthy within this respect; those members of the PH+ group may have been taking charge of several modifiable risk factors, subsequently reducing their risk for cognitive change. This issue may be a consequence of the sampling bias that has been identified in earlier studies whereby more active, healthy older adults are at an increased likelihood to volunteer for health-related research studies (Carter, Elward, Malmgren, Martin, & Larson, 1991).

Finally, while it is possible that above-stated methodological limitations resulted in groups with similar low risk for development of cognitive decline, it is also possible that task difficulty was mismatched with the ability of our study participants, such that the computer tasks were not sensitive enough to pick up differences between our groups (i.e., the tasks may have been too easy). Other approaches for assessing the efficiency of semantic knowledge network have a potentially higher probability of detecting early semantic memory deficiencies. Specifically, all computer tasks were performed at very high accuracy levels, producing a ceilings effect. With limited variability at the upper end of performance, our task is likely to be best for discriminating between individuals at lower ability levels (Lezak, Howieson, & Loring, 2004). Though differences between conditions of the tasks were observed, generally all participants performed very well. Thus, our novel tasks might have greater effectiveness for distinguishing between groups, where at least one sample is at a lower ability level, such as amnestic MCI or early-stage AD populations (Seidenberg, et al., 2009b).

It is, however, premature to assume that subtle disruptions in semantic memory integrity do not exist, or are undetectable, prior to the clinical manifestation of symptoms. Differences between at-risk and control groups are still likely to be detected via neuroimaging techniques.

For example, assessment brain activation during semantic memory tasks regarding knowledge of famous names has been found to discriminate between controls and at-risk samples (Seidenberg, et al., 2009a; Seidenberg, et al., 2009b; Woodard, et al., 2009) and to predict cognitive decline in healthy individuals (Hantke et al., 2013; Woodard et al., 2010). Importantly, behavioral performance was equivalent between groups in each study, demonstrating that subtle differences in semantic memory integrity may still exist even when behavioral performance does not differ. Further, the ability to control for differences in behavioral performance in light of differential activation patterns is an advantage and is consistent with these previous lines of inquiry. For example, research has shown that older adults often "recruit" additional brain regions, particularly in prefrontal areas, as task demands increase (Cabeza, 2002; Cabeza et al., 1997; D'Esposito, Deouell, & Gazzaley, 2003), though their behavioral performance is equal to that of younger participants (Nielson et al., 2006). Similar findings of compensatory recruitment have been observed in samples of individuals at risk for development of AD (Bookheimer et al., 2000). Thus, recruitment theory states that this increased activation helps to compensate for age-related and in some cases pre-clinical neural changes. More recent investigation has shown that similar patterns of recruitment, or increased activation, can be found during semantic memory tasks (Nielson et al., 2006), although one study has demonstrated that increased fMRI activity was associated with a decreased likelihood of cognitive decline in a healthy older sample (Woodard et al., 2010). However, the potential for brain activation patterns during semantic memory tasks to inform decisions regarding the integrity of semantic networks (Seidenberg et al., 2009a; Seidenberg et al., 2009b), and to identify those at risk for future decline (Woodard et al., 2010; Hantke et al., 2013) is apparent. As differences in brain activation patterns were demonstrated in light of otherwise intact performance on semantic recognition tasks, we affirm that lack of

behavioral differences between our two samples does not necessarily indicate that differences in semantic network activation at varying levels of conceptual knowledge specificity do not exist. Future research should focus on examination of temporally graded cortical activation patterns at the neural level rather than the behavioral level for general versus specific knowledge, as most research studies have focused on simple recognition (Sugarman et al., 2012).

Assessment of activation during tasks requiring varying levels of knowledge specificity have added importance in understanding the role of the hippocampus and neocortical circuits in consolidation and retrieval of semantic memories. Previous research has observed a temporally graded decrease in activation with memory age, such that newer memories produce more diffuse patterns of activation, further suggesting a greater reliance on episodic context for retrieval (Woodard, et al., 2007). That is, older memories become more semantically represented with time and rely on more efficiently distributed networks of long-term memory traces (Moscovitch, et al., 2005; Nadel & Moscovitch, 1997). During famous person recognition, the integration of episodic context (e.g., personal significance of the individual) with semantic representation (e.g., knowledge of facts related to the individual) is a likely explanation for changes in neural representation over time. As mentioned above, recent memories are more likely to rely on integration of episodic context. Support for this theorized integration of long-term circuits during recall of famous person knowledge has only been investigated using recognition paradigms, however. Further investigation into activation patterns during tasks requiring varying degrees of specificities of semantic knowledge may further elucidate the role of episodic (or autobiographical) networks during recall of person knowledge. For example, it is probable that specific knowledge relies more heavily on integration of episodic context compared to more general conceptual knowledge (Warrington, 1975; Westmacott, Black, Freedman, & Moscovitch,

2004; Westmacott & Moscovitch, 2003). Observation of different degrees of temporally graded activation patterns for levels of specificity (e.g., moving from familiarity to conceptual knowledge to attribute knowledge) may enhance our understanding of the systematic organization of semantic knowledge in older adults, with the potential to further improve the ability to identify at-risk individuals as well.

Specific Aim 2: Interactive effects of age of acquisition and specificity of knowledge on semantic memory networks for person knowledge in older adults

As outlined above, a review of previous research revealed two commonly observed phenomena that have influenced understanding of the organizational structure of the semantic knowledge network in older adults – 1) the existence of a TG in normal aging (Bizzozero et al., 2008), which is exaggerated in several disease processes (Beatty, Salmon, Butters, Heindel, & Granholm, 1988b; Hodges, et al., 1993) and 2) the systematic structure of conceptual knowledge has been posited to vary based on specific versus general information (Warrington, 1975; Nebes, 1989). With respect to the influence of age of memory acquisition (i.e., the TG) on semantic network organization, previous research suggests that 1) knowledge acquired when an individual is young (i.e., remote knowledge) establishes an initial neural pathway in the semantic network; 2) that repeated exposure to the information strengthens its position within the network (i.e., enduring knowledge); and 3) that it is more difficult to establish pathways for new information (i.e., recent knowledge) given the tenacity of previously established pathways (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Nadel & Moscovitch, 1997; Winocur, et al., 2010). In addition, studies utilizing clinical populations to examine the hierarchical organization of specificity of knowledge within the semantic network suggests increased efficiency and greater integrity of knowledge for general (e.g., recognition familiarity and categorization)

compared to specific knowledge (e.g., attributes and association; Funnell, 1983; Hodges, 1994; Martin & Fedio, 1983; Rapp & Carramaza, 1993; Shallice, 1989: Warrington, 1975). Participants' performance on the Famous Names Semantic Knowledge Tasks generally supported previous hypotheses regarding the organization of semantic knowledge networks for older adults. That is, there was discernable evidence of the effects of age of memory and knowledge specificity on semantic knowledge performance. However, unexpected findings in the accuracy data suggest that when it comes to overall memory integrity, age of memory has a stronger influence than specificity of knowledge in a healthy older adult sample.

Specifically, correct recognition and categorization decisions were organized around a traditional temporal gradient such that accuracy resembled the following pattern: Enduring > Remote > Recent. Comparison of the TG for accuracy across levels of specificity, however, provided some unanticipated results. Specifically, there was not a significant difference in accuracy between recognition and categorization decisions for Enduring and remote famous names, and categorization decisions were significantly more accurate than recognition decisions for recent names. The expected differences in the nature of the TG may not have been observed between recognition and categorization decisions for at least two reasons. First, for the enduring names stimuli, the nearly perfect accuracy within both decision conditions (i.e., Recognition = 99.7% and Categorization = 99.3%) points to a restriction of range on that variable imposed by a ceiling effect. That is, categorization and recognition of enduring famous names may have a nearly equal low difficulty level, which results in near perfect performance for both conditions. This same relationship, however, was also observed for remote famous names. The additional finding of equivalent accuracy between the Recognition and Categorization Tasks for remote names implies that a broader conclusion may be drawn. That is, when it comes to accuracy of

semantic memory retrieval, both decisions types are equally influenced by the remote versus enduring nature of the information. For intact older adults, there is little difference in accuracy between simple recognition familiarity and conceptual semantic knowledge for information acquired earlier in life (i.e., both remote and enduring memories), despite repeated exposure to the enduring stimuli over time. Speed of access within the network for simple recognition versus general knowledge, however, may still differ as discussed in the reaction time results outlined below.

The finding that categorization decisions produced higher accuracy than recognition decisions for recent famous names was also somewhat surprising. It is possible that exposure to the famous names during the Famous Name Discrimination Task may have primed participants' later performance for the Categorization Task, thereby improving their subsequent performance accuracy. This assumption is consistent with the well-documented "hyper-priming" effect that is found within older adults samples, such that older adults tend to benefit greatly from additional cueing or context, compared to younger adults, even when the cueing may be of limited predictive value (Bowles & Poon, 1985, 1988; Howard, McAndrews, & Lasaga, 1981). In addition, older adults may simply be more conservative in making their recognition familiarity decisions. For example, in an early study examining differences in knowledge of famous persons between older and younger adults, Maylor (1990) demonstrated that during famous face recognition older adults were "more cautious" than younger adults and less likely to endorse recognition of a face if they were not 100% sure. This conclusion was drawn from the finding that older participants were able to provide specific details regarding previously presented famous faces that were not endorsed as having been previously seen. Further, during additional experiments examining what Maylor (1990) termed the "tip-of-the-tongue phenomenon" she

demonstrated that when providing names of famous individuals in pictures, older adults were more likely to endorse the individual as unrecognized, even if they felt as though the name was on the tip of their tongue. Unfortunately, Maylor did not group famous names by time epoch. The previously documented decreased familiarity with recently famous individuals among older adults, however, may provide a context in which older adults are more cautious with their recognition decisions (Loacano, et al., 2011).

Final examination of the Famous Names Semantic Knowledge Task accuracy data revealed that, as hypothesized, attribute decisions produced the lowest accuracy. While a general trend for a traditional TG was noted in final results, after an application of a Bonferroni correction for multiple comparisons, decisions for enduring names were no longer statistically more accurate than decisions for remote names. Because we presumed that enduring names were learned at the same time as remote names, the cardinal difference between the two time epochs is that enduring names were updated more frequently through repeated exposure. Thus, it is interesting that despite this important difference in exposure frequency, there was not a substantial difference in accuracy. The fact that attribute accuracy does not differ significantly between enduring and remote stimuli may lead to the erroneous conclusion that given early age of acquisition, specific semantic knowledge does not deteriorate with age. Such a hypothesis is consistent with studies that have documented preserved semantic knowledge in older adults using tasks requiring relatively specific conceptual knowledge (Nilsson, 2003). However, it still seems unlikely given the robust research findings documenting that more specific conceptual knowledge is more susceptible to both aging and disease processes (Funnell, 1983; Hodges, 1994; Martin & Fedio, 1983; Rapp & Carramaza, 1993; Shallice, 1989: Warrington, 1975). These contradictory findings, however, cannot not be unequivocally resolved by the results of

this study. Future studies might control for the time epoch from which the specific attribute knowledge was acquired. For example, for an enduring famous person, their attribute could be remote or relatively recent in nature. Having accounted for this factor may have produced a more significant difference in accuracy between the two conditions in our study.

In contrast to the accuracy data, which produced a few unexpected findings, reaction times offered more substantial support of the related effects of both age of memory and specificity of knowledge on semantic network organization. That is, a traditional TG (i.e., Enduring < Remote < Recent) was produced at each level of conceptual knowledge with reaction times also slowing with increasing specificity. These results produced discernable evidence of an effect of both variables on the rate of semantic network activation such that the fastest RTs were observed for recognition of enduring famous names, while the slowest RTs resulted from attribute decisions about recently famous individuals. Such results indicate that both the age of memory and specificity of information have an influence on the speed of access within the semantic network. These results are consistent with models of semantic memory that purport that a relatively longer and subsequently slower pathway exists to more specific knowledge structures (Collins & Loftus, 1975; McClelland, Rumelhart, & Hinton, 1990), as well as theories positing a hierarchical organization of semantic information (Nebes, 1989; Warrington, 1975;). Our documented observations also offer further support to theories regarding more established pathways for older memories, especially if they have also been systematically updated over time (Nadel, Samsonovich, Ryan, & Moscovitch, 2000; Winocur, 2010). Shorter reaction times are likely to result from the shortest, most established pathways within the semantic network.

These findings integrate several areas of memory research in support of our interactive organizational model and have relevance for understanding the neural substrates of memory

encoding and consolidation for older adults. First, higher accuracy and faster reaction times for remote and enduring names are in agreement with the age of acquisition hypothesis, which suggests that information learned earlier in life results in a greater integrity of this information in long-term memory circuits (Cortese & Khanna, 2007; Ellis, Holmes, & Wright, 2009; Johnston & Barry, 2006). Further, theories regarding the role of the hippocampus in memory consolidation may also be tested through examination of our participants' performance. For instance, the classic Multiple Trace Theory (MTT; Nadel & Moscovitch, 1997; Nadel, Samsonovich, Ryan, & Moscovitch, 2000) and relatively new transformation hypothesis (Winocur et al., 2010) would explain why the best performances would be observed for enduring names and the poorest for recent names. According to MTT, when information is experienced and represented as a memory, the trace consists of an ensemble of bound hippocampal and neocortical neurons. Each time a memory is retrieved, as would be the case with enduring famous names, it is re-encoded and more traces are created. Older memories, especially those with repeated exposure, have more traces in neural memory circuits making them faster and easier to recall. They use this hypothesis to explain the TG for episodic memory following MTL lesions. Our research demonstrating clear TG effects for RT during retrieval of semantic information in healthy older adults suggests that similar principles governing episodic memory consolidation may be applied to semantic memory as well. That is, a greater number of cortical traces proposed for older memories and repeat exposure may also apply to the integrity of semantic information.

Built upon the original principals proposed by MTT, the transformation hypothesis more directly discusses semantic memory. As described, the hippocampus transforms new memory traces highly dependent on medial temporal lobe structures (i.e., episodic events) into cortically represented long-term memory traces. That is, as the hippocampus is involved in facilitating the

creation of multiple neocortical traces for recalling remote episodic memory, so does it play a facilitator role in forming the cortical representation of related semantic information (Winocur et al., 2010). However, our research suggests that this view on semantic memory formation may be limited. Because the hypothesis focuses mostly on episodic memory formation, the lack of discussion on semantic networks seems to imply that once a neocortical network is established for semantic information it remains stagnant. Our findings suggest evidence to the contrary; in fact, semantic knowledge may continue to be influenced and updated by repeated exposure, with older memories still representing well-established pathways as well. Further, our findings are also consistent with recent neuroimaging research demonstrating differential activation of neocortical pathways in remote versus recent memories for famous names (Woodard et al., 2007), again suggesting an ongoing malleability of semantic memory networks. A review of the literature suggests that this ongoing malleability of semantic networks may result from changes over time in the level of episodic/autobiographical information integrated during retrieval (Westmacott et al., 2004).

