Predicting Cognitive Decline in Older Adults Through Multi-Voxel Pattern Analysis

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PREDICTING COGNITIVE DECLINE IN OLDER ADULTS THROUGH MULTI-VOXEL PATTERN ANALYSIS

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A Dissertation submitted to the Faculty of the Graduate School,
Marquette University,
in Partial Fulfillment of the Requirements for
the Degree of Doctor of Philosophy

Milwaukee, Wisconsin

July 2014

ABSTRACT
PREDICTING COGNITIVE DECLINE IN OLDER ADULTS THROUGH MULTI-VOXEL PATTERN ANALYSIS

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Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is associated with cognitive and structural decline beyond what is seen in normal, healthy aging. Functional magnetic resonance imaging (fMRI) research indicates that prior to the onset of measureable cognitive impairment, individuals at-risk for AD demonstrate different patterns of neural activation than individuals at lower risk. Thus, differences in task-activated fMRI may be beneficial in predicting cognitive decline at a "pre-symptomatic" stage.

The present study utilizes multi-voxel pattern analysis (MVPA) of baseline fMRI task-related activation to predict cognitive decline, with the hypothesis that famous and non-famous name task activation will discriminate older adults who go on to experience cognitive decline from those who do not. Ninety-nine cognitively intact older adults underwent neuropsychological testing and a semantic memory fMRI task (famous name discrimination). After follow-up neuropsychological testing 18-months later, participants were grouped as "Stable" (n = 65) or "Declining" (n = 34) based on $\geq$ 1.0 SD decline in performance on cognitive measures. MVPA classification accuracy was 90% for stimulus type (famous and non-famous names), thereby supporting the general approach. Mean MVPA classification accuracy for famous and non-famous names was 83% for both the Stable and Declining groups. Finally, MVPA produced greater than chance classification accuracy of participant groups for both famous name activation (56%) and non-famous name activation (55%) as determined via binomial distribution. The results of the current study suggest that MVPA possesses potential in predicting cognitive decline in older adults.

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The normal process of growing older is accompanied by a variety of cognitive and neurostructural changes. Performance in a variety of cognitive domains declines and specific regions of the brain exhibit atrophy. Functional magnetic resonance imaging (fMRI) research indicates that aging is accompanied by changes in patterns of brain activation. Specifically, older adults demonstrate increased activation in specific regions as compared to younger adults (Grady et al., 1994; Grady, McIntosh, & Craik, 2005; Cabeza, 2002). Currently there are three board categories of proposed explanations behind these age-related changes in activation: compensatory, a change in reliance on cognitive networks, and dedifferentiation (Greenwood, 2007; Li, Lindenberger, & Sikström, 2001; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008).

Alzheimer's disease (AD) is a progressive neurodegenerative disorder that is associated with cognitive and structural decline far above that seen in normal, healthy aging. Neuroimaging studies indicate that individuals at-risk for AD demonstrate different patterns of neural activation than individuals at lower risk (Bassett et al., 2006; Bondi, Houston, Eyler, & Brown, 2005; Lind et al., 2006; Seidenberg et al., 2009b). These changes in task-related fMRI may be beneficial in predicting future cognitive decline in asymptomatic individuals (Bookheimer et al., 2000; Woodard et al., 2010). Previous studies examining AD and prediction of cognitive decline primarily rely on univariate approaches to BOLD analysis. Multivariate approaches to fMRI analysis provide several benefits over univariate analysis, such as the ability to examine patterns of activation as compared to univariate clusters of activation (Hanke, Halchenko, Haxby, & Pollmann, 2010). The current proposed study will use the multivariate approach of

multi-voxel pattern analysis in examining the ability of task-activated fMRI to predict cognitive decline in healthy older adults.

Cognitive Theories of Aging

Neuroanatomical and Cognitive Age-Related Changes. Normal aging is accompanied by a variety of well-established structural and functional changes. Magnetic resonance imaging (MRI) can provide valuable in vivo insight into the structural changes that accompany aging. MRI research indicates that older adults experience a gross reduction in brain weight and volume and a reflective increase in ventrical and sulcal size (Raz & Rodrigue, 2006). This reduction in size is associated with a decrease in synaptic density. Neocortical synaptic density steadily declines, starting in early adulthood and continues to decrease over the course of the lifespan (Terry & Katzman, 2001). Starting at age 30 and continuing through death, an individual experiences an estimated 14% volume loss in grey matter and 26% loss in white matter over his or her lifetime (Jernigan et al., 2001). Furthermore, aging is often associated with subcortical and periventricular white matter hyperintensities (WMH). These bright spots on MRI (i.e., WMH) are representative of axonal loss, demyelinization, dendritic loss and vascular damage (Minati, Grisoli, & Bruzzone, 2007). Correspondingly, WMH are associated with declines in cognitive functioning (Murray et al., 2010).

Age-related changes do not follow a linear progression over time. Instead, structural changes associated with aging accelerate exponentially over the course of the lifespan. A common method for measuring a decrease in brain size is through increases in ventricle size. Younger adults demonstrate an annual increase in ventricular volume of

0.43% while older adults displayed a significantly higher rate of 4.25%. (Raz & Rodrigue, 2006). Correspondingly, white matter volume declines in adulthood, decreasing at an exponential rate over the lifespan (Raz et al., 2005). This decrease in myelinated white matter equates to a drop off in the speed and efficiency of processing information as well as creating a disconnection between neural networks (Bartzokis & Lu, 2009).

Different regions of the brain undergo age-related volume loss at different rates. Brain regions that are the last to myelinate in development are also the first to decline with age. The prefrontal cortex (PFC) and medial temporal lobe appear to be vulnerable to this decline process (Raz & Rodrigue, 2006). The PFC is the anterior region of the frontal lobes and is integral in executive functioning as well as a variety of other cognitive functions (Rajah & D'Esposito, 2005). In the PFC, the aging process is associated with decreases in both grey and white matter volume along with increases in WMH, which are often seen first in the anterior regions before gradually progressing posteriorly (Craik, 2006; Drag & Bieliauskas, 2010; Murray et al., 2010). The volume of the PFC decreases at an estimated rate of 5% every ten years, starting at age 20 (Raz et al., 2004).

Similarly, the medial temporal lobe (MTL) often displays an age-related decrease in volume. With respect to structures within the MTL, the hippocampus demonstrates the largest effect from aging. The hippocampus is a structure in the MTL importantly involved in the formation of new memories (Winocur, Moscovitch, & Bontempi, 2010). Longitudinal studies of the hippocampus indicate that it shrinks at a rate of 1.23% per year over the entire life span. However, hippocampal volume does not decrease at a

linear rate over time. Hippocampal shrinking occurs at a modest rate of <1% before the age of 50 (Good et al., 2001; Raz et al., 2004). At approximately age 55, hippocampal volume declines at an exponentially faster rate, with healthy older adults demonstrating decreases in volume of 1.7% per year (Raz & Rodrigue, 2006; Walhovd et al., 2005). Functional imaging studies show corroborating findings of decreased activity in the hippocampus of older adults during memory tasks as compared to younger adults, suggesting a breakdown in hippocampal integrity (Park et al., 2003).

In conjunction with neuroanatomical changes related to aging, older adults tend to decline in a variety of cognitive domains (Carlson et al., 2008; Reuter-Lorenz & Park, 2010; Salthouse, 2010; Buckner, 2004). While there are individual variations, these changes in cognition are fairly uniform and ubiquitous (Salthouse, 2010). While the next section is organized by neuroanatomical regions, it is acknowledged that classifying cognitive variables strictly by neuroanatomical correlates is an oversimplification and implies a one-to-one ratio of cognitive domain and brain anatomy. Instead, cognitive functioning is undoubtedly the result of a dynamic relationship between brain regions, acting in synchrony to perform complex tasks (Wen et al., 2011). However, for conceptual reasons and continuity, the following section is organized by gross anatomy.

One of the first sets of cognitive processes that decline with age is governed by the frontal lobes (Head, Snyder, Girton, Morris, & Buckner, 2005). The frontal lobes are ubiquitous in cognitive operations, responsible for attention, working memory, and executive functioning (Buckner, 2004). Older adults often report a decline in their ability to pay attention, a process mediated by an area of the frontal lobes known as the prefrontal cortex (PFC) (Postle & Pasternak, 2009). The inability to inhibit certain

stimuli and maintain selective attention creates difficulties in filtering out and ignoring extraneous information. This includes difficulty inhibiting previously learned material and associations as older adults demonstrate difficulty in inhibiting previous targets of attention and no longer relevant information (Hartman & Hasher, 1991; Nielson, Langenecker, & Garavan, 2002). This may result in older adults being more likely to endorse prior, irrelevant stimuli during memory recall. Also, older adults are more likely to make semantic intrusions during a memory recall task as they have more difficulty inhibiting associated words (Kensinger, 2009). Similarly, the ability to switch back and forth between different tasks declines with age (Drag & Bieliauskas, 2010). This inability to engage and disengage attention is often described by older adults as an inability to multitask or maintain divided attention.

Working memory is also another frontally-mediated process that declines with age. Functioning as the brain's short-term store, it allows the brain to briefly hold and perform mental operations. Requiring not only basic memory but also the ability to manipulate information, working memory is a cognitively and resource demanding process. As one might suspect given its dependence on the frontal lobe, working memory is susceptible to age-related decline, especially as task difficulty increases. For example, performance on the cognitively demanding n-back task, which requires holding information in working memory while attending to current stimuli, declines with age at a greater rate than simpler tasks (Dobb & Rule, 1989). Given the brain's difficulty to shift, attend, filter, and inhibit incoming information, the working memory of an older adult is naturally pushed harder than that of a younger adult.

Processing speed is an additional frontal ability negatively affected by age. Older adults show decreases in processing speed on both a motor and cognitive level (Kensinger, 2009). However, reaction time especially decreases when cognitive resources are taxed. For example, making the decision to brake at a yellow light or continue through an intersection takes exponentially more time than simply stopping at a red light (Kensinger, 2009). Similarly, selectively attending or holding information in working memory significantly decreases processing speed and possibly influences the age-related decline seen in other domains (Park et al., 2003). The processing-speed theory of aging proposes that a decrease in the speed of operations causes most age-related cognitive impairment (Salthouse, 1996). The theory posits that older adults are unable to keep up with the pace of incoming information and have difficulty integrating simultaneously experienced information. Critical operations such as encoding, rehearsal, and retrieval of information are degraded or less accurate because older adults are unable to efficiently process stimuli or activate networks (Salthouse, 1996). The brain loses its ability to process large amount of information in a timely manner, creating a 'waterfall effect' in all other cognitive domains (Salthouse, 1996).

Executive functioning is a higher order cognitive construct, contributing to goal-directed behavior, planning, self-regulation, and the ability to efficiently organize and retrieve information (Drag & Bieliauskas, 2010). Executive functioning relies heavily on the PFC and begins to sharply decline after age 60 in conjunction with the deterioration of the integrity of the region (Elderkin-Thompson, Ballmaier, Hellemann, Pham, & Kumar, 2008; Treitz, Heyder, & Daum, 2007). This decrease in the ability to implement efficient cognitive strategies may have a significant impact on all cognitive domains.