Following guidance from the above-mentioned theories on long-term memory traces, our findings may imply that specific versus general semantic knowledge rely more heavily on this integration as well. Research demonstrates that superior remote memory integrity comes from greater, more thoroughly established, cortical representation (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Nadel & Moscovitch, 1997b; Squire & Zola-Morgan, 1991; Winocur, et al., 2010), which theories postulate is true of semantic knowledge relative to episodic events (Moscovitch, Nadel, Winocur, Gilboa, & Rosenbaum, 2006; Winocur et al., 2010). Our finding of more efficient recall for general versus specific semantic knowledge implies that differences in circuits between levels of specificity may exist as well. Recent

proponents of the transformation hypothesis theorize that remote episodic recall results from a dynamic integration of MTL and neocortical networks and not simply the activation of a single engram (Winocur et al., 2010; Tulving, 1983). In a review of supporting research, Winocur and colleagues (2010) suggest that there is greater integrity of the schematic version (e.g., semantic details) of an event supported in the neocortex as compared to the contextual account (i.e., episodic event), which relies more heavily on MTL structures. The integrity of episodic recall depends on the dynamic integration of multiple networks across both neural circuits. The greater the integrity of the established cortical network, the more efficiently the information can be recalled (Winocur et al., 2010). While they use this argument to explain the commonly observed TG, one may make the same points regarding the specific versus general knowledge distinction as well. As general semantic details are believed to be represented in strongly established neocortical pathways (Huff, F. J., et al., 1986; Martin & Fedio, 1983; Nebes, 1989; Warrington, 1975), perhaps the relatively lower efficiency of specific knowledge recall stems from greater reliance on a dynamic interplay of multiple systems that may parallel the integration proposed to govern episodic recall (Moscovitch, et al., 2005; Westmacott, et al., 2004; Westmacott & Moscovitch, 2003). That is, recalling which piece of work is associated with a famous individual may invoke activation of multiple systems of varying integrity and possibly varying cortical representation. For example, remembering that Peggy Lee starred in *The Jazz Singer* may involve activation of one's network of who Peggy Lee is, one's knowledge network for *The Jazz Singer*, and may even invoke some activation of the circuit for the episodic event that represents the first time you saw the movie (Westmacott, et al., 2004). These assumptions are also consistent with research demonstrating that recall of information about famous names relies partially on an episodic memory component as well (Moscovitch, et al., 2005; Winocur et al.,

2010), mainly autobiographical in nature (Nielson et al., 2006; Westmacott, et al., 2004; Westmacott & Moscovitch, 2003). Our results suggest that the integration of multiple circuits, including some inclusion of an episodic memory component, may be more pronounced in the recall of more specific relative to general conceptual knowledge of an individual. If specific conceptual knowledge relies more heavily on a dynamic integration of multiple circuits, it makes sense that recall would be less efficient than for more general knowledge that may rely less on such integration.

While the above is a possible explanation for our results, it may be premature to draw such conclusions. Further research is needed to explore the possibility that specific knowledge requires integration of multiple information networks, in addition to brain imaging studies to directly examine the possibility that recall of specific knowledge evidences broader activation patterns compared to more general knowledge. The concept of multiple network integration for more specific versus general knowledge is, however, consistent with relatively recently proposed models of semantic memory. For example, McClelland, Rumelhart, and Hinton's (1990) connectionist model/ parallel distributing model states that knowledge is composed of distributed connections between networks of concepts. When a concept is retrieved, all connections related to that particular concept and its features within the network are activated. However, specific features or associations may lie outside of a concept's initial activation zone, such that the specific concept itself may also require activation of its conceptual network and its associated features. The theory proposes that energy is directed toward integrating information from several networks of distributed connections. Using the Peggy Lee example above, recognition of Peggy Lee may only require activation of a relatively small area of distributed connections related exclusively to the existence of Peggy Lee. The ability to categorize her as a singer requires

activation of one's concept node of Peggy Lee, one's conceptual knowledge network of singer, and their distributed connections, both of which would be processed simultaneously and integrated based on the information of interest. Her role in the film *The Jazz Singer* would follow a similar process of activation and integration of distributed networks of connections for her, her role in the film, and the film itself. McClelland, Rumelhart, and Hinton's model was originally developed as an attempt to incorporate what we knew about neural processing at the time. Thus, each specific concept node was proposed to represent a neuron and each network to represent a neural memory circuit. While seemingly an elementary explanation for integration of conceptual knowledge, whether general or specific, one can see how proposed integration of conceptual networks (i.e., connectionist model/ parallel distributing model) during recall is consistent with integration of long-term memory circuits as outlined in the transformation hypothesis (Moscovitch, et al., 2005; Winocur et al., 2010).

Specific Aim 3: Interactive effects of age of acquisition and specificity of knowledge on semantic memory networks for conceptual word knowledge in older adults

In addition to our assessment of the organization of conceptual knowledge for famous persons in older adults, we hoped to determine whether similar integrative principles of organization could be applied to general word knowledge. In addition to not observing any group differences on the word semantic knowledge tasks, performances on these tasks did not result in a traditional TG within any of the conditions. Though these results were quite unexpected, it may be too premature to conclude that the effects of age of acquisition do not apply to organization of conceptual knowledge outside of information for famous individuals. Previous research studies have demonstrated the existence of a TG for other forms of semantic knowledge, including general word information (Kopelman, 1989; Kopelman, et al., 2009; Verfaellie, Reiss, & Roth,

1995) and knowledge of famous events (Bizzozero, et al., 2008; Bizzozero, et al., 2005; Bizzozero, et al., 2009; Meeter, et al., 2006). Unlike our study; however, most findings of a temporal gradient utilized clinical samples, including older adults with amnestic MCI (Bizzozero et al., 2009), Alzheimer's Dementia (Greene, J. D. & J. R. Hodges, 1996), or other forms of acquired brain injury affecting medial temporal lobe structures (Bizzozero et al., 2009; Bizzozero et al., 2008; Kopleman, 1989; Kopelman et al., 2009; Verfaellie, Reiss, & Roth, 1995).

Observation of a TG for semantic information outside of person knowledge has been documented in healthy older adults (Bizzozero et al., 2005; Kopelman et al., 2003); however, a TG is typically established using knowledge of famous events, which, like person knowledge, is susceptible to influence of episodic/contextual networks as well (Kopleman et al., 2009). Previous studies utilizing general word knowledge with methods similar to ours

have not been able to demonstrate a TG in healthy older samples (Kopelman, 1989; Verfaellie, Reiss, & Roth, 1995). In fact, a review of the literature has revealed that the only consistent observation of a TG for conceptual word knowledge has been found in individuals with Korsakoff's Syndrome (See Kopleman et al., 2009). For example, in a particularly relevant study, Verfaellie and colleagues (1995) constructed a list of 94 words divided into time epochs based on their entry in to either the *Oxford English Dictionary* or the *Third Barnhart Dictionary of New English*. Unlike our study, time epochs were divided into five-year periods (1955 – 1985) and not decades. A review of their stimulus list even reveals various words that were also common to our stimulus list; however, their less stringent criteria for word inclusion resulted in the use of several acronyms (e.g., AIDS) as well as various multiple-word stimuli (e.g., couch potato). In their report, subjects were either asked to identify the correct definition for the presented stimulus word in multiple-choice format, or they were presented with a definition and

asked to recognize the word associated it. Healthy control subjects did not produce a significant difference in accuracy between any comparisons across successive time epochs. While their study utilized a healthy control sample with an average age several years younger than ours, Kopelman and colleagues (2009), did not demonstrate a TG in their healthy controls using similar methods and an age sample with a mean age nearly identical to ours. Both studies also reported mixed results regarding the presence of the TG in clinical samples. For example, the Verfaellie study found that Korsakoff's patients, when compared with healthy controls and a sample of mixed MTL lesions, were the only sample to produce increasing accuracy with increasing remoteness of memory. On the other hand, Kopelman et al., (2009) only observed the TG phenomenon for individuals with herpes encephalopathy and only within a single task condition. Unfortunately, a review of the literature did not uncover a study that attempted to examine a potential TG for RT during tests of conceptual word knowledge.

Taken together, these results indicate that the possibility of a TG for conceptual word knowledge is possible within a clinical sample; however, results are generally quite complex, with no study demonstrating the existence of a TG in healthy samples. Conceptual knowledge of words may be represented differently across information networks as compared to knowledge of persons or events (Ellis, Young, & Critchley, 1989; Seidenberg et al., 2001). As mentioned above, one possible reason for this finding may be that recall of knowledge for famous individuals (and famous events) relies in part on some activation and integration of episodic context as well (Moscovitch, et al., 2005; Westmacott, et al., 2004; Westmacott & Moscovitch, 2003; Winocur et al., 2010). For example, Westmacott and Moscovitch (2003) suggested that the representation and retrieval of a famous name includes both semantic and episodic components; namely, activation of the autobiographical significance of the individual. In their study, they

demonstrated that famous names of high autobiographical significance were recognized more quickly and accurately than names with low autobiographical significance (Westmacott & Moscovitch, 2003). In a subsequent study, the advantage for names with high autobiographical significance was not demonstrated in a sample of AD patients, though it was still apparent in individuals with semantic dementia. Therefore, the disruption of recall for episodic contextual features may have an effect on efficiency of recall for semantic knowledge, at least when autobiographical significance is high. Similar studies have hypothesized the same influence of autobiographical significance in the recall of semantic details of well-known public events and would help explain the observations of a TG in clinical and healthy samples mentioned above (Bizzozero et al., 2008).

Of significance, there is substantial support from the neuroimaging literature documenting a differential network of activation for the recall of person knowledge when compared to other forms of conceptual knowledge (Cabeza, Anderson, Houle, Mangels, & Nyberg, 2000; Leveroni et al., 2000; Maddock, Garrett, & Buonocore, 2001; Tempini et al., 1998). Specifically, the separate retrieval system for face and name knowledge has been termed the Person-Identity Network (PIN) within the literature. Support for the existence of separate neural networks underlying the PIN comes from both lesion and imaging studies. For example, associative learning and semantic priming studies in clinical samples have demonstrated that both the left and right hemispheres are essential in the operation of the PIN compared to the well-documented differential involvement of left hemisphere systems in the operation of a more general lexical semantic memory system (Ellis et al., 1989; Hanley, 1995; Seidenberg et al., 2001). Imaging studies suggest that there is a more widespread and distinctive neural network operating for retrieval from the PIN than is typically evident for general semantic retrieval tasks

as well (Damasio, Grabowski, Tranel, Hichwa, & Damasio, 1996; Damasio et al., 2001; Fink et al., 1996; Maddock et al., 2001; Sergent, Ohta, & MacDonald, 1992). Specifically, a review of the research for neuroimaging during general semantic knowledge tasks identifies the prefrontal, temporal, anterior cingulate, and cerebellar regions and is mainly left lateralized (Cabeza et al., 2000). On the other hand, imaging research that is specific to the PIN has identified the anterior temporal lobe region, the hippocampal complex and the posterior cingulate (Maddock et al., 2001; Leveroni et al., 2000; Tempini et al., 1998), in addition to the general network outlined previously. The generally broader activation required during tasks examining the PIN supports earlier hypotheses that integration of a greater number of networks is required for completion of famous name semantic knowledge tasks, as compared to tasks only requiring conceptual knowledge of words. Previously discussed theories suggest that the integrated networks are episodic or autobiographical in nature (Moscovitch, et al., 2005; Nielson et al., 2006; Westmacott, et al., 2004; Westmacott & Moscovitch, 2003; Winocur et al., 2010).

Though the existence of a TG for conceptual word knowledge was not observed, RT data showed that access to knowledge was significantly slower as the specificity of information increased. This pattern parallels our findings for the Famous Names Semantic Knowledge Tests and is consistent with an extensive literature theorizing the hierarchical organization of semantic networks (Nebes, 1989; Warrington, 1975). This hierarchical structure of knowledge networks has been demonstrated through lesion studies (Chertkow & Bub, 1990; Waters, 1978; Warrington, 1975), experimentation with lesions samples (Kintsch & Keenan, 1973; Waters, 1978), and recently in our lab using healthy older adults samples (Loacano et al., 2011). Our study did not demonstrate greater accuracy for general versus specific knowledge. Therefore, healthy older adults' overall memory integrity for conceptual word knowledge may not be

affected by level of specificity. Reaction time results, however, indicate that rate of access to conceptual word knowledge differs based on specificity of knowledge. This possibility would be consistent with proposed models of semantic knowledge networks that document disruption of access to knowledge during disease states; however, rate of access to information depends on internal structural organization of the network. For example, both Collins & Loftus' (1975) spreading activation model and McClelland, Rumelhart, and Hinton's (1990) parallel processing model would both suggest that more specific attributes or associations would take longer to access, though their explanations may differ slightly. That is, rate of access would depend on either a greater spread across the concept networks to more remote attributes, as opposed to closely associated categorization or simple recognition (Collins & Loftus, 1975) or the integration of a greater number of distributed networks for specific versus general knowledge (McClelland, Rumelhart, & Hilton, 1990). However, neither model would suggest an absence of recall for conceptual knowledge of a word unless there was some kind of disruption to the network.

In summary, performance on the Word Semantic Knowledge Tasks do not support the interactive organizational effects of both age of memory and specificity of knowledge on the conceptual networks of word meanings. We suggest that the absence of an observable TG for conceptual word knowledge in both the accuracy and RT data likely results from the absence of an episodic/contextual component during recall of these concepts. Research has demonstrated involvement of episodic, mainly autobiographical components, in recalling semantic details related to famous individuals (Moscovitch, et al., 2005; Nielson et al., 2006; Westmacott, et al., 2004; Westmacott & Moscovitch, 2003; Winocur et al., 2010). Further, empirical investigation has uncovered greater brain activation patterns for recall of person knowledge versus general

conceptual knowledge (Damasio, et al., 1996; Damasio, et al., 2001; Fink, et al., 1996; Maddock et al., 2001; Sergent, et al., 1992) in support of possible integration of semantic and episodic/contextual networks. Theories of long-term memory consolidation propose greater efficiency of recall of cortically represented general details as compared to episodic/contextual features of a memory, which are more susceptible to age of acquisition (Moscovitch, et al., 2005; Nielson et al., 2006; Winocur et al., 2010). Thus, the absence of integration of episodic or contextual features (i.e., those observed to be more vulnerable to age of acquisition) during word tasks might help to explain the absence of a TG in our study. On the other hand, RT data does acknowledge that rate of access to general knowledge is significantly faster than that for more specific knowledge, despite equal accuracy. This finding is consistent with proposed models of semantic memory (Collins & Lofuts, 1975; McClelland, Rumelhart, & Hilton, 1990) and theories regarding its hierarchical organizational structure (Warrington, 1975).

CONCLUSIONS

The principal aim of our study was to examine the possible disruption of the semantic knowledge network in older adults at risk for AD based on a positive parental history. Two supplementary aims involved 1) examination of the mutually dynamic effects of age of memory and specificity of information on the organization of knowledge for famous individuals and 2) whether these components could also be used to understand the organizational structure of conceptual word knowledge. Unfortunately, our results did not identify any group differences suggestive of greater disruption of the semantic network for older adults with a parental history of AD. The lack of group differences on behavioral variables could be explained by several possible factors, including sensitivity of the identified risk factor (i.e., self-report of parental AD history), variability in risk between PH+ participants, as well as the relatively high level of

health, activity, and education of the sample. Importantly, the absence of behavioral data suggestive of group differences does *not* mean that the integrity of the semantic network was equal between the two groups. Furthermore, one cannot definitively conclude that research involving varying levels of semantic knowledge specificity is not useful in the early detection of AD. Even in the face of intact behavioral performances, subtle neuro-anatomical changes may be underway that are only detectable through advanced neuroimaging techniques (Sugarman et al., 2012; Woodard et al., 2010). Additionally, the advantages of examining differences in brain activation patterns while controlling for differences in behavioral performance have been discussed (Seidenberg et al., 2009a). Even if our study did not document significant differences in semantic memory performance between our two groups, it does not disparage the use of similar tasks in future research. Additionally, they do not discredit the utility of employing semantic knowledge tasks in understanding the progression of neuropathology in AD (Seidenberg et al., 2009a; Seidenberg 2009b; Sugarman et al., 2012), identification of at-risk individuals (Seidenberg et al., 2009a), or identification of those who will undergo future decline (Hantke et al., 2013; Woodard et al., 2010).

Our supplementary aims were focused on understanding the effects of age of memory and specificity of knowledge in the organization of semantic knowledge networks in older adults. In general, our findings supported our theory of a combined influence of both factors on network organization of knowledge for famous persons. Based on the results of previous research, we suggest that the above-mentioned organizational factors, particularly age of memory, are dependent upon the influence of episodic/contextual networks (Moscovitch, et al., 2005; Nielson et al., 2006; Westmacott, et al., 2004; Westmacott & Moscovitch, 2003; Winocur et al., 2010). That is, research has shown that when recalling the semantic details associated with a famous

individual, the involvement of episodic, especially autobiographical, memory networks are of importance (Nielson et al., 2006; Westmacott, et al., 2004; Westmacott & Moscovitch, 2003). Theories regarding the involvement of the hippocampus in long-term memory, particularly the new transformation hypothesis, help explain why the degree of contextual/episodic network involvement would produce the results observed in our study (Winocur et al., 2010). Specifically, initially formed memories are episodic in nature, are context bound, and reliant on the hippocampus. Over time and through re-exposure, the hippocampus supports the transformation of these memories into distributed networks of schematic versions (i.e., semantic details). Later recall relies on integration of both types of memories. The more reliance on the still hippocampal-bound episodic event, the less efficient the recall (Moscovitch & Nadel, 1998; Moscovitch, et al., 2006; Moscovitch, et al., 2005; Nadel & Moscovitch, 1997, 1998). This theory would explain why enduring names exhibit the most efficient performance followed by remote names, with recent names producing the lowest accuracy and longest RTs. Given the assumptions of the transformation theory, the recent memories rely more heavily on the contextual network (i.e., episodic event) for recall, which has less established and therefore less efficient pathways in long-term memory circuits. We hypothesize that similar principles explain why we also see more efficient performances for recall of general versus specific information about famous individuals. As the theory dictates, less contextually dependent information, which they term "schematic details" or the "gist" of the memory, is stored in more efficient neocortical circuits, which we propose would be dominant in completion of more general knowledge tasks such as simple recognition and categorization. However, we believe that recall of more specific attributes would rely on greater integration of contextual/episodic circuits. Integration would lead to less efficient recall, especially for recent memories as outlined above. If this notion is true, it

could account for the observed effect that the least accurate and slowest performance was obtained for recent specific information. Ultimately, both specific and relatively recent memories rely on activation of relatively less efficient circuits.

We believe that the above conclusions regarding the interactive effects of age of memory and specificity of knowledge on memory network organization and their implications for understanding long-term memory formation are further supported by the fact that we did not observe the same pattern of performance when assessing conceptual word knowledge. Previous research has demonstrated that knowledge of well-known persons or events relies on integration of contextually bound episodic networks, while basic conceptual word knowledge does not. This theory is further supported by neuroimaging studies demonstrating a wider range of activation networks during examination of the PIN compared to activation patterns during other conceptual knowledge tasks (Cabeza et al., 2000; Damasio, et al., 1996; Damasio, et al., 2001; Fink, et al., 1996; Sergent, et al., 1992). The potentially decreased integration of contextual network circuits during conceptual word knowledge tasks means that they may be less susceptible to the effects of memory age. We did find that access to specific information during word knowledge tasks was slower relative to general word categorization. However, this outcome is highly consistent with proposed models of semantic networks originally built to describe relationships between concepts with closer, more efficient, paths to high versus low associates (Collins & Loftus, 1975). Fairly recent attempts at standardizing associative words for semantic priming studies have found categorical features to be high associates, while more specific attributes tend to be labeled as low associates (Nelson, McEvoy, & Schreiber, 1998).

Finally, our investigation of the organization for semantic knowledge networks in older adults extended the research literature by confirming previous theories and illuminating paths

worthy of further investigation. To our knowledge, it is one of the first studies to investigate the effects of age of memory and specificity of knowledge on semantic memory organization in tandem. Further, our results extend support to theories that memories regarding famous individuals rely on integration of contextually bound long-term memory circuits in addition to simple conceptual knowledge networks by documenting decreasing efficiency in performance with decreasing age of acquisition and increasing specificity of knowledge. If our theories regarding the roles of these factors are true, additional investigation should be focused on documented brain activation during completion of tasks similar to ours. Differential activation patterns for general versus specific recall during functional neuroimaging can further our understanding of the neural mechanisms underlying memory encoding and consolidation processes in older adults. In addition, steps should be taken to investigate the performances of other samples of interest on the tasks used in this investigation. Specifically, clinical samples, such as older persons with amnestic MCI and early-stage AD, may help us to understand how the interactive organizational structure proposed in this study is affected by the disease process. Thus far, studies have generally focused on either one factor or the other. Studies employing semantic dementia samples would also be of interest in hopes of further supporting the hypothesis that recent and more specific memories rely on integration of episodic/contextual networks. For example, if one were to compare the performance of older adults with AD to individuals with semantic dementia, potentially opposite or reverse performance patterns could be observed. Finally, additional exploration of similar behavioral performance in younger cohorts would help to further elucidate the effects of age of acquisition on the effects of encoding and consolidation.

LIMITATIONS

As alluded to throughout the discussion, there are various limitations within the current study, several of which would require specific attention in future investigation. First, the sensitivity of self-reported parental history of AD to detecting future decline may be quite low compared to other genetic markers such as ApoE. Future research may wish to employ genetic testing to ensure collection from an experimental sample where level of risk is more quantifiable. Additionally, in our study determination of parental history was through self-report. While care was taken to document how the diagnosis was made, research clearly demonstrates that the only definitive way to confirm AD diagnosis is at autopsy (Ballard et al., 2011). Unfortunately, only two participants reported confirmation of AD diagnosis in their parent at autopsy. It is possible that, while an individual parent was diagnosed as having AD, the true etiology could have varied for some participants' parents. Variations in true etiology would have significantly affected the actual level of risk for an individual placed in our "at-risk" group. Future studies wishing to focus on familial history as a risk factor must take considerable care when determining family member diagnosis history; if possible, participant samples should be garnered from family members of individuals who have a confirmed diagnosis at autopsy. The absence of a younger adult cohort could also be seen as a limitation of the study. The inclusion of a younger adult cohort for comparison would have made it possible to more thoroughly examine the effects of age of acquisition on conceptual knowledge organization. Finally, the lack of assessment of the emotional valence for the stimulus names and words could have added another meaningful component to the study and may have helped to further elucidate the suggested interaction between long-term memory networks during the famous names tasks. The extent of emotional arousal has previously been proposed to influence the amount of episodic/contextual network

integration during semantic recall (Nielson et al., 2006; Westmacott et al., 2004). For famous names tasks, it is possible that the episodic (i.e., autobiographical) component may interact with the degrees of emotionality or vividness for the participant. Recent neuroimaging research has also demonstrated differential activation of brain regions involved in emotion processing for recent versus remote and enduring names (Maddock, 1999).

Table 1.

Neuropsychological Battery Summary Scores

Measure	Scores Used
Dementia Rating Scale (DRS-2)	
	Attention (ATT) SS
	Initiation/Perseveration (I/P) SS
	Construction (CONST) SS
	Conceptualization (CONCEPT) SS
	Memory (MEM) SS
Rey Auditory Verbal Learning Test (RAVLT)	
	Trial 1 SS
	LOT SS
	Delayed Recall SS
Wechsler Memory Scale Revised (WMS-R), Logical Memory Subtest	
	Story A: Short Delay Free Recall SS
	Story B: Short Delay Free Recall SS
	Story A: Long Delay Free Recall SS
	Story B: Long Delay Free Recall SS
Wechsler Adult Intelligence Scale Fourth Edition (WAIS-IV)	
	Processing Speed Index
Wide Range Achievement Fourth Edition (WRAT-IV)	
	Word Reading Subtest SS
	Word Reading Subtest Grade Equivalent
Geriatric Depression Scale Short Form (GDS-SH)	
	Total Raw Score
Positive and Negative Affect Schedule	
	Positive Scale Total Raw Score
	Negative Scale Total Raw
Stroop Color Word Test	
	Interference T - Score

*SS = MOANS age-corrected scaled score; LOT = Learning Over Trials (Total Learning – (5 x Trial 1 raw))

Table 2.

Participant Demographics by Group

	PH– (n = 40)		PH+ (n = 40)			
	M(SD)	# (%)	*M(SD)*	# (%)	*p*	*ES*
Age (years)	68.4 (6.9)		68.9 (7.3)	t = -.395	.727	-0.07
Education (years)	15.1 (2.3)		16.1 (2.1)	t = -2.08	**.041**	**-0.46**
Gender						
Male		9 (22.5)		14 (35.0)		
Female		31 (77.5)		26 (65.0)		
				χ^2 (1) = 1.53	.217	-0.14
Race						
Caucasian		39 (97.5)		35 (87.5)		
AA		0 (0)		5 (12.5)		
Asian		1 (2.5)		0 (0)		
				χ^2 (2) = 7.21	.050	0.27
Physical activity						
Never		2 (5.0)		2 (5.0)		
1-4xs / month		2 (5.0)		7 (17.5)		
Weekly +		36 (90.0)		31 (77.5)		
				χ^2 (2) = 7.15	.067	0.29
Work						
Full time		6 (15.0)		6 (15.0)		
Part time		7 (17.5)		10 (25.0)		
Not Working		27 (67.5)		24 (60.0)		
				χ^2 (2) = .706	.703	0.09
Abstinent from alcohol						
No		24 (60.0)		26 (65.0)		
Yes		16 (40.0)		14 (35.0)		
				χ^2 (1) = 5.01	**.043**	**-0.25**
Regular tobacco use						
Yes		2 (5.0)		2 (5.0)		
No		38 (95.0)		38 (95.0)		
				χ^2 (1) = .001	.999	0.00
Cannabis use						
Yes		1 (2.5)		1 (2.5)		
No		39 (97.5)		40 (97.5)		
				χ^2 (1) = .001	.999	0.00

Note: AA = African American; No participants with alcohol use reported problem drinking; Use of cannabis was on a non-regular basis and for medical purposes. Comparisons significant at an alpha level of .05 are presented in bold font. ES = Effect Size; Cohen's d for continuous variables phi and Cramer's V for categorical.

Table 3.

Characteristics of Parental AD Diagnosis for PH+ Group

Sex of parent		N	Percentage
	Male	9	22.5
	Female	31	77.5
Diagnosis Source			
	PCP	15	37.5
	Neurologist	8	20.0
	Neuropsychologist	3	7.5
	Psychiatrist	1	2.5
	Geriatric Team	10	25.0
	Autopsy	2	5.0
	Unknown	1	2.5

* PCP = Primary Care Physician; Total N = 40

Table 4.

Neuropsychological Testing Performance by Group

		PH– (n = 40)		PH+ (n = 40)			
		M	*(SD)*	*M*	*(SD)*	*p*	*d*
DRS-2							
	ATT	10.53	(.93)	10.45	(1.4)	.778	.064
	I/P	11.05	(1.0)	11.27	(.86)	.284	-.240
	CONST	10.00	(0.0)	9.98	(0.0)	.999	***
	CONCEPT	11.27	(1.4)	11.28	(1.4)	.784	-.007
	MEM	12.10	(1.5)	12.00	(1.7)	.694	.062
RAVLT							
	Trial 1	11.02	(2.9)	10.90	(2.2)	.829	.049
	LOT	10.79	(2.3)	10.40	(2.7)	.487	.099
	Delayed Recall	12.15	(2.2)	11.80	(2.0)	.467	.169
WMS-R							
	Story A SDFR	11.42	(2.9)	12.05	(2.6)	.320	-.226
	Story B SDFR	11.38	(2.0)	11.70	(2.1)	.486	-.158
	Story A LDFR	12.48	(2.7)	12.59	(2.0)	.832	-.048
	Story B LDFR	11.68	(2.8)	12.03	(2.1)	.539	-.143
WAIS-IV							
	PSI	109.07	(12.4)	108.87	(11.1)	.940	.017
WRAT-IV							
	Word Reading	106.65	(14.2)	110.57	(15.4)	.242	-.263
GDS							
	Total Raw	2.13	(1.7)	2.74	(2.0)	.148	-.331
PANAS							
	Positive Raw	37.31	(5.2)	38.33	(5.4)	.397	-.194
	Negative Raw	13.23	(3.1)	13.72	(4.6)	.588	-.124
STROOP							
	Interference T	57.51	(5.1)	58.11	(6.2)	.650	-.106

*DRS = Dementia Rating Scale-2; RAVLT = Rey Auditory Verbal Learning Test; LOT = Learning Over Trials (Total Learning – (5 x Trial 1 raw)); WMS-R = Wechsler Memory Scale Revised; WAIS-IV = Wechsler Adult Intelligence Scale – Fourth Edition; PSI = Processing Speed Index; WRAT-IV Wide Range Achievement Test – Fourth Edition; GDS = Geriatric Depression Score; PANAS = Positive and Negative Affect Schedule ** Scores for the DRS, RAVLT, and WMS are presented in Mayo's Older American's age-corrected scaled scores; WAIS-IV, WRAT-IV, and STROOP scores are based on age-corrections available in the standard administration manual.

Table 5.