Long-term memory (LTM) is another cognitive domain negatively impacted by age (Albert & Knoefel, 1994). One broad category within LTM is declarative (i.e., explicit) memory, which is the ability to recall facts and events (Brickman & Stern, 2009). Declarative memory can be further broken into semantic, episodic, and source memory. Semantic memory refers to the retention of general facts and knowledge. This type of memory tends to be the most stable memory system across the life span. Compared to episodic memory, semantic knowledge is "crystallized" and tends to increase gradually across the entire life span, showing only minimal decline in late life (Brickman & Stern, 2009; Hedden & Gabrieli, 2004).

Episodic memory refers to the explicit retention and retrieval of personal events (Wheeler & Ploran, 2009). Going beyond semantic memory, episodic memory incorporates the "who, what, where, when," of a specific memory (Brickman & Stern, 2009). While differentiated from semantic memory, the two systems constantly interact (e.g., episodic information binds together to create semantic networks). A significant difference between the two is the sharp age-related decline of episodic memory. Because episodic memory relies heavily on the age-effected medial temporal lobes and prefrontal cortex, older adults often demonstrate difficulty encoding and recalling specific details (Brickman & Stern, 2009). Instead, older adults often rely on cues and recognition instead of explicit recall. Reflective of this, older adults tend to do better on items that have a greater associative and recognition component as compared to free recall (Albert & Knoefel, 1994). Older adults depend on familiarity for memory recall and struggle with explicitly remembering information, often only recalling the gist of a conversation (Craik 2006).

Similarly, older adults often report a decline in the source memory (i.e., recalling the context in which information was learned). For example, older adults perform significantly worse than younger adults at remembering who provided specific information in a conversation as well as details about the individual (Schacter, Kaszniak, Kihlstrom, & Valdiserri, 1991). This inability to effectively recall information may be caused by ineffective encoding and recall due to compromised frontal and hippocampal integrity (Düzel, Schütz, Yonelinas, & Heinze, 2011; Gilsky, Rubin, & Davidson, 2001; Persson et al., 2006).

In summary, age-related changes in cognitive functioning are not uniform across cognitive domains. Episodic recall, attention, and working memory performance often demonstrate the sharpest declines while semantic memory remains relatively stable. This beings said, the interactive nature of memory systems makes it very difficult to parse out the age-related decline of one system from another. Most likely, the age-related cognitive decline is reflective of the anatomical changes associated with aging and each structure's integrated role with cognitive functioning.

Neuroimaging and Aging. One of the most consistent findings in aging research is that older adults display increased brain activation in specific areas relative to younger adults. One of the first neuroimaging studies examining aging involved positron emissions tomography (PET). Grady and colleagues (1994) noted that older adults displayed activation in areas of the brain that was not activated by young adults during the same task. Specifically, there was an unexpected increase in bilateral activation of the PFC during tasks with older adults as compared to younger adults. This pattern of decreased asymmetry is often referred to as the hemispheric asymmetry reduction in

older adults (HAROLD) model (Cabeza, 2002). This reduction in neural asymmetry of activation has been demonstrated across a variety of tasks and cognitive processes including working memory (Reuter-Lorenz et al., 2000), episodic memory (Cabeza et al., 1997), word recognition (Anderson et al., 2002), executive processes (Nielson et al., 2002), and the visual system (Park et al., 2004; Voss et al., 2008).

The HAROLD model lies in direct contrast to the long-standing Right Hemi-Aging model, which states that the right and left hemispheres of the brain are impacted differently by aging. Proponents state that right hemisphere processes decline at a faster rate than the left hemisphere (e.g., spatial abilities decline more rapidly than verbal abilities) (Dolces, Rice, & Cabeza, 2002). This asymmetrical degradation forces older adults to adapt new cognitive strategies, relying primarily on the left hemisphere. While this model accounts for bilateral activation during right lateralized task, the model would predict decreased activation of the right hemisphere during left lateralized tasks. This prediction of unilateral activation has not been supported in subsequent functional neuroimaging findings (Stebbins et al., 2002). Similarly, bilateral activation has been a consistent finding regardless of adaptations of new verbal cognitive strategies by older adults (Logan, Sanders, Snyder, Morris, & Buckner, 2002). In summary, findings to support the Right Hemi-Aging model have been inconsistent, with no clear pattern of lateralization across studies and provide no clear explanation for neuroimaging findings (Dolces et al., 2002; Schear & Nebes, 1980).

Despite proposing a model to predict activation, the HAROLD model does not take a firm position on the underlying cause or functionality of the age-related asymmetry of brain activity. Whether age-related increases in neural activation are beneficial,

detrimental, or inconsequential is an ongoing debate. Currently, there are three broad categories of proposed causes behind the phenomenon: compensation, a change in reliance on cognitive networks, and dedifferentiation.

The compensation theory postulates that age-related increases in neural activation enhances cognitive performance and counter-balances cognitive decline. The frontal lobes in particular are often cited as playing a compensatory role in cognitive functioning and displaying the strongest correlation with age-related overactivation (Cabeza et al., 2004). Concordantly, a multitude of other studies suggest age-related compensatory frontal activation occurs across a variety of cognitive domains including: frontal recruitment during inhibitory tasks (Langenecker & Nielson, 2003; Nielson et al., 2002), ventral and dorsal prefrontal cortex recruitment during memory tasks, and frontal and parietal recruitment during attention tasks (Grady, 2008). Similarly, prefrontal activation has been shown to be associated with a decrease in hippocampal volume, suggesting that the frontal lobes compensate for brain atrophy and degrading networks (Perrson et al., 2006).

Rossi et al. (2004) used transcranial magnetic stimulation (TMS) to investigate the possibility of age-related frontal overactivation playing a beneficial role in cognition. TMS is a technique that involves stimulating an individual's scalp with a magnet, inducing a virtual and temporary lesion by briefly disrupting neural signaling. The authors' findings suggest frontal lobe overactivation plays a role in successful task performance as healthy older participant performance during a memory task was impaired when TMS was administered to either hemisphere. In contrast, young adults only demonstrated impaired performance when the expectedly active region was

temporarily lesioned. This finding suggests that age-related bilateral activation is serving a purpose in cognitive functioning. In another study, healthy older adults with bilateral frontal activation performed better than older adults with unilateral activation on a measure of recall and source memory, suggesting that older adults who engage compensatory activation cognitively perform at a higher level than those who do not (Cabeza, Anderson, Locantore, & McIntosh, 2002).

Another age-related finding consistent with compensation is a reduction in occipitotemporal activation coupled with increased activation in the frontal lobes (Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008). Often referred to as the posterior to anterior shift in aging (PASA), the frontal lobe is presumed to actively compensate for the decrease in processing ability that occurs with age and as correlated with better task performance. In a study by Davis et al. (2008), increased occipital activation was correlated with decreased frontal activation, suggesting a negative relationship between the regions. PASA occurs regardless of task difficulty, suggesting PASA to be an age-related process as compared to a change in cognitive strategies or overstimulation of the networks (Davis et al., 2008).

The theory that the frontal lobes play a compensatory role for other deteriorating brains regions creates an interesting dichotomy because the frontal lobes are one of the first regions to demonstrate decline and atrophy. One consideration is that the frontal lobes allow for a top-down approach to cognitive processing, compensating for other deteriorating cognitive processes (Reuter-Lorenz & Cappell, 2008). This hypothesis also accounts for the increased parietal activation (i.e., poster cingulate activation) often associated with aging; regions important in the ability to guide attention. Secondly, the

activation of prefrontal cortex is often associated with feelings of familiarity. Perhaps as the integrity of the hippocampus declines and explicit memory becomes compromised, older adults begin to depend more on abilities mediated by the prefrontal lobes, such as familiarity and gist (Reuter-Lorenz & Cappell, 2008). This theory is also supported by the maintained ability of older adults to remember the essence of an event despite a decline in explicit memory.

Reuter-Lorenz & Cappell (2008) propose a specific theory to account for the hyperactivation often seen in aging, termed the compensation-related utilization of neural circuits (CRUNCH) theory. Relying heavily on compensation theory, CRUNCH is based on several findings and assumptions. First, both older and younger adults recruit neural resources during cognitive tasks in proportion to task difficulty. In other words, as the task difficulty increases, so does neural activation. Secondly, declining neural efficiency causes older adults to engage compensatory mechanisms earlier than younger adults. By depleting neural resources at lower loads, older adults are left with little cognitive reserve during more difficult tasks. Once the individual's cognitive reserve is exhausted, the compensatory circuits become too taxed and activation reaches a plateau (Schneider-Graces et al., 2010; Stern, 2006). This plateau varies greatly on individual factors as individuals with a greater cognitive reserve (e.g., more education) may reach the limits of their capacity at a much older age than those with less cognitive reserve (Daffner et al., 2011). Concordantly, younger adults tend to use the same regions as older adults when tasks are subjectively comparable in difficulty (Schneider-Garces et al., 2010). This finding suggests that younger and older adults both employ recruitment but older adults need to recruit earlier to perform at a comparable level.

The scaffolding theory of aging and cognition (STAC) proposes another variation on the compensation hypothesis (Goh & Park, 2009; Park & Reuter-Lorenz, 2009). STAC states that in order to combat the neural insults characteristic of aging (e.g., neurofibrillary plaques and tangles), the brain is constantly undergoing neural reorganization. Cognitive performance in older adults is optimized as new neural connections are formed, old ones are recruited, and weakened ones are discarded. In this way, the brain attempts to maintain cognitive homeostasis despite its active deterioration. This reorganization is a process present across the lifespan, facilitating the development of new neural circuits to allow optimal performance. Therefore, scaffolding is not a response to aging but a response to maintain neural efficiency in the face of a cognitive challenge (Park & Reuter-Lorenz, 2009). For example, during the acquisition of a novel skill, neural activity is diffuse and inefficient. Different, more defined regions activate as the task is rehearsed. These new regions presumably provide a more efficient circuitry for skilled performance. However, even during an over learned task, the initial circuitries from when the task was novel are minimally active (Petersen, van Mier, Fiez, & Raichle, 1998). The prefrontal cortex is believed to play an integral part in the learning of novel tasks. STAC posits that as the integrity of the skilled circuitry of the brain becomes compromised, the original prefrontal circuitry is recruited. This inefficiency is further exacerbated as larger areas of the brain deteriorate, resulting in a further need for neural recruitment. As the less efficient networks compensate for the more efficient circuitry, task performance becomes more error prone (Park & Reuter-Lorenz, 2009). Eventually, the brain is unable to employ adequate scaffolding, resulting in significant cognitive decline.

Greenwood (2007) proposed a similar model of aging, stating that neural plasticity allows for functional reorganization in regions experiencing age-related change. As individuals experience decline in specific cognitive domains, changes in processing strategies are necessary to maintain cognitive performance (e.g., relying on top-down encoding). Similar to the neural reorganization that occurs following a stroke or traumatic brain injury, Greenwood proposes that homologous regions gradually compensate for the function of atrophying areas. This suggests that intervention strategies, such as appropriate cognitive training, could result in the innervation of adjacent regions and delay cognitive decline.