Mean Percentage Accuracy by Condition for Famous Names Semantic Knowledge Tasks

		PH– (n = 40)		PH+ (n = 40)					Whole Sample
Task	Time Epoch	*M(SD)*	Range	*M(SD)*	Range	*t*	*p*	*d*	*M(SD)*
FNDT									
	Non-Famous	95.0 (7.7)	71-100	96.0 (7.9)	60-100	-.604	.548	-.139	95.5 (7.8)
	Enduring	99.7 (1.1)	95-100	99.3 (1.7)	95-100	-1.14	.253	-.264	99.6 (1.4)
	Remote	93.9 (9.4)	68-100	94.0 (8.2)	70-100	.052	.959	.221	94.7 (8.7)
	Recent	87.2 (9.0)	68-100	87.6 (10.6)	68-100	.177	.860	.198	88.0 (9.8)
Categorization									
	Enduring	98.9 (2.0)	95-100	96.7 (5.4)	75-100	-2.38	.024	.005	98.2 (4.1)
	Remote	94.7 (5.9)	70-100	95.1 (5.0)	85-100	.305	.761	.175	95.3 (5.5)
	Recent	91.2 (9.5)	68-100	91.76 (8.7)	60-100	.227	.821	.190	92.3 (9.0)
Attributes									
	Enduring	90.7 (8.1)	65-100	92.7 (8.5)	70-100	1.02	.309	.071	92.1 (8.3)
	Remote	90.0 (9.4)	65-100	88.2 (10.7)	55-100	-.747	.457	.104	90.1 (10.0)
	Recent	83.0 (14.2)	40-100	84.0 (9.5)	55-100	.395	.694	.159	84.3 (12.1)

* FNDT = Famous Name Discrimination Task; Accuracy is shown as percentage of correct responses within each condition

Table 6.

Split Plot ANOVA for PH+ and PH- Groups on Famous Names Semantic Knowledge Tasks Accuracy

Effect	df	Mean Σ squ.	F	*p*	Partial η^2
Semantic Level	1.83	.282	67.70	**<.001**	**.488**
Semantic Level x Group	1.93	.014 e-3	0.036	.956	.001
Time Epoch	1.90	.415	71.29	**<.001**	**.501**
Time Epoch x Group	1.90	.003	0.485	.607	.007
Semantic Level x Time Epoch	3.58	.019	6.201	**<.001**	**.080**
Semantic Level x Time Epoch x Group	3.58	.005	1.70	.156	.023

* DF = Degrees of Freedom; Huyhn-Feldt corrected DF and p-value reported when Mauchly's Test of Sphericity was significant; Critical values and effect sizes for significant main effects and interactions are in bold.

Table 7.

Simple Main Effects for Time Epoch by Level of Semantic Knowledge Interaction on Famous Names Semantic Knowledge Task Accuracy

	Mean	Std. Dev.	St. Error	t	df	*p*	*d*
FNDT							
Enduring Names > Remote Names	.049	.092	.010	5.55	74	**<.001**	**1.29**
Remote Names > Recent Names	.066	.078	.009	6.80	76	**<.001**	**1.56**
Categorization							
Enduring Names > Remote Names	.027	.080	.006	4.37	75	**<.001**	**1.01**
Remote Names > Recent Names	.036	.091	.010	3.43	75	**<.001**	**.792**
Attributes							
Enduring Names = Remote Names	.022	.090	.010	2.20	76	.031	.504
Remote Names > Recent Names	.056	.107	.012	4.62	77	**.015**	**1.05**
Enduring Names							
Recognition > Categorization	.016	.038	.004	3.66	73	**<.001**	**.856**
Categorization > Attributes	.062	.077	.008	6.93	74	**<.001**	**1.61**
Remote Names							
Categorization = Recognition	.009	.077	.008	1.11	76	.270	.254
Recognition > Attributes	.047	.087	.009	4.74	76	**<.001**	**1.08**
Recent Names							
Recognition < Categorization	-.038	.078	.009	-4.92	74	**<.001**	**-1.1**
Categorization > Attributes	.074	.092	.010	7.00	75	**<.001**	**1.61**

* Accuracy is presented as the quotient of correct responses over total trials; Bold p-values indicate significant difference after applying a Bonferonni correction for multiple comparisons; "Mean" refers to the difference in means between compared variables. Interpretation of significance is based on a Bonferroni adjusted critical value of $p < .041$ e-1.

Table 8.

Mean Reaction Time in Milliseconds by Condition for Famous Names Semantic Knowledge Tasks

		PH– (n = 40)		PH+ (n = 40)					Whole Sample
Task	Time Epoch	*M(SD)*	Range	*M(SD)*	Range	*t*	*p*	*d*	*M(SD)*
FNDT									
	Non-Famous	1090.24 (189.4)	784-1756	1119.46 (228.9)	847-1651	-.611	.543	-.141	1104 (209)
	Enduring	800.77 (112.3)	589-1138	742.47 (247.7)	709-1161	-1.30	197	.045	772 (191)
	Remote	908.89 (138.1)	654-1280	934.33 (179.1)	679-1492	.697	.488	.112	920 (159)
	Recent	1066.98 (167.3)	699-1522	1025.10 (169.7)	734-1562	-1.09	.279	.064	1049 (168)
Categorization									
	Enduring	1591.98 (325.4)	1083-2665	1528.54 (305.3)	836-2366	-.888	.377	.086	1570 (315)
	Remote	1674.93 (385.5)	1109-2763	1705.28 (362.6)	1241-3024	.363	.718	.164	1684(367)
	Recent	1848.37 (479.2)	1083-3439	2714.49 (344.2)	1406-2830	-.459	.648	.148	1826(416)
Attributes									
	Enduring	2341.55 (626.8)	1351-3766	2187.02 (513.4)	1466-3766	-1.20	.233	.053	2264(575)
	Remote	2647.06 (736.9)	1527-4284	2600.25 (638.5)	1583-4734	-.300	.691	.158	2616(686)
	Recent	2778.46 (781.3)	1534-4635	2714.49 (630.1)	1447-4526	-.399	.765	.175	2744(707)

* FNDT = Famous Name Discrimination Task; Reaction time was calculated for correct responses after removal of scores that fell two standard deviations above or below the mean for the sample's correct responses within that condition. Reaction times presented in milliseconds.

Table 9.

Split Plot ANOVA for PH+ and PH- Groups on Famous Names Semantic Knowledge Tasks Reaction Time

Effect	df	Mean Σ squ.	F	*p*	Partial η^2
Semantic Level	1.28	234952503.9	544.66	**<.001**	**.882**
Semantic Level x Group	1.28	98734.2	.233	.961	.003
Time Epoch	2.00	6609511.0	114.02	**<.001**	**.606**
Time Epoch x Group	2.00	105063.1	1.81	.167	.024
Semantic Level x Time Epoch	3.76	429673.8	15.63	**<.001**	**.448**
Semantic Level x Time Epoch x Group	3.76	11719.2	.427	.777	.006

* DF = Degrees of Freedom; Huyhn-Feldt corrected DF and p-value reported when Mauchly's Test of Sphericity was significant; Critical values and effect sizes for significant main effects and interactions are in bold.

Table 10.

Simple Main Effects for Time Epoch by Level of Semantic Knowledge Interaction on Famous Names Semantic Knowledge Tasks Reaction Times

	Mean	Std. Dev.	St. Error	t	df	*p*	*d*
FNDT							
Enduring Names < Remote Names	-276.8	236.9	27.18	-5.43	75	**<.001**	**-1.25**
Remote Names < Recent Names	-124.8	157.1	17.90	-6.97	76	**<.001**	**-1.59**
Categorization							
Enduring Names < Remote Names	-128.6	235.0	26.60	-4.83	77	**<.001**	**-1.10**
Remote Names < Recent Names	-137.6	237.5	26.89	-5.11	77	**<.001**	**-1.16**
Attributes							
Enduring Names < Remote Names	-357.4	354.1	40.10	-11.98	77	**<.001**	**-2.73**
Remote Names < Recent Names	-123.0	351.4	39.79	-3.09	77	**<.001**	**-.704**
Enduring Names							
Recognition < Categorization	-797.8	259.1	29.71	-26.82	75	**<.001**	**-6.19**
Categorization < Attributes	-705.7	408.1	46.23	-15.27	77	**<.001**	**-3.49**
Remote Names							
Recognition < Categorization	-766.4	328.2	37.40	-20.48	76	**<.001**	**-4.69**
Categorization < Attributes	-934.5	456.9	52.76	-17.71	77	**<.001**	**-4.03**
Recent Names							
Recognition < Categorization	-781.4	354.7	40.42	-19.33	76	**<.001**	**-4.43**
Categorization < Attributes	-919.9	431.8	48.90	-18.81	77	**<.001**	**-4.28**

* Reaction times are presented in miliseconds; Bold p-values indicate significant difference after applying a Bonferonni correction for multiple comparisons; "Mean" refers to the difference in means between compared variables. Interpretation of significance is based on a Bonferroni adjusted critical value of $p < .041$ e-1.

Table 11.

Mean Percentage Accuracy by Condition for Word Semantic Knowledge Tasks

		PH– (n = 40)		PH+ (n = 40)					Whole Sample
Task	Time Epoch	*M(SD)*	Range	*M(SD)*	Range	*t*	*p*	*d*	*M(SD)*
Word Recognition									
	Non-Words	91.3 (7.7)	54-100	94.0 (6.7)	68-100	-1.21	.229	-.282	92.6 (9.7)
	1960s	87.9 (10.0)	70-100	89.4 (9.4)	70-100	.677	.501	.155	88.7 (9.7)
	1970s	90.2 (7.4)	70-100	92.9 (9.4)	80-100	1.59	.115	.026	91.7 (7.4)
	1980s	94.8 (7.9)	70-100	97.5 (4.3)	90-100	1.85	.069	.016	96.3 (6.5)
	1990s	91.0 (5.5)	80-100	91.8 (6.1)	70-100	.644	.522	.121	91.3 (5.8)
	2000s	86.4 (9.8)	60-100	87.5 (8.3)	70-100	.544	.581	.135	87.1 (9.0)
Word Categorization									
	1960s	93.9 (7.8)	70-100	98.5 (3.5)	90-100	3.22	.002	.000	96.5 (6.5)
	1970s	95.6 (5.5)	80-100	96.3 (5.4)	80-100	.555	.580	.137	96.1 (5.4)
	1980s	96.6 (5.8)	80-100	96.6 (5.8)	80-100	1.91	.061	.014	95.6 (6.2)
	1990s	95.2 (6.0)	80-100	97.2 (5.6)	80-100	1.41	.154	.036	96.3 (5.8)
	2000s	91.5 (7.8)	70-100	93.3 (6.7)	80-100	1.02	.307	.071	92.7 (7.3)
Word Attributes									
	1960s	93.1 (9.6)	60-100	94.8 (7.3)	70-100	.867	.389	.091	94.7 (8.5)
	1970s	93.4 (8.4)	60-100	96.4 (7.1)	80-100	1.69	.095	.022	95.6 (7.9)
	1980s	95.6 (5.5)	80-100	93.5 (8.5)	70-100	-1.28	.202	.047	94.9 (7.2)
	1990s	97.0 (5.7)	80-100	96.2 (5.4)	70-100	-.625	.534	.125	96.4 (5.5)
	2000s	95.2 (6.4)	80-100	97.2 (5.1)	80-100	1.44	.152	.035	97.4 (5.8)

Accuracy is shown as percentage of correct responses within each condition

Table 12.

Split Plot ANOVA for PH+ and PH- Groups on Word Semantic Knowledge Tasks Accuracy

Effect	df	Mean Σ squ.	F	*p*	Partial η^2
Semantic Level	1.71	.275	48.18	**<.001**	**.415**
Semantic Level x Group	1.71	.012	2.08	.136	.003
Decade	4.00	.038	8.41	**<.001**	**.110**
Decade x Group	4.00	.002	.351	.843	.005
Semantic Level x Decade	8.00	.035	9.389	**<.001**	**.121**
Semantic Level x Decade x Group	8.00	.004	1.023	.417	.015

* DF = Degrees of Freedom; Huyhn-Feldt corrected DF and p-value reported when Mauchly's Test of Sphericity was significant; Critical values and effect sizes for significant main effects and interactions are in bold.

Table 13.

Simple Main Effects for Decade by Level of Semantic Knowledge Interaction on Word Semantic Knowledge Tasks Accuracy

	Mean	Std. Dev.	St. Error	t	df	*p*	*d*
Word Recognition							
1960s = 1970	-.028	.106	.012	-2.36	75	.021	-.545
1970s < 1980s	-.406	.088	.010	-4.53	75	**<.001**	**-1.04**
1980s < 1990s	-.407	.075	.008	5.45	75	**<.001**	**1.25**
1990s > 2000s	.044	.094	.010	4.13	75	**<.001**	**0.95**
Word Categorization							
1960s = 1970	.001	.074	.008	.127	74	.899	.029
1970s = 1980s	.006	.076	.009	.760	74	.450	.176
1980s = 1990s	-.009	.077	.009	-1.04	73	.300	-.243
1990s > 2000s	.037	.083	.009	3.87	73	**<.001**	**.905**
Word Attributes							
1960s = 1970	-.009	.091	.010	-.881	74	.381	-.204
1970s = 1980s	.004	.105	.012	.331	73	.741	.077
1980s = 1990s	-.019	.084	.010	-1.94	73	.056	-.454
1990s = 2000s	.002	.078	.009	.300	73	.765	.070
1960s Words							
Recognition < Categorization	-.076	.104	.012	-6.23	73	**<.001**	**-1.45**
Categorization = Attributes	.019	.095	.011	1.70	72	.094	.400
1970s Words							
Recognition < Categorization	-.042	.086	.010	-4.19	72	**<.001**	**-.987**
Categorization = Attributes	.004	.081	.009	.435	72	.665	.102
1980s Words							
Recognition = Categorization	.008	.007	.008	.903	73	.369	.211
Categorization = Attributes	.006	.086	.010	.684	73	.469	.160
1990s Words							
Recognition < Categorization	-.050	.072	.008	-5.92	73	**<.001**	**-1.38**
Categorization = Attributes	-.002	.069	.008	-.341	72	.734	.173
2000s Words							
Recognition < Categorization	-.056	.038	.011	-4.84	73	**<.001**	**-1.04**
Categorization < Attributes	-.037	.082	.009	-3.83	72	**<.001**	**-.902**

* Accuracy is presented as the quotient of correct responses over total trials; Bold p-values indicate significant difference after applying a Bonferonni correction for multiple comparisons; "Mean" refers to the difference in means between compared variables. Interpretation of significance is based on a Bonferroni adjusted critical value of $p <$ 2.27 e-3.

Table 14.

Mean Reaction Time in Milliseconds by Condition for Word Semantic Knowledge Tasks

		PH– (n = 40)		PH+ (n = 40)					Whole Sample
Task	Time Epoch	*M(SD)*	Range	*M(SD)*	Range	*t*	*p*	*d*	*M(SD)*
Word Recognition									
	Non-words	1126.68(257.8)	697-1625	1122.86 (269.9)	766-1797	.063	.950	.014	1124(262)
	1960s	1010.67(259.2)	614-1779	1030.97 (213.6)	753-1564	.371	.710	.165	1018 (236)
	1970s	1211.07(291.2)	698-1850	1140.86 (192.3)	817-1652	-1.24	.217	.050	1179(249)
	1980s	1047.06(232.2)	660-1689	1087.20 (213.8)	739-1577	.779	.439	.102	1076(222)
	1990s	1038.68(247.3)	667-1630	1018.83 (200.3)	726-1864	-.385	.701	.162	1028(224)
	2000s	1045.20(219.5)	673-1591	1036.17 (205.4)	706-1433	-.185	.854	.198	1044(211)
Word Categorization									
	1960s	1218.20 (511.4)	1218-3381	1942.79 (345.7)	1369-2602	-1.02	.308	.072	1987(438)
	1970s	1891.15 (401.0)	1243-3102	1815.74 (343.1)	1328-2988	-.871	.387	.091	1855(373)
	1980s	1903.57 (408.7)	1198-2797	1888.86 (329.8)	1206-2666	-.171	.865	.203	1890(370)
	1990s	1732.60 (310.2)	1148-2516	1739.88 (269.9)	1243-2293	.108	.914	.215	1736(289)
	2000s	2045.02 (514.5)	1320-3150	1953.24 (333.6)	1483-2866	-.915	.364	.085	1995(435)
Word Attributes									
	1960s	2300.77 (556.3)	1292-3414	2111.22 (333.0)	1394-3076	-1.79	.078	.018	2193(466)
	1970s	2309.52 (508.1)	1476-3673	2133.35 (348.5)	1671-3076	-1.75	.084	.019	2209(442)
	1980s	2319.46 (635.9)	1514-4077	2121.45 (352.5)	1422-2988	-1.67	.099	.023	2196(521)
	1990s	2334.44 (550.1)	1481-3585	2231.94 (382.6)	1418-3160	-.939	.351	.082	2279(474)
	2000s	2387.62 (673.0)	1345-4026	2172.64 (413.2)	1343-2992	-1.67	.100	.023	2261(566)

* Reaction time was calculated for correct responses after removal of scores that fell two standard deviations above or below the mean for the sample's correct responses within that condition. Reaction times presented in milliseconds.

Table 15.

Split Plot ANOVA for PH+ and PH- Groups on Word Semantic Knowledge Tasks Reaction Time

Effect	df	Mean Σ squ.	F	*p*	Partial η^2
Semantic Level	1.45	176146084.4	751.73	**<.001**	**.915**
Semantic Level x Group	1.45	511788.6	2.148	.132	.030
Decade	3.82	233646.5	4.998	**.001**	**.067**
Decade x Group	3.82	44469.8	.951	.432	.013
Semantic Level x Decade	7.47	541578.9	15.811	**<.001**	**.184**
Semantic Level x Decade x Group	7.47	29446.4	.860	.544	.012

* DF = Degrees of Freedom; Huyhn-Feldt corrected DF and p-value reported when Mauchly's Test of Sphericity was significant; Critical values and effect sizes for significant main effects and interactions are in bold.

Table 16.

Simple Main Effects for Decade by Level of Semantic Knowledge Interaction on Word Semantic Knowledge Tasks Reaction Time

	Mean	Std. Dev.	St. Error	t	df	*p*	*d*
Word Recognition							
1960s < 1970	-156.3	179.8	20.6	-7.57	75	**<.001**	**-1.78**
1970s > 1980s	101.0	164.4	18.9	5.32	74	**<.001**	**1.23**
1980s = 1990s	45.0	156.3	18.0	2.49	74	.015	.578
1990s = 2000s	-11.8	137.0	15.7	-.750	75	.456	-.173
Word Categorization							
1960s > 1970	141.6	308.7	35.8	3.94	73	**<.001**	**.922**
1970s = 1980s	-41.9	274.8	31.9	-1.31	73	.193	-.306
1980s > 1990s	160.2	262.8	30.5	5.24	73	**<.001**	**1.22**
1990s < 2000s	-264.2	310.9	36.1	-7.31	73	**<.001**	**-1.71**
Word Attributes							
1960s = 1970	-15.6	309.8	35.7	-.436	74	.664	-.101
1970s = 1980s	9.8	300.3	34.6	.024	74	.981	.005
1980s = 1990s	-62.1	330.7	38.1	-1.62	74	.108	-.376
1990s = 2000s	12.3	316.7	36.5	.063	74	.950	.014
1960s Words							
Recognition < Categorization	-971.9	342.8	39.8	-24.3	73	**<.001**	**-5.68**
Categorization < Attributes	-208.3	354.9	42.5	-5.01	72	**<.001**	**-1.18**
1970s Words							
Recognition < Categorization	-669.6	299.5	34.8	-19.2	73	**<.001**	**-4.49**
Categorization < Attributes	-363.8	276.7	32.3	-11.2	72	**<.001**	**-2.63**
1980s Words							
Recognition < Categorization	-811.1	314.5	36.8	-22.0	72	**<.001**	**-5.18**
Categorization < Attributes	-314.5	331.0	38.7	-8.12	72	**<.001**	**-1.91**
1990s Words							
Recognition < Categorization	-701.7	228.9	26.6	-26.3	73	**<.001**	**-6.15**
Categorization < Attributes	-554.8	340.9	39.9	-13.9	72	**<.001**	**-3.27**
2000s Words							
Recognition < Categorization	-952.2	359.4	41.7	-22.7	73	**<.001**	**-5.31**
Categorization < Attributes	-277.4	347.1	40.6	-6.83	72	**<.001**	**-1.50**

* Accuracy is presented as the quotient of correct responses over total trials; Bold p-values indicate significant difference after applying a Bonferonni correction for multiple comparisons; "Mean" refers to the difference in means between compared variables. Interpretation of significance is based on a Bonferroni adjusted critical value of $p <$ 2.27 e-3.

Figure 1.

Example of Famous Name Discriminability Task

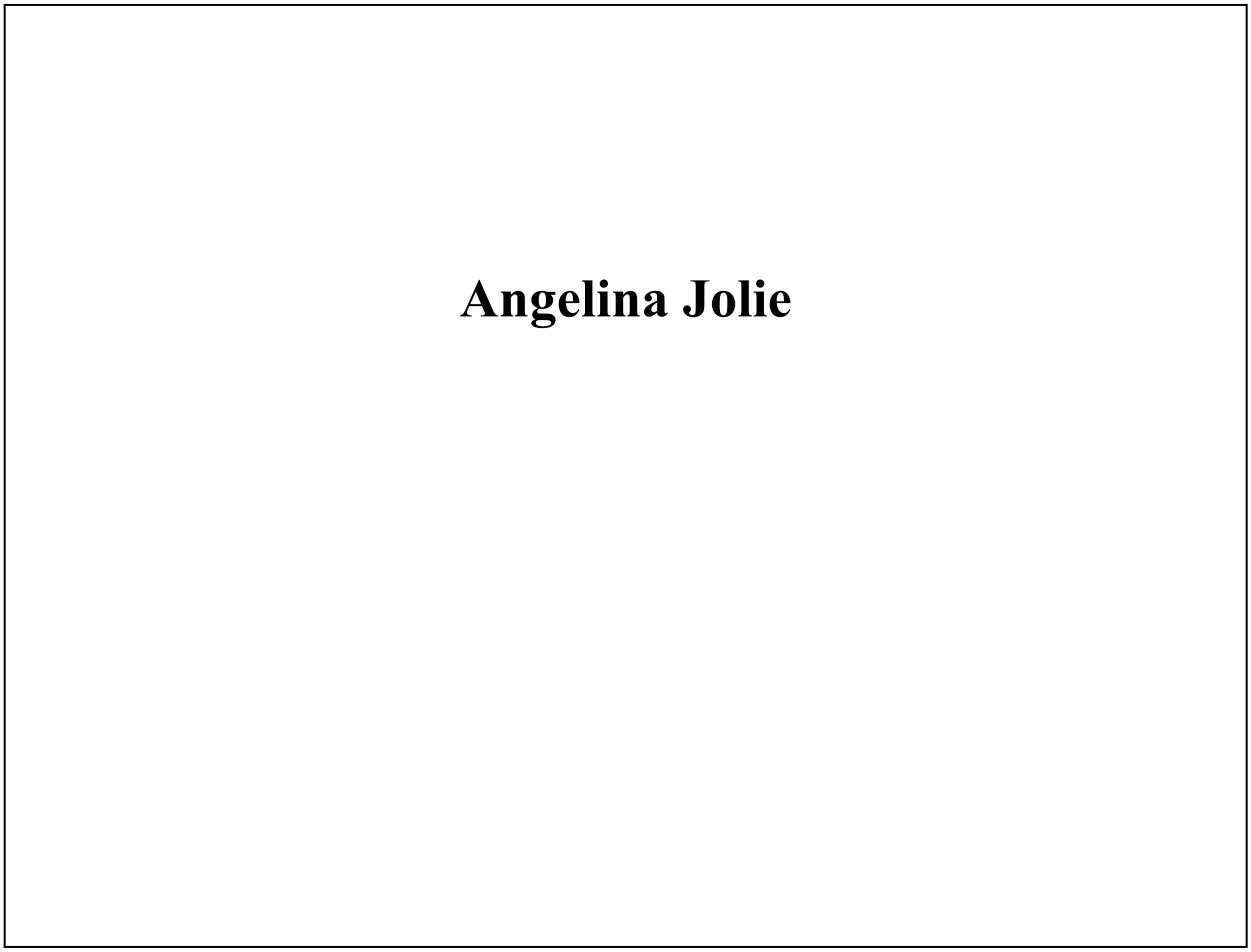


Figure 2.

Example of Famous Names Categorization Knowledge Task

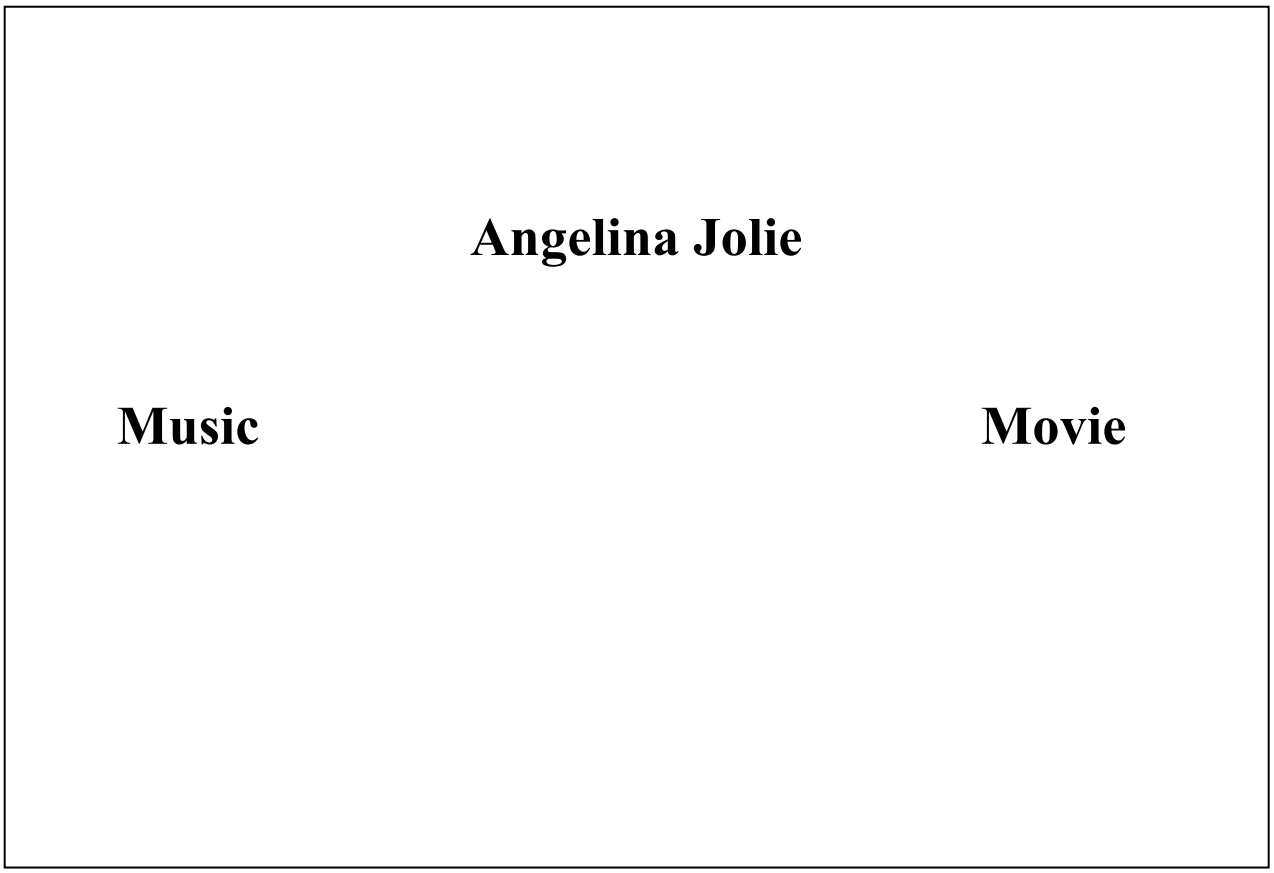


Figure 3.

Example of Famous Names Attributes Knowledge Task

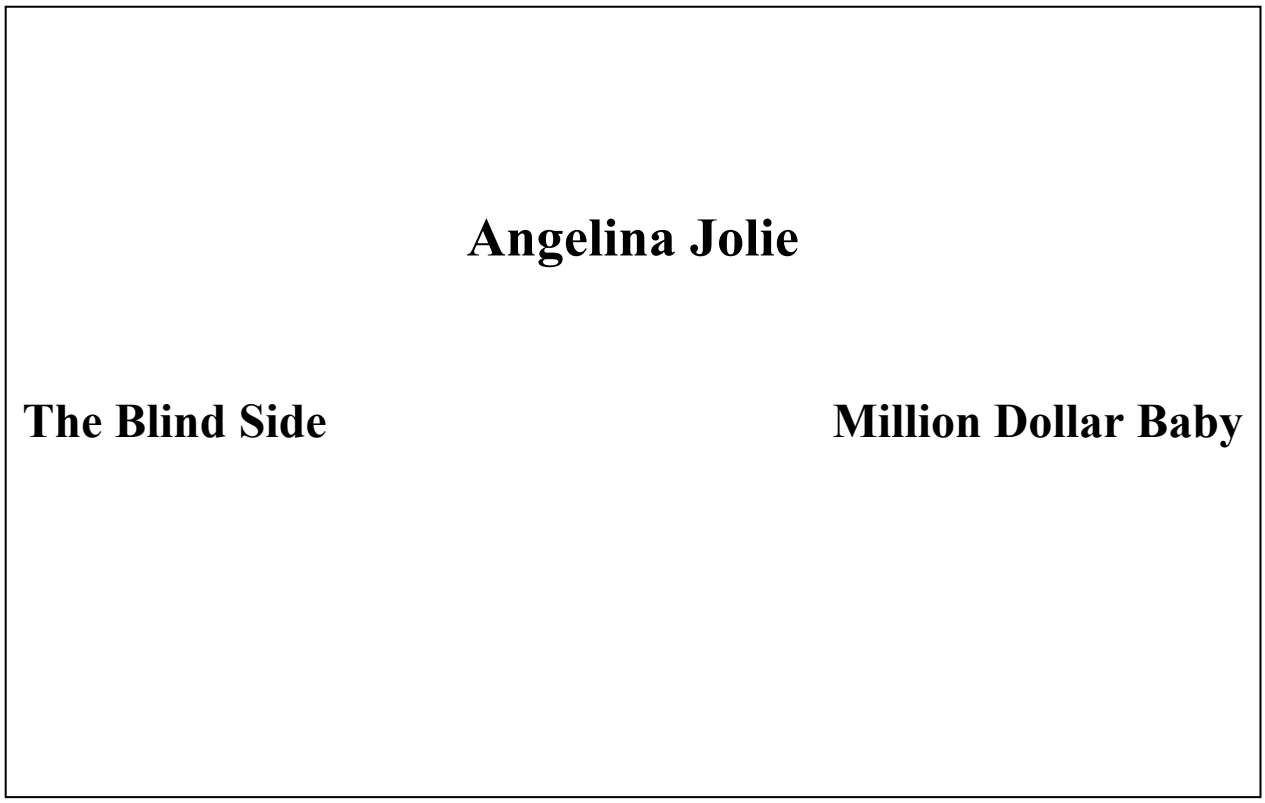


Figure 4.