Importantly, an alternative theoretical position to the above mentioned compensation models is that the increased activation seen in older adults does not serve a beneficial function. Instead, older adults may not be able to activate networks as selectively as younger adults. As neural connections in older adults break down, hyperactivation occurs in a fairly non-selective manner with no functional benefit (Li et al., 2001). For example, a breakdown in white matter tracts in the corpus collosum may reduce the brain's ability to inhibit less appropriate activation and may account for the bilateral activation seen in the HAROLD model (Sullivan & Pfefferbaum, 2006). A breakdown in effective activation corresponds with deficient neuromodulation, resulting in "noisy" processing (Li et al., 2001). Correspondingly, a decrease in dopamine receptors in the brain appears to modulate cognitive performance on working memory, episodic memory, and processing speed tasks with dopamine binding being a greater factor in performance than chronological age (Backman et al., 2000; Rubin, 1999). Interestingly, a study with primates found that the administration of dopamine agonists

alleviates age-related cognitive decline in older monkeys (Arnsten, Cai, Murphy, & Goldman-Rakic, 1994). Thus, decreased dopamine modulation leads to ineffective cognitive processing (Li et al., 2001). This decrease in effective neural operations alters the signal-to-noise ratio of neural processing and increases the amount of spatial neural activation (Li et al., 2001). Encoding of new information is less efficiently and succinctly represented in the brain due to deteriorating neural networks (Li et al., 2001). While the neural noise theory of age-related increases in activation attempts to provide an interestingly link between neuromodulation, cognitive performance, and neuroimaging, its theoretical prediction of increased activation equating to decreased cognitive performance is not directly supported by current compensatory findings (Rossi et al., 2004).

Another emerging theory attempting to explain overactivation in aging combines components of the compensation and neural noise theories, postulating that increased neural dedifferentiation and an inability to suppress activation (task and non-task related) necessitates the brain to invoke compensatory neural resources (Reuter-Lorenz & Cappell, 2008). In older adults, task-related neural dedifferentiation is correlated with increased frontal activation (Park et al., 2004). Similarly, the large, non-task related default-mode network (DMN) of the brain shows differential activation between old and young adults. Consisting of the posterior cingulate cortex, medial prefrontal cortex, medial temporal, and angular gyrus, the DMN is comprised of regions involved in the integration of semantic processing, self-monitoring, attention, and autobiographical functions (Greicius, Supekar, Menon, & Dougherty, 2009; Supekar et al., 2010). Active when individuals are not directly involved in a cognitive task, this network is suppressed

when cognitive demands are increased. Specifically, the greater the task demand, the less activation one would expect in the DMN. However, older adults display less deactivation (i.e., more activation) of the DMN as compared to young adults (Persson, Lustig, Nelson, & Reuter-Lorenz, 2007). These differences in deactivation are magnified as the difficulty of the task increases. This may account for some of the increased activation seen in regions associated with the DMN that are commonly associated with overactivation or neural noise. Also, given the function of the brain regions associated with the DMN, a decrease in attention and multi-tasking abilities would be predicted, consistent with the cognitive deficits associated with aging (Drag & Bieliauskas, 2010). However, this theory does not take into account the increase in cognitive performance commonly associated with increased activation and is still fairly new in its formulation.

While each aging theory was presented separately, none appear to account for all aged-associated variance in cognitive performance and neural activation. It is possible that these theories are not mutually exclusive and a combination of theories may best account for age-related changes. The CRUNCH theory of aging, proposing active recruitment of neural resources, and the Scaffolding theory of aging, based on a reorganization of neural networks, both espouse neural plasticity and compensation as integral to the process of aging. Even theories seemingly incompatible with a compensation hypothesis, such as neural noise and DMN dysfunction, may play an integral part in conceptualizing age-related activation. It is possible that aging is associated with a complex process of neural changes best explained through several mechanisms. For example, a breakdown of neural networks and neuromodulation may necessitate compensatory reorganization and recruitment in order to maintain cognitive

performance (Reuter-Lorenz & Cappell, 2008). An inability to suppress the DMN may also cause a change in cognitive performance and dictate a change in effective neural functioning (e.g., compensatory reliance on top-down processing). Future research examining the mechanism and function of increased neural activation may provide further insight and provide a complete picture of the presumably complex process of aging.

Alzheimer's Disease

As described earlier, some cognitive decline is expected in aging. However, for some individuals, cognitive decline goes beyond what would be considered normal, healthy aging. Alzheimer's disease is one example of pathological aging associated with increased cognitive decline. This section will review the relevant literature on Alzheimer's disease (AD). Topics to be covered include a brief overview of the disease and its progression, risk factors for developing AD, and neuroimaging findings.

An Overview of AD. AD is a progressive neurodegenerative disorder associated with a decline in cognitive functioning and the ability to perform activities of daily living, eventually resulting in dementia and death (Buckner, 2004). There is increasing evidence that the neuropathological process of AD begins long before its clinical onset, with neurological changes beginning even before the age of 30 (Braak & Braak, 1991; Ghebremedhin, Schultz, Brakk, & Brakk, 1998). Preclinical AD is often characterized by two distinct phases. First, there is a latent period with no cognitive impairment. While asymptomatic, these individuals display abnormal neural activity and increased neuropathology as compared to individuals undergoing normal aging. Increased activation during this stage is often assumed to be compensatory for very early AD-related pathology (Seidenberg et al., 2009b).

The second phase, Mild Cognitive Impairment (MCI), is characterized by a modest impairment in cognitive processing (Petersen et al., 2001). An individual must report subjective cognitive complaints as well as obtain neuropsychological scores 1.5 standard deviations below what would be expected given his or her age and education (Kensinger, 2009). Despite a decline in cognition, activities of daily living and global

cognitive functioning remain intact (Belleville, Sylvain-Roy, de Boysson, & Menard, 2008). This caveat creates a distinction between MCI and a diagnosis of AD. Memory is typically the first domain to decline, resulting in a diagnosis of amnestic-MCI (aMCI). However, some cases first present with mild problems in executive, language, or visual spatial functioning (Brooks & Loewenstein, 2010). These cases are classified as non-amnestic, single, or multi-domain MCI.

A diagnosis of MCI increases the risk of developing AD, which is estimated at 10-15% per year as compared to 1-2% per year for cognitively intact individuals (Petersen, 2004). Individuals experiencing decline across multiple cognitive domains tend to have a faster rate of progression to AD as compared to individuals with focused deficits (Loewenstein et al., 2004). The presence of multiple cognitive impairments may be representative of increased severity of AD related pathology. However, a diagnosis of MCI does not equate to a future diagnosis of AD. Even after a diagnosis at a specialty memory disorder clinic, regression from MCI to non-MCI status ranges from 10-15% (Peterson et al., 1999). There are several possible explanations for this regression. For example, perhaps the diagnosis was a false positive and an individual performed poorly on neuropsychological measures one day but more representative of his or her cognitive functioning on another, demonstrating a regression to the mean. Regardless of the reason, there remains controversy over classifying all cases of MCI as early AD. A diagnosis of MCI occurs when an individual meets criteria for a collection of symptoms. Current technology is not at a point of differentiating MCI as early AD or other disorders which may have similar early stage symptomology (e.g., vascular dementia). Similarly, indicating an individual has converted from MCI to AD is slightly deceiving. The

individual has not changed from one disorder to another, rather, his or her symptoms have crossed a threshold of severity that now meet criteria for AD.

A diagnosis of probable AD requires memory impairment plus a decline in at least one other area of cognition (e.g., attention). These symptoms must be irreversible and impact activities of daily living (Kensinger, 2009). However, a definitive diagnosis of AD can currently only be made by confirming the presence of significant AD-related neuropathology, which is done post-mortem. The progression of AD is gradual with the average patient living 8-10 years after a diagnosis of probable AD (Prince, Woo, Doraiswamy, & Petrella, 2008).

The mesial temporal lobe and hippocampus are the earliest regions to show atrophy with AD (den Heijer et al., 2010; Hirano & Zimmerman, 1962; Scahill, Schott, Stevens, Rossor, & Fox, 2002). The frontal, temporal and parietal cortices are increasingly affected as the disease progresses (Braak & Braak, 1991). The neuropathology must be in excess to the amount seen in normal aging (which also primarily affects the hippocampus and frontal lobes). For example, in AD, the hippocampus shrinks at a rate of 3-4% per year, much higher than the 1.7% decrease seen in same-aged healthy older adults (Jack et al., 2000). Also common in AD is a loss of myelin and cortical thinning along with grey matter atrophy (Bookheimer & Bruggren, 2009; Thompson & Toga, 2009)

Theories on the mechanism of AD. The most commonly cited theory explaining the mechanism of AD is the amyloid hypothesis. The insoluble amino acid Amyloid-β (Aβ) is derived from the breakdown of the amyloid precursor protein and accumulates in extracellular space (Kok et al., 2009). Aβ deposits are also typically found in the brain of

normally aging individuals (Rodrigue, Kennedy, & Park, 2009). However, individuals with AD demonstrate much greater than normal levels of Aβ, more diffusely spread across the brain. The accumulation Aβ deposits and tau proteins are one of the major neuropathological hallmarks of the disease (Arnold, Hyman, Flory, Damasio, & Van Hoesen, 1991; Fennema-Notestine, McEvoy, Hagler, Jacobson, & Dale, 2009). This increase of Aβ deposits is presumed to be the result of an imbalance between Aβ production and clearance (Mawuenyega et al., 2010; Xiong, Yang, Gong, & Zhang, 2010). These excess deposits build-up as plaques in the central nervous system and are theorized to cause synaptic dysfunction and trigger apoptotic cell death (Rodrigue et al., 2009; Yu et al., 2006). Amyloid plaque accumulation begins in the temporal and orbitofrontal cortex, before spreading to the rest of the frontal lobe and into the parietal lobe (Kepe, Huang, Small, Satyamurthy, & Barrio, 2010).

In contrast, tau tangles tend to aggregate first in the transentorhinal (i.e., medial inferior) areas before migrating into limbic, posterior cingulate, parietal and frontal areas (Braak & Braak, 1991). In healthy cells, tau binds to microtubules to stabilize the cell (Lee et al., 2005). However, in AD, tau fails to properly bind and intercellular tau tangles accumulate in neuron bodies, axons, and dendrites, disrupting cell function and eventually death (Moreira, Zhu, Smith, & Perry, 2009). Following cell death, insoluble tau tangles accumulate in the brain and are believed to be central to AD pathogenesis (Lee et al., 2005).

As the aggregation of Aβ deposits and tau tangles are associated with synaptic failure and cell death, the hippocampus and prefrontal cortex are often the first areas of the brain to experience pathological changes, resulting in a decline in memory and

executive functioning (Price & Morris, 1999). Additionally, there is evidence that Aβ deposits gradually impair synaptic plasticity, disrupting memory formation and processing (Haass & Selkoe, 2007). Post-mortem research indicates that tau tangles and amyloid plaques occur as early as middle age in asymptomatic at-risk individuals, implying that the development of AD is a long and insidious process (Braak & Braak, 1991).