Estimated Frequency of usage for "microwave"

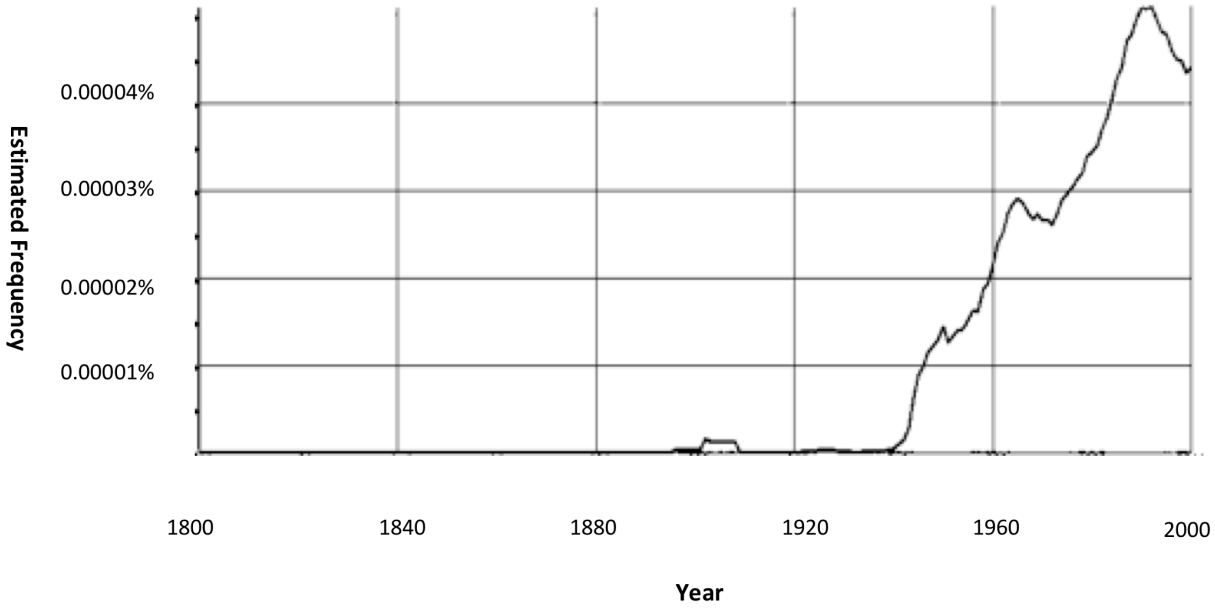


Figure 5.

Example of Word Recognition Task

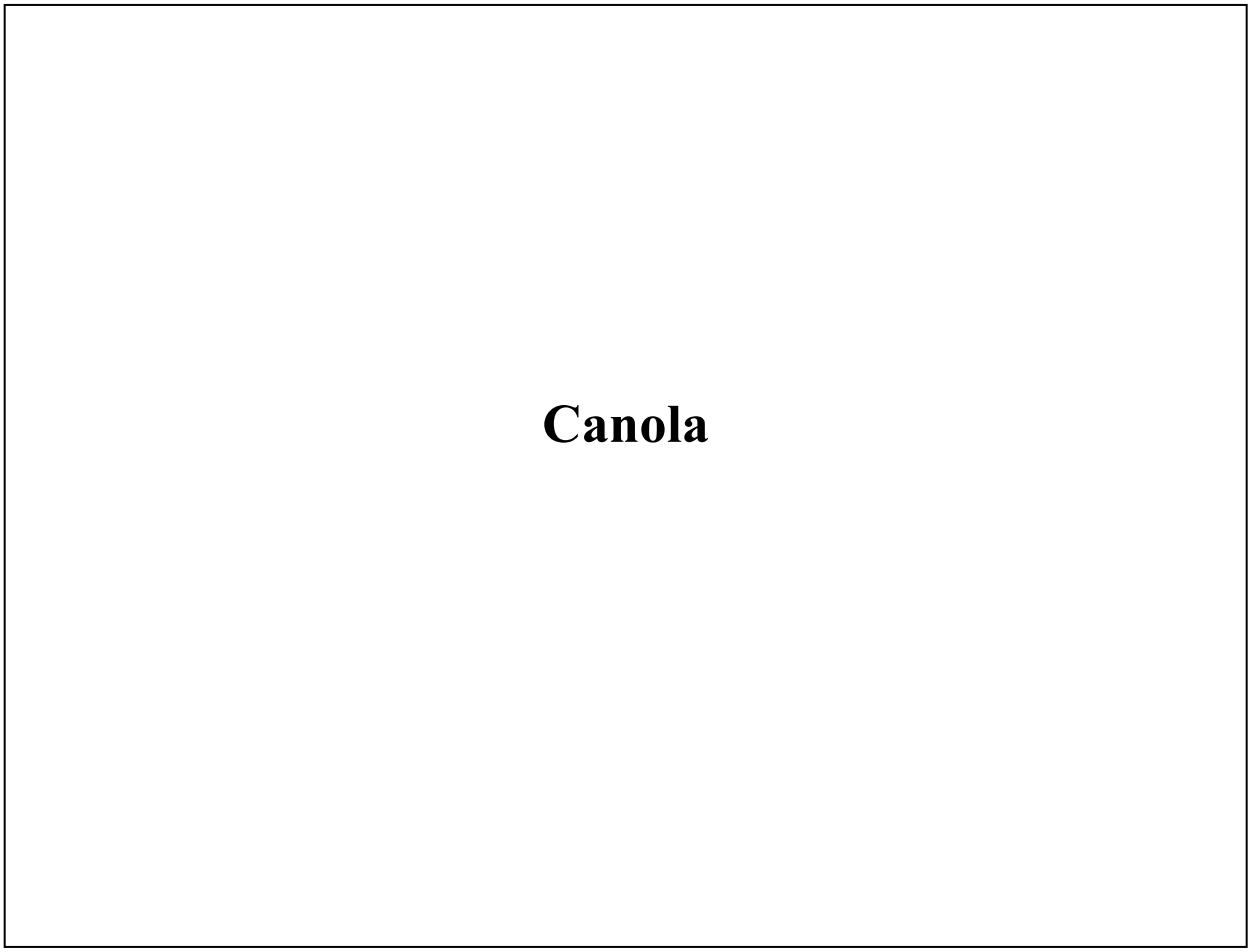


Figure 6.

Example of Word Categorization Task

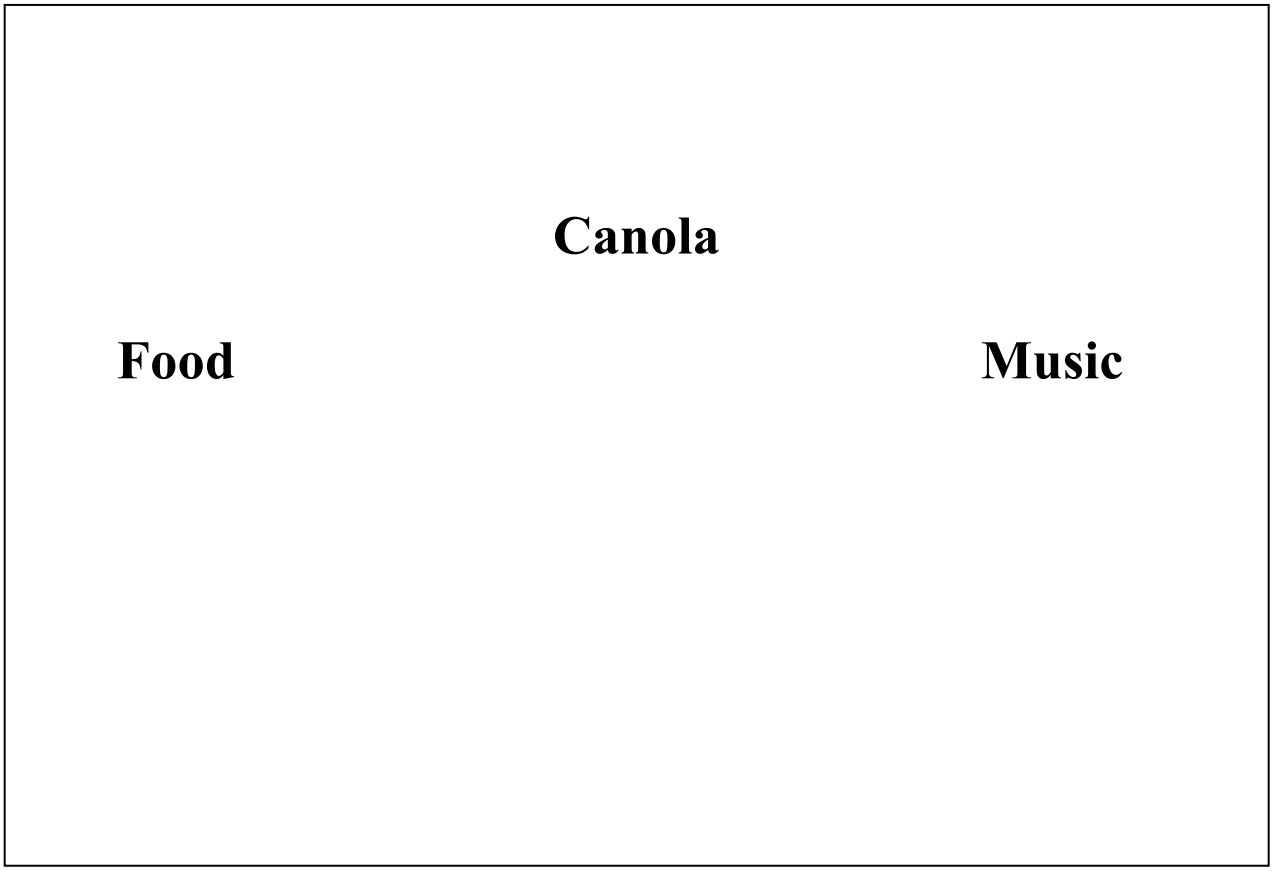


Figure 7.

Example of Attribute Knowledge Task for Words

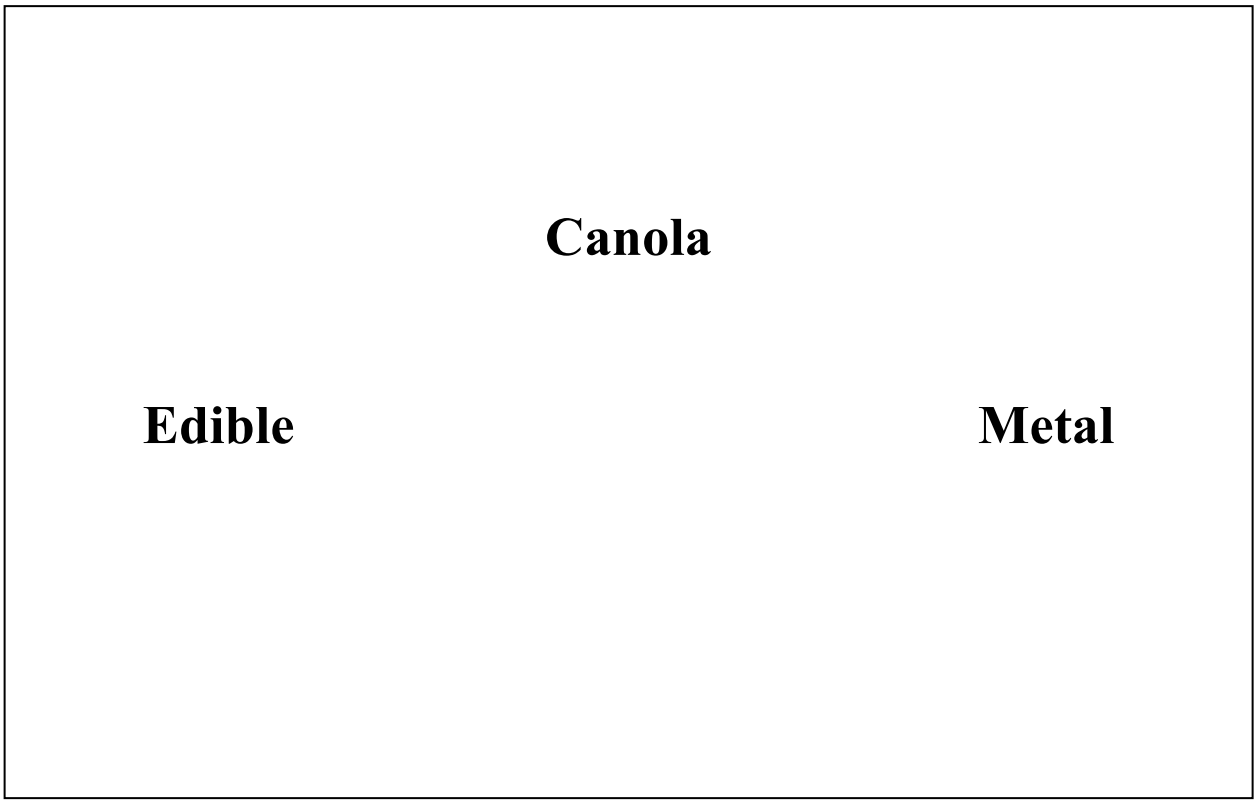
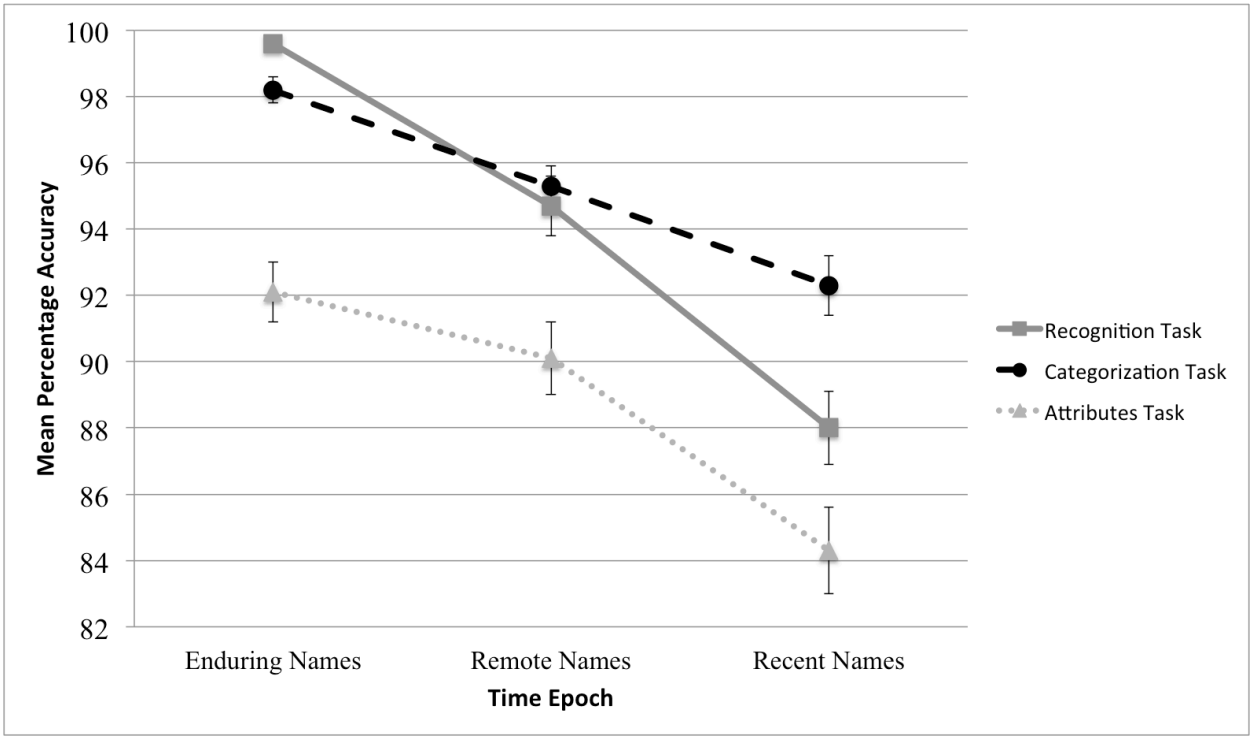


Figure 8.

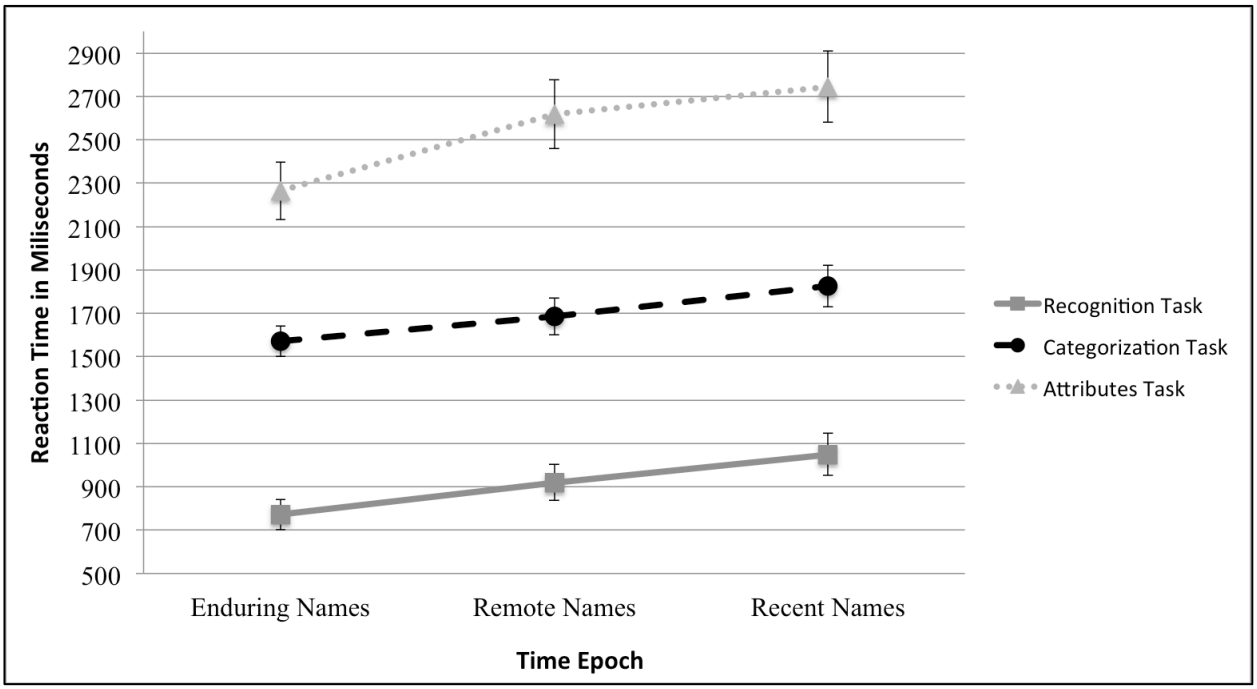
Effects of Level of Semantic Knowledge and Time Epoch on Famous Names Semantic Knowledge Tasks Accuracy



Note: Error bars represent the standard error for each data point.

Figure 9.

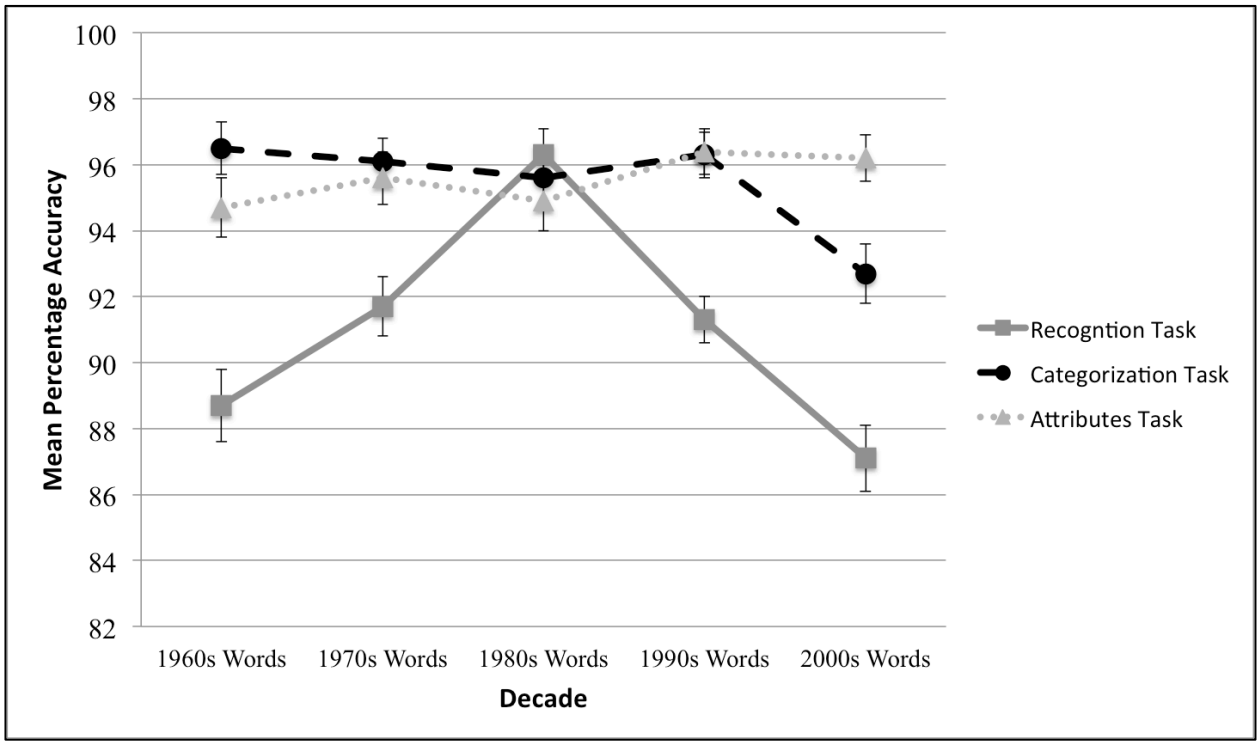
Effects of Level of Semantic Knowledge and Time Epoch on Famous Names Semantic Knowledge Tasks Reaction Time



Note: Error bars represent the 95% confidence interval for each data point.

Figure 10.

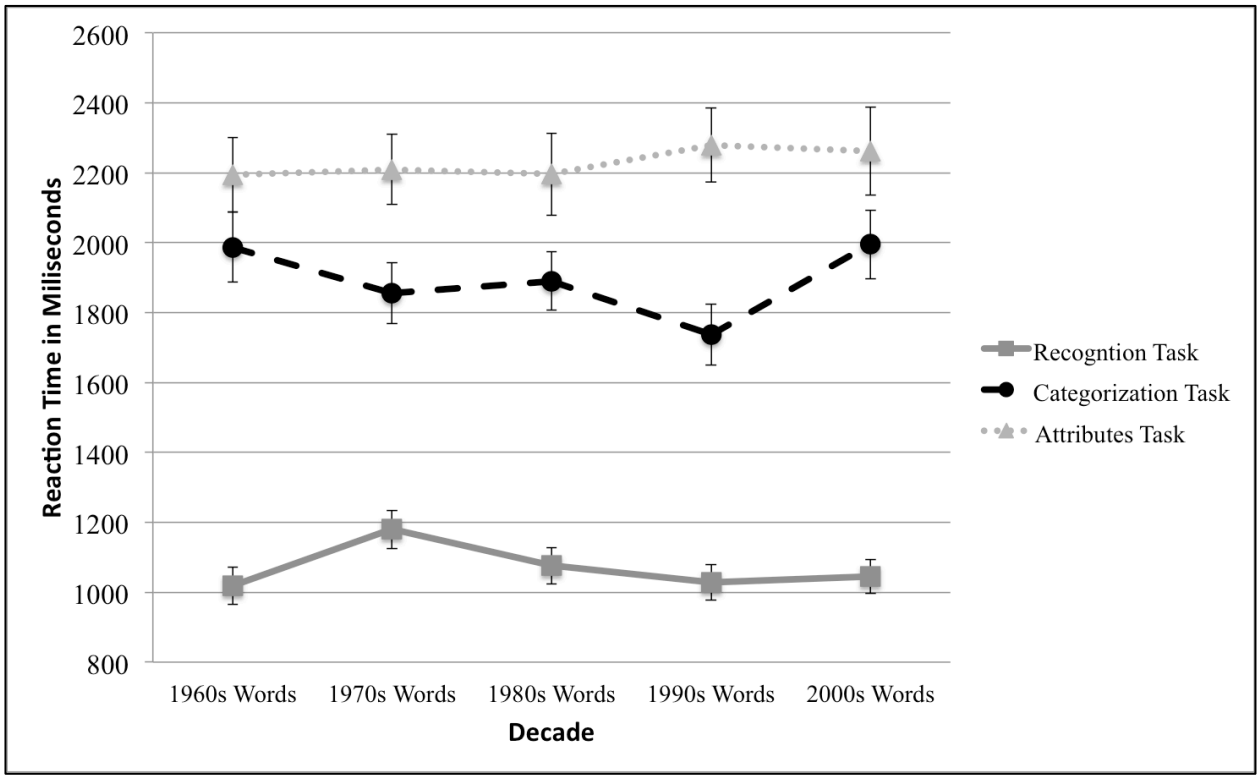
Effects of Level of Semantic Knowledge and Decade on Word Semantic Knowledge Tasks Accuracy



Note: Error bars represent the standard error for each data point.

Figure 11.

Effects of Level of Semantic Knowledge and Decade on Word Semantic Knowledge Tasks Reaction Time



Note: Error bars represent the 95% confidence interval for each data point.

APPENDIX 1

Subject Information Form

Subject Number : _____

Date of Testing :_____ Time of Testing: _____

Glasses?: _____ Hearing Aid?: _____

Color Blind?: _____ Gender _____

Demographic Background

1. What is your year of birth? _____ Age: _____

2. Are you employed outside of your home?
___ Yes, full-time If *yes*, what is your job title? _____
___ Yes, part-time
___ No

3. Which race or ethnic category best describes you?
___American Indian/Native American
___Asian
___Black/African American
___White/Caucasian
___Spanish/Hispanic
___Other

4. What is the highest grade you completed in school?
___8th grade or less
___Some high school
___High School Graduate/GED
___Some college or technical school
___College graduate
___Post-graduate

5. How many **Total Years of Education** have you completed?
_____

6. List your preferred writing hand: ___ Left ___ Right

7. Have you ever smoked cigarettes? ❑ Yes ❑ No ❑ Don't Know

If *no*, go to Question #8
If *yes*, in the past month, have you smoked any cigarettes at all? ❑ Yes ❑ No ❑ Don't Know

How many cigarettes on average do you smoke each day?

❑ Occasionally, but not daily
❑ 1-9 cigarettes
❑ 10-19 cigarettes
❑ 20-29 cigarettes
❑ 30 or more cigarettes

8. In the past month, have you had any alcoholic beverages? If *no*, go to #9. ❑ Yes ❑ No ❑ Don't Know

a. If yes, on average, how many days per week do you drink alcoholic beverages?

❑ Less than once per week
❑ 1-2 days
❑ 3-4 days
❑ 5-6 days
❑ Every day in past month

b. Have you ever felt you should cut down on your drinking? ❑ Yes ❑ No ❑ Don't Know
c. Have people annoyed you by criticizing your drinking? ❑ Yes ❑ No ❑ Don't Know
d. Have you ever felt bad or guilty about your drinking? ❑ Yes ❑ No ❑ Don't Know

e. Have you ever had a drink first thing in the morning to steady your nerves or to get rid of a hangover? ❑ Yes ❑ No ❑ Don't Know

9. Are there any reasons, like serious emotional problems, mental illness, or too much stress, that would make it hard for you to be in a research study? ❑ Yes ❑ No ❑ Don't Know

10. Have you used any illegal drugs in the past year? ❑ Yes ❑ No ❑ Don't Know

11. Do you think that you have a problem with your memory? ❑ Yes ❑ No ❑ Don't Know

12. Has anyone told you that you have a memory problem? ❑ Yes ❑ No ❑ Don't Know

13. Did you have any learning problems in school? ❑ Yes ❑ No ❑ Don't Know

14. Have you ever had previous neuropsychological testing? ❑ Yes ❑ No ❑ Don't Know

Medical History

15. Have you ever been diagnosed as having:

a. Heart disease ❑ Yes ❑ No ❑ Don't Know

If *yes*, what kind? _____

b. Hypertension (high blood pressure) ❑ Yes ❑ No ❑ Don't Know
c. Diabetes mellitus ❑ Yes ❑ No ❑ Don't Know
d. Thyroid disease (specify:_____) ❑ Yes ❑ No ❑ Don't Know
e. Cancer (specify:_____) ❑ Yes ❑ No ❑ Don't Know
f. Head injury requiring medical attention ❑ Yes ❑ No ❑ Don't Know
g. Kidney disease ❑ Yes ❑ No ❑ Don't Know
h. Liver disease (e.g., hepatitis or cirrhosis) ❑ Yes ❑ No ❑ Don't Know
i. Syphilis, AIDS, HIV (specify:_____) ❑ Yes ❑ No ❑ Don't Know
j. High cholesterol ❑ Yes ❑ No ❑ Don't Know
k. Lung disease ❑ Yes ❑ No ❑ Don't Know

If *yes*, what kind? _____

m. Arthritis ❑ Yes ❑ No ❑ Don't Know
n. Stroke or transient ischemic attack (TIA) ❑ Yes ❑ No ❑ Don't Know
o. Psychiatric disorders ❑ Yes ❑ No ❑ Don't Know

If *yes*, what kind?