However, the amyloid hypothesis has come under recent scrutiny as treatments targeting Aβ have demonstrated mixed results (Castellani et al., 2009; Serrano-Pozo et al., 2010). Also, there is a weak correlation between the amount of Aβ deposits and the level of dementia as large deposits of Aβ may be encountered in individuals who are asymptomatic (Dickson et al., 1992; Price & Morris, 1999). It has been traditionally assumed that these asymptomatic individuals with Aβ deposits are in a stage of preclinical AD, possessing neuropathology that is not significant enough to cause cognitive symptoms.

Opponents of the amyloid hypothesis posit that perhaps the excess Aβ and tau tangles found in individuals with AD is a downstream representation of inflammation and cell cycle dysfunction and not directly tied to etiology (Castellani et al., 2009). Specifically, microglia may undergo a self-sustaining inflammatory response, resulting in an eventual accumulation of neurotoxins, the formation of tau tangles, an accumulation of Aβ, and cell death (Glass, Saijo, Winner, Marchetto, & Gage, 2010). The production of Aβ may be a directly protective response to oxidative stress before becoming pathological, as the accumulation of Aβ (due to a lack of proper clearance of apoptotic cell remains facilitated by a genetic mutation) may perpetuate the inflammation process

(Glass et al., 2010; Hardy & Selkoe, 2002; Moreira et al., 2009). Recent discussion points to a complex AD pathogenesis, incorporating both Aβ-dependent and independent mechanisms (Pimplikar, Nixon, Robakis, Shen, & Tsai, 2010).

Cognition and AD. AD is characterized by a decrease in cognitive abilities above and beyond that of normal aging. There is considerable evidence that the pathological cognitive decline associated with AD is more than simply accelerated aging. Individuals at-risk for late onset AD tend to look cognitively normal up until the age of 65 before diverging from healthy aging (Jorm et al., 2007). Individuals experiencing healthy aging undergo changes primarily in the frontostriatal system and hippocampus, preferentially impacting the PFC. In contrast, AD related pathology involves significant volume loss of the entorhinal cortex, progressing to the hippocampus and cingulate (Hedden & Gabrieli, 2004). Longitudinal studies indicate a gradual cognitive decline, beginning with episodic memory, followed by executive functioning, language, and visuospatial abilities (Bennett et al., 2002; Lambon Ralph, Patterson, Graham, Dawson, & Hodges, 2003).

Episodic memory, which is dependent on the entorhinal cortex and hippocampus, is understandably one of the earliest cognitive domains impacted (Wierenga & Bondi, 2007). Complaints in episodic memory-related performance are often the first symptom of AD and episodic memory rapidly declines over the three years prior to diagnosis of AD (Mickes et al., 2007). Even in individuals diagnosed with MCI, performance on episodic memory measures is often 1.5 to 2 standard deviations below that of healthy older adults (Petersen et al., 1999). Individuals with AD experience difficulty in the effortful encoding of information as opposed to retrieval (Johnson, Storandt, Morris, Langford, & Galvin, 2008). A drop in learning over multiple trials appears to be one of

the more sensitive indicators of early AD and reflects an inability to retain information over time (Brooks & Loewenstein, 2010). Interestingly, memory performance in individuals diagnosed with MCI do not benefit from categorical priming or cueing (Belleville et al., 2008). This lack of improvement despite being provided cognitive strategies is not found in healthy older adults and represents a deficit of encoding, a process dependent on AD-compromised structures such as the hippocampus (Belleville et al., 2008). Support for a deficit of encoding is further provided by studies examining recognition. Individuals with MCI and AD often demonstrate deficits on forced choice recognition and face recognition, indicating information is not encoded as compared to a deficit in retrieval (Dudas, Clague, Thompson, Graham, & Hodges, 2005; Hudson et al., 2006).

Similarly, individuals diagnosed with MCI demonstrate difficulties with source memory and in binding information to its temporal context. In a study by Lowenstein et al. (2004), subjects were presented with a list of 10 common objects. A second list of 10 objects all semantically related to the first list was presented to the subjects. Finally, subjects were asked to recall the first list of objects. Subjects diagnosed with MCI and AD demonstrated more interference from the second list as compared to healthy older adults, reflective of a deficit in efficiently encoding and binding items to their temporal context.

Along with episodic performance, a decline in executive functioning can be seen as early as 1.5 to 3.5 years before a diagnosis of AD (Chen et al., 2001). Deficits in attention and executive functioning may be connected via difficulty in set-shifting and attending to relevant material (Brickman & Stern, 2009). Similarly, significant declines

in other frontal functions like attention, processing speed and working memory are all associated with a diagnosis of AD. Deficits in attention have been indicated as differentiating between patients with a diagnosis of AD and healthy older adults (Twamley, Ropacki, & Bondi, 2006). Previous studies examining working memory and processing speed in individuals with MCI found deficits in the Digit Symbol and Block Design subtests of the Wechsler Adult Intelligence Scale (Flicker et al., 1991). However, both of these tests involve physical dexterity and can be greatly impacted by declines in psychomotor speed as compare to a pure mental processing speed deficit. A more recent study emphasizing verbal measures found significant impairment on several working memory tasks in individuals with AD but selective impairment in MCI (Belleville et al., 2007). Specifically, individuals with MCI demonstrated intact ability on certain inhibitory tasks and working memory deficits on only more difficult trials, indicating that frontal functioning declines slower and more selectively than pure memory encoding in early MCI. However, even early deficits in attention and encoding are detrimental to other cognitive processes and significantly impact functioning as they decline over time.

Visuospatial, semantic, and language abilities, all associated with the parietal and medial temporal lobe respectively, tends to decline later in the progression of the disease. Patients diagnosed with MCI often show decreases on measures of semantic processing, category fluency, word finding ability, and naming (Adlam, Bozeat, Arnold, Watson, & Hodges, 2006; Kramer et al., 2006). Person identification and word retrieval (e.g., remembering the name of an object) is particularly impacted in individuals diagnosed with MCI and AD. While language abilities are not as severely impacted as other domains (e.g., episodic memory) early in the progression of AD, recent reports indicate

language tasks have the ability to predict a diagnosis of AD six years a priori in asymptomatic individuals (Rosen et al., 2005).

Individuals with a diagnosis of MCI demonstrate a significantly pronounced decline in semantic memory as compared to those experiencing healthy aging and demonstrate a deficit in the retrieval of semantic knowledge along a gradient (Hodges & Patterson, 1995; Seidenberg et al., 2009a). Remote information is more easily remembered as compared to recent information, suggesting a difficulty in encoding and integrating new information into previously formed networks (Seidenberg et al., 2009a). Anatomically, recent semantic information invokes activity in regions directly impacted by AD, such as the hippocampus (Douville et al., 2005) and entorhinal cortex (Haist, Bowden, & Mao, 2001). A decrease in semantic access is also seen in non-demented adults who are at-risk for AD, suggesting a slow decline in semantic ability over the course of the disease (Seidenberg et al., 2009a). Similarly, Chan and colleagues (1993) argue that individuals with AD experience a breakdown in the structure and organization of semantic knowledge as compared to a deficit in semantic retrieval (Chan, Butters, & Salmon, 1997). This deterioration of semantic networks was found to be predictive of future cognitive decline in individuals diagnosed with AD (Chan, Salmon, Butters, & Johnson, 1995)

While there has been a recent push to discover neuropsychological tests sensitive enough to detect preclinical AD, these individuals are asymptomatic by definition. Among neuropsychological tests, measures examining executive functioning and list learning have demonstrated the most promise in predicting future decline but are also imperfect predictors (Chen et al., 2000).

Risk Factors for AD. Research indicates that not all individuals possess an equal predisposition to developing AD. A history of head trauma, depression, a low level of education, exposure to toxins, and diabetes are all environmental and health risk factors related to an increased risk for developing AD (Muller-Spahn & Hock, 1999). Similarly, increased age and being female, hypothesized due to decreased estrogen following menopause, increases the risk of developing AD (Webber et al., 2005). There are currently three commonly accepted genetic risk factors for AD: an inherited genetic mutation, the presence of an APOE ε4 allele, and an unknown genetic contribution associated with possessing a family history of AD (Bookheimer & Burggren, 2009).

The inherited genetic mutation is commonly associated with cases of AD occurring before the age of 65, also known as early-onset AD (Mayeux, 2010). The early-onset autosomal dominant inherited mutation is associated with the presenilin-2 (PS-2) gene on chromosome 1, the presenilin-1 (PS-1) gene on chromosome 14, and the amyloid precursor protein (APP) gene on chromosome 21 (Bookheimer & Burggren, 2009). A mutation on any of these genes results in an overproduction or inability to clear beta amyloid, resulting in plaques, neurofibrillary tangles and subsequent cognitive decline (Bookheimer & Burggren, 2009). While mutations on each gene result in similar pathology, each one presents with a slightly different variation. A mutation of the PS-1 gene is not only associated with early-onset AD but also Pick's disease, frontotemporal dementia, and many other diseases (Bertram, Lill, & Tanzi, 2010). The PS-1 has also been associated with hippocampal hyperactivation during memory encoding, suggestive of presymptomatic AD-related changes (Quiroz et al., 2010). A mutation of the PS-2 gene on chromosome 1 presents a slightly more variable age of onset than PS-1 and APP

(Levy-Lahad et al., 1995). A mutation of the APP gene results in a somewhat different presentation, with an emphasis on vascular features (Basun et al., 2008).

While early onset AD makes up only 5% of all cases of AD, its occurrence can be predicted through genetics and its etiology is better understood than the form of AD that occurs later in life (Bookheimer & Burggren, 2009). Clinically, the presentation is very similar to the more commonly known late-onset AD (AD occurring after the age of 65) with a continual decline in cognitive functioning followed by an impairment in activities of daily living. Given its strongly genetic component, prediction of who will develop early-onset AD is easier and onset of the disorder occurs at a significantly younger age—typically in the 40's and 50's (Bookheimer & Burggren, 2009).

Late-onset AD is often associated with the presence of one or both copies of the ε4 allele on the apolipoprotein-E (APOE) gene (Saunders, 1993). The APOE gene is found on chromosome 19 and associated with amyloid and tau production (Bookheimer & Burggren, 2009; Bookheimer et al., 2000). APOE is a lipoprotein that removes cholesterol from the blood and carries it to the liver as well as being involved in neuronal development and repair. APOE consists of a pairing of ε2, ε3, or ε4 alleles. There is evidence that the ε2 allele provides an unknown protective factor against AD and cognitive decline (Corder et al., 1994; Wilson, Bienias, Berry-Kravis, Evans, & Bennett, 2002). The ε3 allele is the most common (75% in Caucasians) and individuals possessing this genotype are considered to be at a neutral risk for AD (Finch & Sapolsky, 1999). The ε4 allele is associated with cardiovascular disease, poor outcome following TBI, and age-related cognitive impairment (Filippini et al., 2009). Further, APOE ε4 is also associated with the presence of senile plaques, neurofibrillary tangles, and increased risk

for AD (Ghebremedhin et al., 1998; Kok et al., 2009). In a recent study, individuals possessing APOE ε4 demonstrated increased levels of senile plaques as compared to ε4 negative individuals by the age of 30 years old. By age 60, 40.7% of ε4-carriers possessed senile plaques as compared to only 8.2% of ε4 negative subjects (Kok et al., 2009). Individuals with an ε4 allele are 3-4x more like to develop AD than those without and experience an earlier and faster cognitive decline (Martins, Oulhaj, de Jager, & Williams, 2005; Saunders et al., 1993). The allele is strongly associated with decreased hippocampal, amygdala, entorhinal, parahippocampal, and temporal pole volume in older adults (Biffi et al., 2010; Reimann et al., 1996). Also, parietal and hippocampal atrophy has been found in individuals possessing an APOE ε4 allele as young as 40-years-old, suggesting that ε4 is associated with neural changes long before the onset of clinical symptoms (Tohgi et al., 1997). The presence of an ε4 allele works in a dose dependent manner, with individuals possessing the 4/4 genotype at greater risk than those with only one ε4 allele, who are at still greater risk than those that do not possess any (e.g., 3/3 genotype). Interestingly, possessing a 2/4 genotype creates a neutral risk for AD, similar to that of the 3/3 genotype. Still, APOE status is an imperfect predictor as only 20% of individuals with an ε4 allele will develop AD in his or her lifetime (Bookheimer & Burggren, 2009).