1. Depression ❑ Yes ❑ No ❑ Don't Know
2. Anxiety, panic ❑ Yes ❑ No ❑ Don't Know
3. Schizophrenia, psychotic ❑ Yes ❑ No ❑ Don't Know
4. Bipolar (manic depression) ❑ Yes ❑ No ❑ Don't Know
5. Postpartum depression ❑ Yes ❑ No ❑ Don't Know

p. Other neurological conditions _____

General Health and Lifestyle

26. Height_____ Weight:_____

27. How would you rate your current health? ❑ Poor ❑ Fair ❑ Good ❑ Very Good ❑ Excellent

28. How many times per month do you engage in physical activities or exercise?

❑ Never ❑ Once a month ❑ 1-4 times per month ❑ More than once per week

29. How many times during a typical week do you engage in light to moderate physical activity that lasts at least 30 minutes? (e.g., walking, swimming, bicycling, dancing, gardening, yardwork, strenuous housework)

❑ Never ❑ 1 time ❑ 2 times ❑ 3 times ❑ 4 times ❑ 5 times ❑ 6 times ❑ Daily

APPENDIX 2

Family History Questionnaire

FAMILY HISTORY QUESTIONNAIRE

Directions:

In this set of questionnaires, you will find 4 sections: 1) section 1 will ask you to provide some general information; 2) section 2 will ask you to provide information about your parents; 3) section 3 will be about your siblings; If you are adopted, please indicate that by checking the box on the bottom of this page. You do not need to complete the rest of the questionnaire. We ask that you provide as much detail as you can. Some of the questions will ask you to write down an age (for example, at what age was your relative diagnosed with Alzheimer's disease). If you are not sure of the exact dates, make a reasonable estimate. All the information you give will be held in strictest confidence. You will not be identified by name or initials in any publications resulting from this study. Information will be stored in a protected computer database. Only certain members of the research team will have access to this information.

SECTION 1: GENERAL INFORMATION

What is your name?: ☐

What is your current address: ☐

☐

☐ ☐ ☐

City State Zip Code

Today's Date: ☐☐ / ☐☐ / ☐☐☐☐

Verify gender. **You are:** ○ **M** **or** ○ **F**

Are You Adopted?

☐ Yes ☐ No ☐ Unknown

If YES, you do not need to complete out the rest of the questionnaire.

Section 2: Parents

This section will ask you some general questions and about the cognitive history of your Parents. Each parent will be asked about separately.

Family History for Your MOTHER

What is your MOTHER's name? _____

What is his year of birth? ☐☐☐☐ Is she a TWIN? ☐ Yes ☐ No ☐ Unknown
If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is she still living? ☐ Yes ☐ No

If she is still living, what is her current age? ☐☐☐

If she is deceased, what was her age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has she ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in her judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has she shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has she ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did her memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was she ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was she ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did she ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did she lose consciousness? ☐ Yes ☐ No

Family History for Your FATHER

What is your FATHER's name? _____

What is his year of birth? ☐☐☐☐ Is he a TWIN? ☐ Yes ☐ No ☐ Unknown
If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is he still living? ☐ Yes ☐ No

If he is still living, what is his current age? ☐☐☐

If he is deceased, what was his age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has he ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in his judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has he shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has he ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did his memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was he ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was he ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did he ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did he lose consciousness? ☐ Yes ☐ No

Section 3: Siblings

This section will ask you some general questions and about the cognitive history of your siblings. Each brother and sister will be asked about separately. You can provide information for up to 5 brothers and 5 sisters. If you have any additional siblings you would like to report on, please let us know.

Are You An Only Child?

☐ Yes ☐ No ☐ Unknown

If YES, you do not need to complete the next section.

Family History for BROTHER #1

Is he a HALF-Brother? ☐ Yes ☐ No If YES, does he have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is his year of birth? ☐☐☐☐ Is he a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is he still living? ☐ Yes ☐ No

If he is still living, what is his current age? ☐☐☐

If he is deceased, what was his age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has he ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in his judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has he shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has he ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did his memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was he ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was he ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did he ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did he lose consciousness? ☐ Yes ☐ No

Family History for BROTHER #2

Is he a HALF-Brother? ☐ Yes ☐ No If YES, does he have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is his year of birth? ☐☐☐☐ Is he a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is he still living? ☐ Yes ☐ No

If he is still living, what is his current age? ☐☐☐

If he is deceased, what was his age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has he ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in his judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has he shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has he ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did his memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was he ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was he ever diagnosed with Parkinson's disease? ☐☐☐

☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made?

Did he ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)? ☐☐☐
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin?

Did he ever have a head injury requiring medical attention? ☐☐☐
☐ Yes ☐ No ☐ Unknown If YES, at what age?
If YES, Did he lose consciousness? ☐ Yes ☐ No

Family History for BROTHER #3

Is he a HALF-Brother? ☐ Yes ☐ No If YES, does he have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is his year of birth? ☐☐☐☐ Is he a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is he still living? ☐ Yes ☐ No

If he is still living, what is his current age? ☐☐☐

If he is deceased, what was his age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has he ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in his judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has he shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has he ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did his memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was he ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was he ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did he ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did he lose consciousness? ☐ Yes ☐ No

Family History for BROTHER #4

Is he a HALF-Brother? ☐ Yes ☐ No If YES, does he have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is his year of birth? ☐☐☐☐ Is he a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is he still living? ☐ Yes ☐ No

If he is still living, what is his current age? ☐☐☐

If he is deceased, what was his age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has he ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in his judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has he shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has he ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did his memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was he ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was he ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did he ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did he lose consciousness? ☐ Yes ☐ No

Family History for BROTHER #5

Is he a HALF-Brother? ☐ Yes ☐ No If YES, does he have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is his year of birth? ☐☐☐☐ Is he a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is he still living? ☐ Yes ☐ No

If he is still living, what is his current age? ☐☐☐

If he is deceased, what was his age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has he ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in his judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has he shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has he ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did his memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was he ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was he ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did he ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did he ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did he lose consciousness? ☐ Yes ☐ No

Family History for SISTER #1

Is she a HALF-Sister? ☐ Yes ☐ No If YES, does she have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is her year of birth? ☐☐☐☐ Is she a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is she still living? ☐ Yes ☐ No

If she is still living, what is her current age? ☐☐☐

If she is deceased, what was her age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has she ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in her judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has she shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has she ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did her memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was she ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was she ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did she ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did she lose consciousness? ☐ Yes ☐ No

Family History for SISTER #2

Is she a HALF-Sister? ☐ Yes ☐ No If YES, does she have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is her year of birth? ☐☐☐☐ Is she a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is she still living? ☐ Yes ☐ No

If she is still living, what is her current age? ☐☐☐

If she is deceased, what was her age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has she ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in her judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has she shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has she ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did her memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was she ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was she ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did she ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did she lose consciousness? ☐ Yes ☐ No

Family History for SISTER #3

Is she a HALF-Sister? ☐ Yes ☐ No If YES, does she have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is her year of birth? ☐☐☐☐ Is she a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is she still living? ☐ Yes ☐ No

If she is still living, what is her current age? ☐☐☐

If she is deceased, what was her age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has she ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in her judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has she shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has she ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did her memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was she ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was she ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did she ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did she lose consciousness? ☐ Yes ☐ No

Family History for SISTER #4

Is she a HALF-Sister? ☐ Yes ☐ No If YES, does she have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is her year of birth? ☐☐☐☐ Is she a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is she still living? ☐ Yes ☐ No

If she is still living, what is her current age? ☐☐☐

If she is deceased, what was her age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has she ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in her judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has she shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has she ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did her memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was she ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was she ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did she ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did she lose consciousness? ☐ Yes ☐ No

Family History for SISTER #5

Is she a HALF-Sister? ☐ Yes ☐ No If YES, does she have the same mother or father as you do?

☐ Same Mother ☐ Same Father ☐ Unknown

What is her year of birth? ☐☐☐☐ Is she a TWIN? ☐ Yes ☐ No ☐ Unknown

If YES, what type? ☐ Identical ☐ Fraternal ☐ Unknown

Is she still living? ☐ Yes ☐ No

If she is still living, what is her current age? ☐☐☐

If she is deceased, what was her age at death? ☐☐☐

What was the cause of death? _____

Since age 40, **has she ever had any memory problem?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, have **there been any changes in her judgment, thinking, behavior or ability to function?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Since age 40, **has she shown any signs of confusion?**
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Has she ever been confined to a nursing home for any reason?
☐ Yes ☐ No ☐ Unknown If YES, what was the reason? ☐

If you answered YES to any of the above questions, **Did her memory problems, confusion, or decline begin slowly or did they begin suddenly?**
☐ Slowly ☐ Suddenly ☐ Unknown

Was she ever diagnosed with Alzheimer's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have high blood pressure that had to be medically treated?
☐ Yes ☐ No ☐ Unknown If YES, at what age did this treatment begin? ☐☐☐

Was she ever diagnosed with Parkinson's disease?
☐ Yes ☐ No ☐ Unknown If YES, at what age was the diagnosis made? ☐☐☐

Did she ever have a stroke, mini-stroke or TIA (Transient Ischemic Attack)?
☐ Yes ☐ No ☐ Unknown If YES, at what age did these problems begin? ☐☐☐

Did she ever have a head injury requiring medical attention?
☐ Yes ☐ No ☐ Unknown If YES, at what age? ☐☐☐
If YES, Did she lose consciousness? ☐ Yes ☐ No

APPENDIX 3

Recent Famous Names

1. Eliot Spitzer
2. Michael Bloomberg
3. Eli Manning
4. Michael Vick
5. Rene Zellweger
6. Lindsay Lohan
7. Jennifer Lopez
8. Michael Phelps
9. Anne Hathaway
10. Sarah Palin
11. Karl Rove
12. Rachel Ray
13. Tina Fey
14. George Lopez
15. John Ashcroft
16. Russell Crowe
17. Heath Ledger
18. Christina Aguilera
19. Angelina Jolie
20. Miley Cyrus

APPENDIX 4

Enduring Famous Names

1. Stevie Wonder
2. Jimmy Carter
3. Robert De Niro
4. Dwight Eisenhower
5. Barbara Walters
6. Sylvester Stallone
7. Paul Newman
8. Nelson Mandela
9. Dustin Hoffman
10. Judy Garland
11. Steve Martin
12. Neil Diamond
13. Clint Eastwood
14. Aretha Franklin
15. Steven Spielberg
16. Robert Redford
17. Lucille Ball
18. Diana Ross
19. Joan Rivers
20. Jay Leno

APPENDIX 5

Remote Famous Names

1. David Niven
2. Imogene Coca
3. Don Ameche
4. Roger Maris
5. Jack Palance
6. Mel Torme
7. Peggy Lee
8. Paul Anka
9. Richard Burton
10. Mitzi Gaynor
11. Lorne Greene
12. Floyd Patterson
13. Steve Lawrence
14. Gary Hart
15. Jim Nabors
16. Norman Mailer
17. Burt Lancaster
18. Barry Goldwater
19. Rock Hudson
20. Kim Novak

APPENDIX 6

Word Stimuli by Decade

1960s

1. Microwave
2. Disco
3. Aerobics
4. Counterculture
5. Reggae
6. Sitcom
7. Unitard
8. Bionic
9. Skateboard
10. Grunge

1970s

1. Miniseries
2. Fajita
3. Canola
4. Bodyboard
5. Videocassette
6. Gearhead
7. Charbroil
8. Prochoice
9. Transgender
10. Karaoke

1980s

1. Infomercial
2. Redux
3. Microbrewery
4. Paparazzi
5. Wannabe
6. Yuppie
7. Spreadsheet
8. Multitasking
9. Autocorrect
10. Download

1990s

1. Cyberspace
2. Webcam
3. Stonewash
4. Hyperlink
5. Frankenfood
6. Portobello
7. Snowboard
8. Website
9. Bluetooth
10. Email

2000s

1. ebook
2. Podcast
3. Sudoku
4. Waterboarding
5. Smartphone
6. Turducken
7. Buzzkill
8. Blog
9. Ringtone
10. Spyware

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ABSTRACT

ASSESSMENT OF THE SEMANTIC KNOWLEDGE NETWORK IN OLDER ADULTS WITH FAMILIAL HISTORY OF ALZHEIMER'S DISEASE

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Current techniques for the treatment of Alzheimer's disease rely on early implementation, which necessitates the need for accurate and early identification of individuals most at risk for future cognitive decline. Research has demonstrated the usefulness of examining the temporal gradient for long-term semantic knowledge in identification of such individuals. The assessment of the temporal gradient within varying levels of knowledge specificity, however, has received considerably less attention. In this study, we aimed to contrast accuracy and reaction times for semantic memory tasks tapping multiple dimensions of semantic specificity from multiple time epochs in adult children with and without a parental history of AD. Two supplementary aims involved: 1) examination of the integrative effects of age of memory (i.e., the temporal gradient) and specificity of information on the organization of famous person knowledge in older adults and 2) whether these effects could also be used to understand the organizational structure of conceptual word knowledge. While no group differences were observed on our novel tasks, we believe that understanding task performance at this stage is of benefit for future studies. The potential use of similar tasks in neuroimaging studies is discussed within the context of literature documenting the utility of brain activation patterns during semantic memory tasks. Finally,

behavioral performance on our tasks indicates that both the age of memory and specificity of knowledge are influential in the organization of semantic networks for person knowledge. Performance on conceptual word knowledge tasks, however, does not produce a similar temporal gradient for long-term memory. We believe that this is due to the integration of episodic/autobiographical networks during recall of person knowledge. Theoretical implications of these findings for understanding the encoding and consolidation processes of long-term memory circuits and hippocampal involvement in semantic memory formation are discussed.

AUTOBIOGRAPHICAL STATEMENT

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Selected Publications and Presentations:

Holcomb, Erin M., Millis, Scott R., Hanks, Robin A. (2012). Measuring Comorbid Disease in Persons with Traumatic Brain Injury: Evaluation of the Modified Cumulative Illness Rating Scale. *Archives of Physical Medicine and Rehabilitation,* 93(8) 1338-1342.

Whitman, R. Douglas, **Holcomb, Erin**, Zanes, Jason. (2010). *Hemispheric Collaboration in Creative Subjects: Cross-Hemisphere Priming in a Lexical Decision Task*. Creativity Research Journal, 22(4) 109 – 118.

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Holcomb, E.M., Zuverza-Chavarria, V., Wang, Z., Lucas, T., Woodard, J.L., & Whitman, R.D. (2011). Lateral cognitive processing and belief updating within a sociopolitical context. Presented at the *39th Annual Meeting of the International Neuropsychological Society*, Boston, MA.

Holcomb, E.M., Woodard, J.L., Calamari, J.E., Dux, M.C., Messina, M., Pontarelli, N., Socha, J., DeJong, B., & Armstrong, K.M. (2011). Serial position effects as predictors for change in global cognition as measured by the Dementia Rating Scale-2. Presented at the *39th Annual Meeting of the International Neuropsychological Society*, Boston, MA.