While APOE ε4 has been associated with a variety of deleterious effects in aging, there is controversy that it may serve a beneficial purpose during the lifespan (Han & Bondi, 2008). In younger individuals, APOE ε4 is associated with increased episodic memory performance and more efficient use of neural resources during a functional neuroimaging task (Mondadori et al., 2006). Also, the ε4 allele has been associated with

higher IQ scores and better performance on a variety of neuropsychological measures in younger adults (Yu et al., 2001; Han et al., 2007). Han & Bondi (2008) propose that APOE ε4 is an antagonist pleiotropic gene (i.e., its expression results in both beneficial and detrimental effects that vary with age). The authors posit that younger adults possessing an ε4 allele experience a boost in frontal-executive processes. Over time, these same individuals begin accumulating plaques and tangles which begin to interfere with neurological functioning. In older age, ε4 individuals compensate for cognitive decline by invoking the frontal circuitry solidified in young age. While intriguing, future research and longitudinal studies are necessary to test the merit of this hypothesis.

A family history of AD also appears to be a significant risk-factor. Individuals with one first degree relative diagnosed with AD demonstrate twice the likelihood to develop AD as those without. Those with two first degree relatives demonstrate an eight-time higher occurrence of AD (Devi et al., 2000; van Duijin et al., 1991). The unknown genetic component family history contributes to risk for AD occurs above and beyond the APOE ε4 gene and impacts brain functioning before clinic onset. At-risk asymptomatic offspring of individuals with late-onset AD (unrelated to APOE status) demonstrate differences in activation during both memory encoding and recall as compared to healthy subjects without a family history of AD (Basset et al., 2006). Similarly, a family history of AD is associated with decreased white matter integrity in asymptomatic individuals as young as 50-years of age (Bendlin et al., 2010). A family history of AD appears to provide a unique contribution to risk for AD and there is evidence that family history and APOE ε4 may interact in a dose-related manner with individuals possessing both risk

factors showing increased AD-related pathology and aberrant activation (Ridha et al., 2006; Seidenberg et al., 2009b).

fMRI activation from at-risk to AD. A growing body of evidence suggests that individuals who are at-risk for AD demonstrate aberrant activation in specific brain regions (Pike et al., 2007; Wierenga & Bondi, 2007). Often, hyperactivation occurs in regions critical in semantic and episodic encoding and retrieval, both systems affected early in the process of AD (Bondi et al., 2005; Seidenberg et al., 2009b). In a study by Wishart et al. (2006), APOE ε4 carriers demonstrated increased bilateral frontal and parietal activation despite equivalent performance during an auditory verbal learning task. Other studies support this finding with asymptomatic individuals at-risk for AD invoking greater bilateral prefrontal activation than matched controls, presumably to compensate very early AD pathology (Han et al., 2007a). This pattern of hyperactivation in selective regions (i.e., temporal, parietal, and frontal lobes) is also seen in ε4 carriers during episodic visual encoding (Bondi et al., 2005). Similarly, asymptomatic individuals with a family history of AD (yet negative for APOE ε4) demonstrate increased activation in the frontal and temporal lobes (Bassett et al., 2006; Johnson et al., 2006).

Interestingly, this pattern of task-related hyperactivation is not uniform across the brain. A study by Lind et al. (2006), reported reduced activation in select regions in asymptomatic ε4 carriers during a semantic task. Specifically, individuals displayed decreased activation in the left inferior parietal cortex and bilaterally in the anterior cingulate. The right hippocampus expressed diminished response concerning the novelty of a stimulus. Similarly, a recent study by Adamson and colleagues (2011) found

decreased hippocampal activation during a simple spatial encoding task in asymptomatic ε4 carriers. These findings are consistent with previous studies indicating very early hippocampal atrophy in at-risk individuals and deficits in the encoding of novel information seen in AD (Belleville et al., 2008; Toghi et al., 1997). Also, the right hippocampus is less sensitive in differentiating familiar and novel stimuli and ε4 carriers tend to activate the right hippocampus to a greater degree than the left (Bondi et al., 2005; Wierenga & Bondi, 2007).

Healthy older adults possessing an ε4 allele demonstrate increased activation during tasks in regions impacted by AD outside memory encoding and retrieval. Asymptomatic APOE ε4 positive older adults demonstrate increased activation in the fusiform gyrus, bilateral medial prefrontal cortex, and perisylvian fissure during a confrontational naming despite equivalent performance (Wierenga et al., 2010). These regions, all believed to be integral in language, are also selectively attacked in early AD. Working memory tasks, another cognitive domain significantly impacted by AD, also invoke increase frontal and parietal activation in individuals possessing an ε4 allele (Filbey et al., 2006).

As the disease progresses, hyperactivation in AD-related regions often progress to hypoactivation (Dickerson et al., 2005; Machulda et al., 2003; Small, Perera, de La Paz, Mayeux, & Stern 1999; Sperling, 2007). The medial temporal lobe, an area showing increased task-related activation in those at-risk for AD, demonstrates significantly decreased activation in individuals diagnosed with MCI or AD in comparison to healthy older adults (Machulda et al., 2003). The hypoactivation seen later during AD is often conceptualized as corresponding to a depletion of cognitive reserve (Stern, 2006). As the

neuropathological burden becomes too great, neuronal recruitment significantly decreases and subsequently, cognitive performance (Buckner, 2004; Sperling, 2007). However, this pattern of hypoactivation is not ubiquitous across the brain, as compensatory recruitment occurs even in mild stages of AD (Celone et al., 2006). Similar to the hypothesized compensatory activity seen in healthy aging, individuals with a diagnosis of probable AD demonstrate prefrontal recruitment during episodic and semantic memory tasks, with higher neural activity in these compensatory regions correlating with better task performance (Grady et al., 2003).

As in healthy aging research, the functionality or cost related to hyperactivation is debated. In a study by Starr et al. (2005), participants with a diagnosis of probable AD and healthy older adults were presented with an episodic/working memory task and a semantic memory task, both gradually increasing in difficulty. In both tasks, patients with probable AD recruited brain regions for easier tasks concordant with brain regions recruited by healthy controls during more difficult tasks. These findings appear to support the CRUNCH theory of aging, suggesting a common mechanism of recruitment regardless of age-related or AD-related pathology (Reuter-Lorenz & Cappell, 2008).

Using Neuroimaging to Predict Future Cognitive Decline

There has been a tremendous push in AD research to find a way to intervene and slow down the progression of the disease. Estimates indicate that there are currently 35.6 million people currently living with dementia worldwide, with AD accounting for the majority of those cases. Further projections suggest that 86 million people worldwide will suffer from AD by the year 2050 (Alzheimer's Disease International, 2009). There is currently no cure for AD and treatments are generally limited, emphasizing slowing down the progression of the disease as compared to a reversal. Detecting and diagnosing AD before clinical onset would allow the possibility of intervention before the presence of irreversible pathology. Given its occurrence late in life, a delay in onset of five years could equal a decrease of 50% in AD prevalence while a delay of 10 years would make the disease virtually irrelevant (DeKosky & Marek, 2003). As the current commonly cited risk-factors (a family history of AD and the presence of APOE4) are imperfect predictors, the need for an increased ability to predict who will and who will not develop AD is paramount. Task-activated fMRI has shown promise for predicting cognitive decline.

Functional Magnetic Resonance Imaging (fMRI). fMRI examines the correlation of increased blood flow following neural activation, providing an indirect measure of task-related neural activity. The magnetic resonance imaging technique most often used to examine brain function is BOLD (blood oxygenation level dependent) contrast (Amaro and Barker, 2006). BOLD fMRI is based on the correlation between neuronal activation and blood flow to the activated region, which is accompanied by increases in oxyhemoglobin concentration (Huettel et al., 2008).

fMRI appears to be particularly sensitive at detecting early changes in neural activity associated with AD (Sperling, 2007). By stressing brain networks that are susceptible to AD, task-activated imaging potentially detects very early pathology. Asymptomatic individuals possessing a genetic risk and/or a family history of AD show increased BOLD activation in regions affected early in the progression of the disease (e.g., hippocampus, prefrontal, and parietal regions) (Bondi et al., 2005; Houston et al., 2005). Episodic and semantic memory related activation is commonly used to tap these compromised networks. In a study by Bookheimer et al. (2000), individuals possessing an ε4 allele demonstrated increased episodic task activation as compared to those possessing an ε3 allele. Furthermore, these at-risk individuals demonstrated a greater cognitive decline at a one-year follow-up, suggesting increased activation in regions affected early in the progression of AD is predictive of future cognitive decline. In another study using an episodic task (visual encoding), greater activation in the hippocampus in individuals diagnosed with MCI was predictive of greater cognitive decline at a 5-year follow-up (Miller et al., 2008). These changes in activation occur before the detection of any structural changes, suggesting that fMRI may be more sensitive to identifying early AD than structural MRI examining solely differences in volume (Lind et al., 2006; Miller et al., 2008; O'Brien et al., 2010; Persson et al., 2006; Seidenberg et al., 2009b; Smith et al., 2005).

Individuals with MCI and AD frequently demonstrate a disruption in semantic processing and organization (Chan et al., 1993; Seidenberg et al., 2009a). This is not surprising given the proclivity of AD to impact the PFC and MTL, both regions integral in the processing and retrieval of semantic information. In a study by Chan et al. (1995),

semantic network integrity significantly predicted cognitive decline in patients with AD over a one-year interval. Similarly, a recent study indicated poor performance on the semantic task of famous face recognition was predictive of conversion to AD at a two-year follow-up (Estevez-Gonzalez et al., 2004). Despite its predictive quality, semantic performance declines less consistently as compared to episodic performance (Hodges & Patterson, 1995). This is suggestive of the diffuse and robust nature of semantic networks. Cognitive performance on semantic tasks remains relatively preserved as compared to episodic performance yet semantic activation differences are seen between asymptomatic at-risk older adults and healthy controls (Seidenberg et al., 2009b).

Neuroimaging combined with other biomarkers have been examined as predictors of future cognitive decline. Using a logistic regression, Woodard et al. (2010), reported the presence of APOE ε4 and decreased semantic activation as the most effective combination of factors for predicting cognitive decline in older adults. These two variables predicted cognitive decline more accurately than a family history of dementia and the structural MRI based predictor of hippocampal volume.

Multi-Voxel Pattern Analysis (MVPA). Pattern classification algorithms provide an alternative to traditional fMRI univariate analysis. Based within computer science, pattern classification takes known items from a data set and creates rules that can efficiently categorize new items (Huettel et al., 2008; O'Toole et al., 2007). One such technique, multi-voxel pattern analysis (MVPA) is a multivariate classification technique that examines patterns of activation related to a stimulus type or cognitive state.

While both MVPA and traditional subtraction fMRI analysis rely upon changes in BOLD activation, there are fundamental differences between the two approaches.

Traditional BOLD analysis aims to detect regional differences of activation that infer the involvement of a region in a task (Mur, Bandettini, & Kriegskorte, 2009). Individual voxel differences are examined using univariate statistics, directly comparing the activation of a given region across conditions (Kriegeskorte, Goebel, & Bandettini, 2006). Regions are assumed to activate broadly and areas of activation are coalesced into clusters, further decreasing the spatial sensitivity of the analysis. Furthermore, the univariate analysis of fMRI data through t-tests relies on the assumption that the activation of a voxel is independent of other voxels, which is not necessarily true (O'Toole et al., 2007).

In contrast, MVPA examines content-related patterns of activation through multivariate statistics (Hanke et al., 2010). The analysis is information-based, focusing on which patterns of activation (as compared to regions) represent an experimental condition. Therefore, there is no need for large cluster of activation thresholds and differences in activation between neighboring voxels can be examined rather than negated within an ROI (Huettal, 2008). MVPA works under the assumption that cognitive dimension *x* is represented by brain activity *y* by measuring how much the pattern of neural activity *y* changes as a function of *x* (Norman, Polyn, Detra, & Haxby, 2006).

MVPA is based on the theory that performing a cognitive function (e.g., recalling a specific event) involves reactivating a specific constellation or network of neurons. These networks of activation can be examined using fMRI, identifying unique condition-based patterns of activity (Cox & Savoy, 2003; Polyn, Natu, Cohen, & Norman, 2005). Within a condition, voxels that significantly activate more frequently are assumed to

share a common characteristic (e.g., activate only for faces) (Haynes & Rees, 2006). Previous research indicates that MVPA can effectively characterize stimulus color and motion in the visual cortex (Seymour, Clifford, Logothetis, & Bertels, 2009), representations of faces and objects in the ventral temporal cortex (Haxby et al., 2001), and differences in visual cortex activation between older and younger adults (Carp, Park, Polk, & Park, 2011).

The process of MVPA is typically divided into several steps (Chadwick, Bonnici, & Maguire, 2012; Mur et al., 2009; Norman et al., 2006; Pereira, Mitchell, & Botvinick, 2009). The aim of the first step is to demonstrate that the neural activation related to the experimental conditions can be discriminated from one another with reasonable accuracy (O'Toole et al., 2007). The data are divided into training and testing sets for analysis. The training set is used to create a classifier (the multivariate classification algorithm) for each group and/or condition. A training set can be delineated through a variety of ways. For example, the data set may be divided with a portion dedicated solely to training and the rest to testing the classifier. Alternately, a leave-one-out approach (described in more detail later) may be employed. The training data are then used to create a decision boundary that classifies patterns of activation as being associated with one variable (e.g., stimulus, group) or another (Huettel et al., 2008; O'Toole et al., 2007).

While there are a variety of different classification algorithms, the majority of MVPA studies rely on linear classifiers. Linear classifiers are more rigid than non-linear approaches, resulting in less overfitting of the data. If a classification boundary is too flexible, overfitting of training data may result in a high rate of classification but a low

discrimination (i.e., data may always appear to match a condition, even if it is not appropriate) (Misaki et al., 2010).

Similarly, the inclusion of too many voxels may result in overfitting and increased noise (Pereira et al., 2009). Understandably, voxels that highly discriminate between conditions result in better classification accuracy (Misaki et al., 2010). By including too many voxels in an analysis, the highly discriminating voxels may become lost in noise. There are several ways to combat the inclusion of too many noisy voxels. One such technique, known as searchlight analysis, examines a specified radius around each voxel and determines how well each block of adjacent voxels differentiate each condition (Kriegeskorte et al., 2006). This technique is optimal for examining small, defined regions of the brain. Another popular and well validated method is to focus the analysis on specific ROIs based on anatomical or functional data (Coutanche, Thompson-Schill, & Schultz, 2011; Etzel, Gazzola, & Keysers, 2009; Pereira et al., 2009). By doing so, the number of voxels used by the classifier is decreased and focused on appropriate regions that allow for best discrimination. Even large ROIs may result in overfitting of data and poor classification accuracy due to the addition of noisy voxels that do not add to the ability of the classifier to discriminate conditions (Misaki et al., 2010). Also, recent findings suggest that focused ROIs may outperform searchlight analysis when examining clinical symptoms severity (Coutanche et al., 2011). Overall, using feature selection results in higher classification accuracy than whole brain analysis. Furthermore, activity based ROIs appear to outperform other discrimination methods (Mitchell et al., 2004).

One popular linear classifier, support vector machine (SVM), creates a decision boundary that optimally classifies each experimental condition then widens the boundary

equally in both directions until it cannot be widened further without including a stimulus data point (See Figure 1 for example) (Mur et al., 2009). These secondarily widened boundaries are known as support vectors (Misaki et al., 2010; Mur et al., 2009). Voxels on either side of the decision boundary are then weighed to best discriminate the two conditions. Simply put, voxels that respond more for one condition than the other are given a corresponding positive weight or negative weight while voxels that respond similarly to both conditions are given a weight of zero (Mur et al., 2009). There are a variety of other classification techniques (e.g., Fisher linear discriminant analysis) that employ different approaches to defining a decision boundary (for further review, see Misaki et al., 2010 or Mur et al., 2009). However, recent research suggests that Linear SVM performs better than a variety of other classifiers with event-related BOLD fMRI (Misaki et al., 2010; Mitchell et al., 2004). Thus, utilizing activity based ROIs to limit voxel selection, then applying a linear SVM for classification appears to offer the most potential for optimal MVPA performance.

For the final step of MVPA, the testing set is examined against the training set to examine at the classifiers ability to correctly classify a given variable. This technique can be used to determine how well a classifier can predict a given stimulus (Norman et al., 2006) or a examine group differences in activation (Carp et al., 2011; Coutanche et al., 2011).

There are several concerns which should be addressed when testing the classifier. As previously mentioned, it is important to be cautious of the regions and number of voxels included in the creation of a classifier in order to prevent overfitting. However, it is also desirable to train a classifier with as much data as possible for it to be efficient and

robust (Pereira et al., 2009). A "leave-one-out" cross validation technique is one such way to decrease the variability of the classifier while avoiding bias. In this approach, one subject is left out of the training run (i.e., the creation of the classifier) and the remaining subjects become the trainers. The ability of the newly created classifier is then tested against the sole subject who was left out of the analysis. The process is then repeated on all subjects, indicating the classifiers accuracy. Doing so prevents each subject's data from biasing the classifier while including as many subjects as possible in the analysis. Theoretically, if a classifier has truly captured the relationship between an independent and dependent variable, it should be able to classify examples it has not seen before at a high specificity (Pereira et al., 2009). Therefore, the null hypothesis would be that a classifier is unrelated to the experimental condition and predicting at chance.

Looking beyond methodological issues, recent research suggests MVPA may be a viable candidate for examining age-related changes in neural activation and cognitive decline. Using MVPA, Carp and colleagues (2011) reported that older adults demonstrate decreased task-related neural specificity as compared to younger adults. Furthermore, decreases in MVPA measures of neural specificity have been correlated with decreased fluid processing ability in older adults, suggesting a relationship between MVPA and cognitive decline (Park, Carp, Herank, Park, & Polk, 2010). However, there is a dearth of further research in regards to using MVPA to predict cognitive decline or examine AD.

Integration of Background Research

Because healthy aging is accompanied by cognitive, structural and neural changes that progress at different rates and AD is characterized by similar but exacerbated changes and slopes of decline, distinguishing possible AD-related changes from healthy aging at the earliest possible point may provide the best prognosis for early intervention. Neuroimaging has shown some promising results at distinguishing these trajectories prior to behavioral symptom onset (Bookheimer et al., 2000; O'Brien et al., 2010; Woodard et al., 2010), but highly effective approaches are still being sought.

Pattern classification algorithms, including MVPA, present an alternative to traditional fMRI analysis, which may be effective in predicting future cognitive decline. The popularity of MVPA has dramatically increased in recent years, yet research has primarily focused on defining methodology and examining specific regions (e.g., visual cortex) with little clinical application. Looking beyond the visual cortex, Carp and colleagues (2011) recently examined differences in the degree of neural distinctiveness between young and older adults using a searchlight methodology. The authors reported increased dedifferentiation in older adults as compared to younger adults in the visual cortex, inferior parietal cortex, and lateral prefrontal cortex, consistent with previous aging research (Reuter-Lorenz et al., 2000; Cabeza et al., 1997; Park et al., 2004). These findings suggest that dedifferentiation occurs fairly globally throughout the aging brain, including regions susceptible to AD. However, at this time MVPA has not been applied to early detection of AD.

The current study proposes examining the ability of MVPA to predict cognitive decline in healthy older adults. A pattern classification algorithm will be used to examine

differences in activation between older adults who experience subsequent cognitive decline at an 18-month follow-up and those who do not. The aims of the current study include:

I. To examine the ability of MVPA to discriminate famous and non-famous names in healthy older adults.

II. To examine the ability of famous and non-famous names for classifying older adults who go on to experience cognitive decline or remain cognitively stable.

The hypotheses that will be tested in the current study are as follows:

I. MVPA of famous and non-famous names will demonstrate differential patterns of activation in healthy older adults.

II. Using MVPA, famous and non-famous names will discriminate older adults who go on to experience cognitive decline from those who do not.

Method

Participants. The participants included in this analysis are part of an ongoing longitudinal study. Healthy older adults between the ages of 65 and 85 years were recruited to participate in the study through local newspaper advertisements. Of the 459 individuals screened, 99 participants met the study inclusion criteria, agreed to provide a blood sample for APOE genotyping, undergo neuropsychological testing, and undergo the event-related fMRI task. Participants were excluded if they reported a history of neurological disease, medical illness that may affect brain functioning (e.g. hypertension), a psychiatric disturbance or substance abuse meeting DSM-IV Axis I criteria, a Geriatric Depression Scale score greater than 10 (falling in the depressed range), neuropsychological scores falling out of the cognitively intact range (see cognitive testing) or the current use of psychoactive medication. Genotyping was determined using PCR method (Saunders et al., 1996) and DNA was isolated with Gentra Systems Autopure LS for Large Sample Nucleic Acid Purification. Exclusion criteria related to the fMRI included pregnancy, weight appropriate for height, ferrous objects within the body, claustrophobia, and an inability to see the task stimuli in the scanner. Only right-handed participants were included based on the Edinburgh Handedness Inventory (Oldfield, 1971).

Cognitive Testing. All participants underwent neuropsychological testing on the same day of their scanning in order to evaluate cognitive status. All subjects were required to be within the cognitively intact range to be included in the study. Tests include the Mini-Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975), the Dementia Rating Scale -2 (DRS-2; Jurica, Leitten, & Mattis, 2001; Mattis, 1988), the Rey

Auditory Verbal Learning Test (RAVLT; Rey, 1958), the Geriatric Depression Scale (GDS; Yesavage et al., 1982), and the Lawton Activities of Daily Living Scale (ADLs; Lawton & Brody, 1969).

The DRS-2 measures cognitive functioning in five domains with a maximum score of 144. The RAVLT contains a list of 15 words that are aurally presented to participants over five trials. Following each trial, participants were instructed to recall as many words from the original list from memory as possible. Following the fifth trial, participants were presented a second distractor word list for one trial, and then asked to recall the original list that was previously repeated the five times (Immediate Recall). Following a 30-minute delay, participants were asked to again recall the original list (Delayed Recall).

Cut-off scores that resulted in exclusion from the study were: a score less than 28 on the MMSE, a score of greater than 1.5 standard deviations below the mean for the participants age and gender on the RAVLT Delayed Recall and Long Term Percentage Retention, an age and education corrected MOANS on the DRS-2 that fall in the demented range (Lucas et al., 1998), and ADLs scores outside the normal range. Eighteen months later, the participants underwent the same neuropsychological battery (alternative forms were used on the RAVLT and DRS-2).

Participants were placed into the cognitive declining group based on a $\geq$ 1.0 SD decrease, compared with locally developed norms, on any of the following cognitive tests (primarily episodic measures): DRS-2 total score, RAVLT sum of trials 1-5, or RAVLT delayed recall. Standardized residual change scores were computed for each of the outcome measures to adjust for baseline performance, practice effect, and regression to

the mean. The Cognitively Stable group contained all participants who did not experience a -1.0 SD decline on outcome measures. The value of -1.0 SD as a cut-off for cognitive decline represents a decrease in functioning that, yet while not clinically significant, has been shown to be associated with smaller hippocampal volumes at baseline, differential patterns of fMRI BOLD activation, and a higher incidence of APOE ε4 (Hantke et al., 2013; Seidenberg et al., 2013; Woodard et al,. 2010). Differences in APOE ε4 status, a family history of AD, gender, age, and education and group membership was examined through t-tests.

Image Acquisition. Whole-brain, event-related functional MRI was conducted on a General Electric (Waukesha, WI) Signa Excite 3.0 Tesla short bore scanner equipped with a quad split quadrature transmit/receive head coil. Echoplanar images were collected using an echoplanar pulse sequence (TE = 25 ms; flip angle = 77 degrees; field of view (FOV) = 24 mm; matrix size = 64 x 64). Thirty-six contiguous axial 4-mm-thick slices were selected to provide coverage of the entire brain (voxel size = 3.75 x 3.75 x 4 mm). The interscan interval (TR) was 2 seconds. High-resolution, three-dimensional spoiled gradient-recalled at steady-state (SPGR) anatomic images were acquired (TE = 3.9 ms; TR = 9.5 ms; inversion recovery (IR) preparation time = 450 ms; flip angle = 12 degrees; number of excitations (NEX) = 2; slice thickness = 1.0 mm; FOV = 24 cm; resolution = 256 x 224). Foam padding was used to reduce head movement within the coil.

fMRI task: The event-related scanner task consisted of the presentation of 30 easily recognized names of famous persons and 30 names of non-famous persons. The study consisted of three separate versions of the scanner task, with each participant being

randomly assigned to view one of three different sets of famous and non-famous names. 180 stimuli (90 famous and 90 non-famous including all 3 versions of the task) were selected from a pool of 784 names based on participants' ability to correctly classify the stimuli as famous or non-famous. All selected stimuli demonstrated a >90% successful classification rate in healthy older adults (Douville et al., 2005). Participants were instructed to press a button with their right index finger if the name was famous and their right middle finger if the name was not famous. Stimuli were each presented for 4 seconds with randomly interspersed 4 second intervals of a centrally placed fixation crosshair to introduce jitter, thereby allowing improved deconvolution of the individual response trials. During the presentation of the fixation crosshair, participants were not asked to respond. The study began and ended with a 12-second fixation. The total time for a single imaging run was 5 minutes 24 seconds. The order of the stimuli was counter-balanced among groups. Using a high accuracy, low effort semantic memory task allows for maintained performance even in older adults (Douville et al., 2005). Furthermore, the current semantic task has been shown to activate regions associated with early AD (Seidenberg et al., 2009b; Woodard et al., 2009).

Image Analysis. The Analysis of Functional NeuroImages (AFNI) software package (Cox, R. 1996) was used to generate functional images. Each image time series was time shifted to the beginning of the TR and then spatially registered to reduce the effects of head motion using a rigid body iterative linear least squares method. A deconvolution analysis was employed to extract a hemodynamic response (HRF) for famous and unfamiliar names from the time-series. Only correct trials were used in the analysis. HRFs were modeled for the 0-16 second period post-stimulus onset. The HRFs

were then transposed so that the value of the HRF at trial onset is zero. Motion parameters were incorporated into the model as nuisance regressors. Calculation of the area under the curve (AUC) was performed by summing the hemodynamic responses at time points 4, 6, and 8 seconds post-trial onset. Anatomical and functional scans were transformed into standard Talairach space (Talairach & Tournoux, 1988) to allow for group comparisons. A 6mm Gassuian full-width half-maximum blur was used to account for anatomical variability between subjects (Op de Beeck, 2010). Despite the pattern-based focus of MVPA, spatial smoothing has been found to slightly increase classification accuracy or have no significant impact, even within subjects (Etzel, Valchev, & Keysers, 2011).

MVPA Analysis. Aging is associated with increased neural activation and neural noise (Carp et al., 2011; Li et al., 2001). In order to boost the signal-to-noise ratio, functional ROIs were used to decrease the number of voxels used in the MVPA. Functional maps were generated across groups using a traditional univariate 3d voxel-wise t-test, creating an OR mask of famous and non-famous names to restrict the analysis to relevant regions. This allowed for the analysis to be focused on regions susceptible to AD and most likely to demonstrate meaningful activation for both conditions. The statistical threshold was established using a Monte-Carlo simulation technique using the AlphaSim program with a *p*-value of .001. A summary description of the methods for Aim 1 and Aim 2 are provided in Table 1.

Aim 1 - MVPA for famous and non-famous names. In order to examine the ability of MVPA to delineate famous and non-famous stimuli-based activation, the AUC for each condition in a scan run was collapsed across subjects then averaged. This resulted

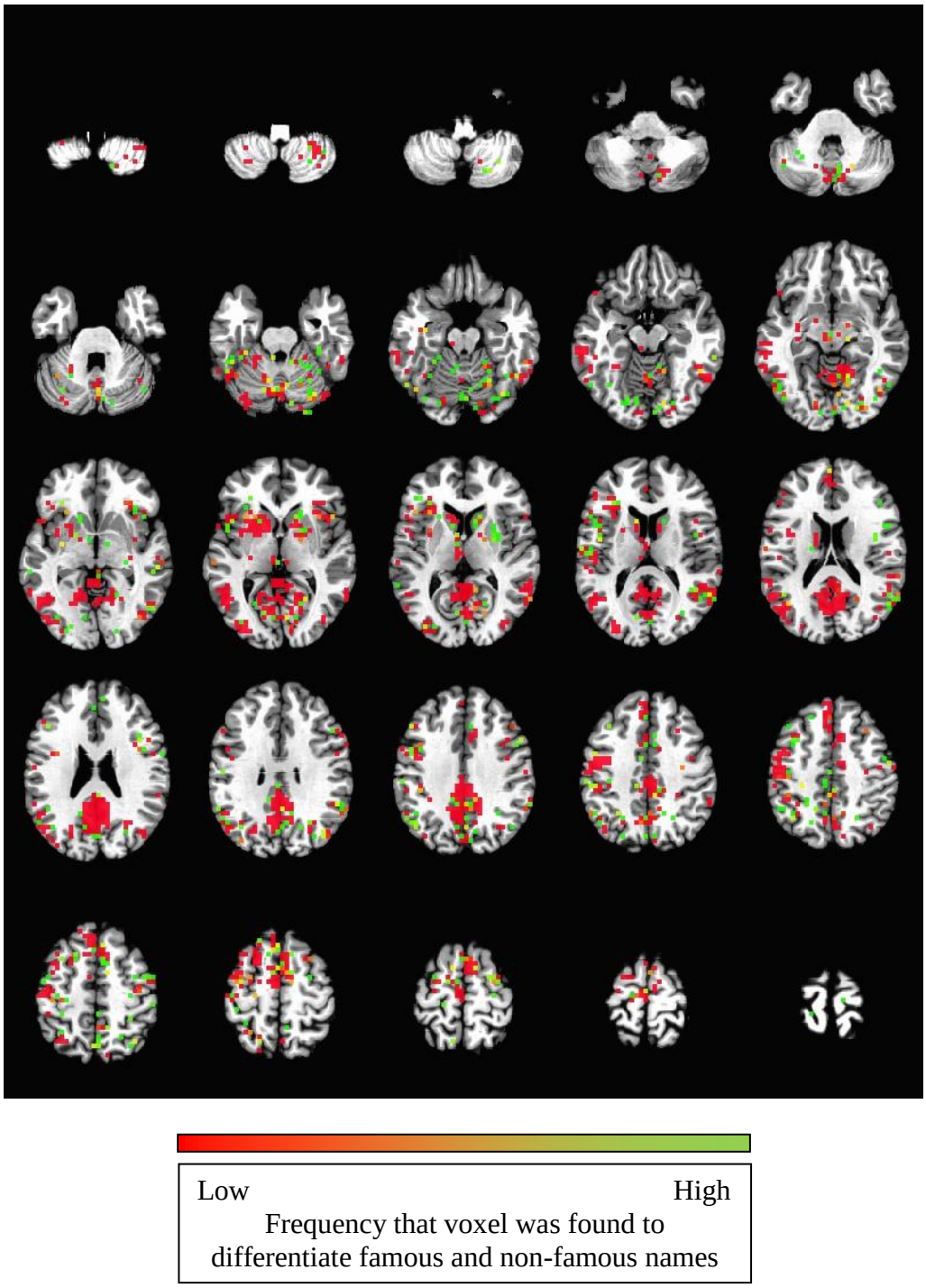
in an average AUC for famous and non-famous names using all180 names (90 famous and 90 non-famous).

A feature selection process was used to select voxels in the previously mentioned OR mask whose signals significantly deviate between the two conditions, utilizing a voxelwise analysis of variance (ANOVA) with a $p = 0.05$ individual probability threshold (Yoon, et al., 2008). Of note, MVPA does not utilize the subtraction methodology traditionally used in univariate fMRI analysis; instead, all voxels showing activation within the OR mask are included in the ANOVA. Based on the results of the ANOVA, the less informative voxels were regarded as noise and removed from the analysis. Results of the feature selection process are shown in Figure 1.

Table 1. Description of Multi-Voxel Pattern Analysis methods.

Aim 1: MVPA of Famous and Non-Famous Names	**Aim 2: MVPA of Cognitive Decline**
Pre-MVPA Steps - Merge all 99 participants - Average AUC for each famous name (90 stimuli) - Average AUC for each non-famous name (90 stimuli)	**Pre-MVPA Steps** - Participants separated into Stable and Declining groups - Famous name AUC averaged for each participant - Non-famous AUC averaged for each participant
MVPA - Insert stimuli into MVPA as regressors - Focus MVPA by running feature selection within OR mask - Test ability of MVPA to classify stimulus type (famous vs non-famous names) using leave-one-out methodology. 1. Leave one averaged stimulus file out of the training run 2. Test the ability of the newly created classifier's accuracy against this stimulus file 3. Repeat for all famous and non-famous names (180 repetitions) - Examine summarized classifier accuracy	**MVPA** - Insert stimuli into MVPA as regressors - Focus MVPA by running feature selection within OR mask - Test ability of MVPA to properly classify participants into Stable/Declining groups using leave-one-out methodology. 1. Leave one averaged participant file out of the training run 2. Test the ability of the newly created classifier's accuracy against this participant's file 3. Repeat for all participants (99 repetitions) - Examine summarized classifier accuracy - Perform entire process for both famous and non-famous names.

Figure 1. Aim 1 classification maps based on the feature selection process for famous and non-famous name stimuli. The montage is the result of merging all 177 feature selection masks (i.e., all presented stimuli, both famous and non-famous). Colors higher in intensity represent voxels selected more consistently across subjects as being important in differentiating between the two conditions.

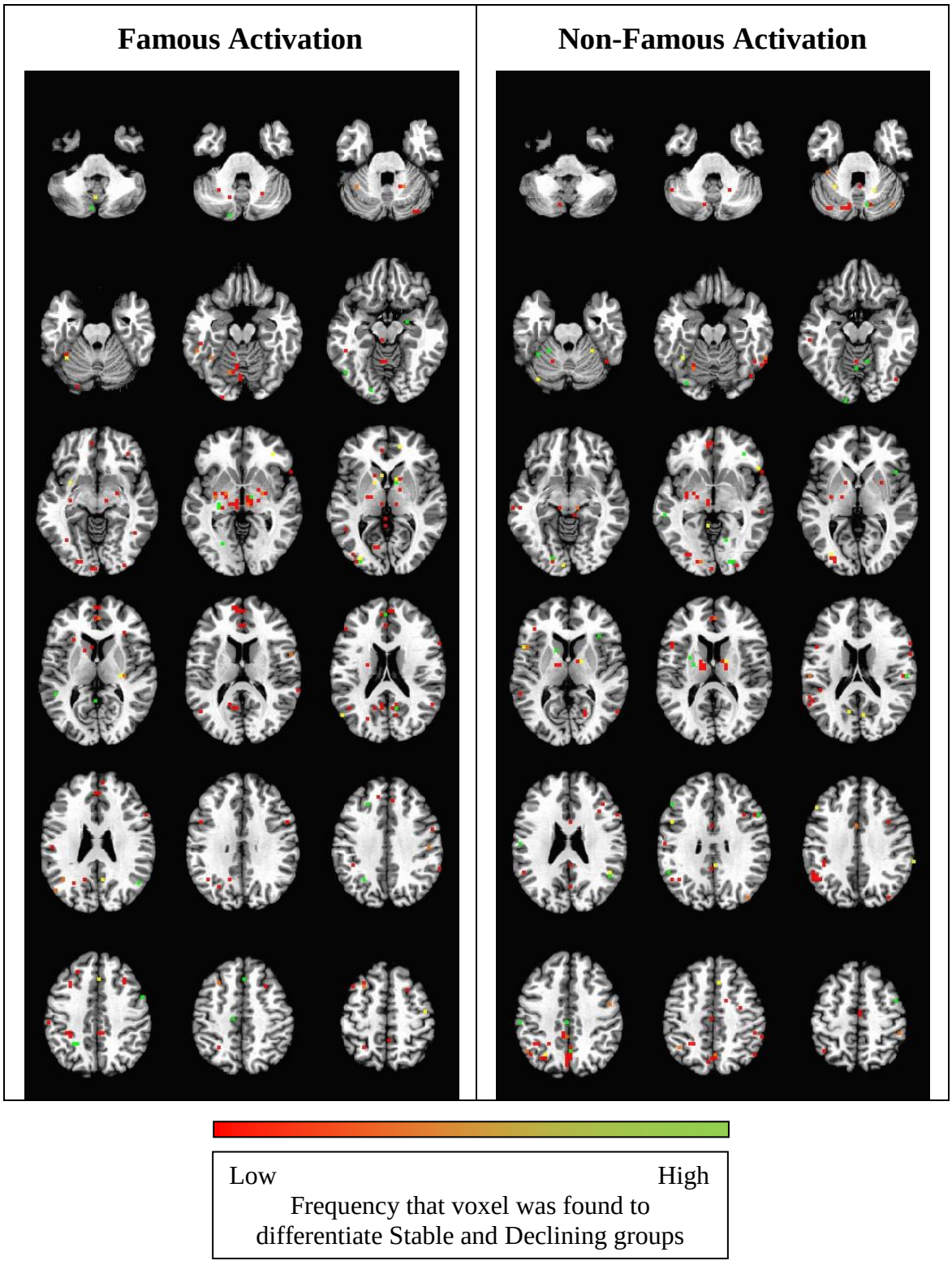


The exemplar patterns of famous and non-famous names were then used as the trainer and testing data. A leave-one-out methodology was utilized to decrease the variability of the classifier while avoiding bias. In this approach, the averaged AUC activation for a stimulus (i.e., a specific name) was left out of the training run (i.e., the creation of the classifier) and the remaining names become the trainers. The ability of the newly created classifier is then dichotomously tested against the sole averaged stimulus file that was left out of the analysis. The process is then repeated on all famous & non-famous names, resulting in a summary percentage of the classifier's accuracy for correctly delineating a stimulus as famous or non-famous (Haxby et al., 2001).

Binomial distribution was used to determine if the classifier's ability to correctly delineate between famous and non-famous task-based activation MVPA performed above chance. All pattern analyses were implemented in MATLAB with the assistance of the Princeton Multi-Voxel Pattern Analysis toolbox (Detre et al., 2006).

Aim 2 - MVPA for prediction of cognitive decline. To examine the ability of MVPA to correctly classify participants who experience cognitive decline and those who did not, a subsequent feature selection process of famous and non-famous name activation was performed between groups, creating a "stable" and "declining" classifier activation pattern for each condition (Figure 2). The ability of the classifier to correctly place subjects into the decliner or non-decliner group was tested. In other words, the regressor for Aim 1 is the stimulus condition (famous vs non-famous) while in Aim 2, the regressor is participant cognitive decline status (declining vs stable).

Figure 2. Aim 2 classification maps based on the feature selection process for the Stable and Declining groups. Both montages are the result of merging all 99 feature selection masks (i.e., collapsing groups). Colors higher in intensity represent voxels selected more consistently across subjects as being important in differentiating the Stable and Declining group.



It is desirable to train a classifier with as much data as possible (Pereira et al., 2009). A "leave-one-out" cross validation was once again employed, very similar to the stimulus condition MVPA described above. In this scenario, one subject was left out of the training run and the remaining subjects were utilized as trainers. The ability of the subsequent training classifiers (decliner or stable classifier) was then tested against the sole subject who was left out of the analysis. The process was then repeated on all subjects for both conditions, providing the accuracy of each condition (famous or non-famous names) to properly classify each individual into the either the decliner or non-decliner group based on patterns of activation. In other words, a separate classification accuracy score was computed for each condition collapsed across subjects. The testing run was then repeated 20 times for each condition to account for variance across testing runs. Binomial distribution was used to test if the classification accuracy of the MVPA performed above chance (Fu et al., 2008). The comparison of the ability of famous and non-famous names to correctly classify group membership was examined using paired samples t-test (Fu et al., 2008).

Results

Neuropsychological testing scores between stable and declining groups. At the 18-month follow-up testing, 34 of 99 participants (34%) were classified as cognitively Declining based on the above described criteria; two of these 34 met diagnostic criteria for MCI at follow-up (Peterson, 2000). The remaining 65 participants were classified as Stable. There were no significant differences between the Stable and Declining groups for age, education, gender, fMRI task performance, or the retest interval between the baseline and follow-up evaluation (see Table 2).

Table 2. Sample characteristics and fMRI behavioral data for Stable and Declining groups

	Stable (*n*=65) Mean *(SD)*	Declining (*n*=34) Mean *(SD)*	*p*	η^2
Sample characteristics				
Age in years	72.2 (5.0)	73.9 (4.7)	0.09	0.03
Education in years	15.0 (2.5)	14.7 (3.0)	0.56	0.01
Sex	18M/47F	10M/24F	1.00	-
Possession of APOE ε4 allele	20 (31%)	20 (59%)	***0.01***	-
Retest interval in days	549.7 (39.2)	560.9 (41.4)	0.20	0.02
SM task performance				
% Correct hit - famous names	92.7 (7.4)	91.6 (7.2)	0.48	<0.01
% Correct rejections - unfamiliar names	96.8 (4.5)	96.0 (8.0)	0.53	<0.01
RT famous names, msec	1271 (222)	1270 (163)	0.98	<0.01
RT unfamiliar names, msec	1662 (347)	1593 (360)	0.36	<0.01
Neuropsychological measures				
Lawton ADL				
Baseline	5.0 (0)	5.0 (0)	-	-
Follow-up	4.9 (0.1)	4.9 (0.3)	0.17	0.03
GDS Total				
Baseline	2.6 (2.7)	1.8 (2.3)	0.16	0.02
Follow-up	2.7 (2.5)	1.9 (2.4)	0.14	0.02
MMSE				
Baseline	29.4 (0.8)	28.8 (1.3)	***0.02***	0.06
Follow-up	29.5 (1.0)	29.0 (1.3)	***0.03***	0.05
DRS-2 Total				
Baseline	140.4 (3.0)	139.4 (4.0)	0.16	0.02
Follow-up	139.4 (2.1)	135.9 (4.9)*	***<0.01***	0.14
RAVLT Trials 15				
Baseline	50.0 (8.7)	45.8 (8.2)	***0.02***	0.53
Follow-up	49.9 (8.5)	40.0 (7.3)*	***<0.01***	0.27
RAVLT Delayed Recall				
Baseline	9.9 (2.3)	9.0 (2.8)	0.12	0.03
Follow-up	10.2 (2.6)	6.3 (2.4)*	***<0.01***	0.36

Note. APOE = apolipoprotein E; M=male; F = female; SM = semantic memory; ADL=Activities of Daily Living; GDS=Geriatric Depression Scale; MMSE=Mini-Mental State Exam; DRS-2 = Mattis Dementia Rating Scale-2; RAVLT = Rey Auditory Verbal Learning Test, RT=reaction time, * = significant decrease ($p<.05$) from baseline to follow-up.

Although all participants performed within normal limits at baseline testing, the Declining group scored significantly lower on the MMSE and the RAVLT Trials 1-5. The presence of one or both APOE ε4 alleles was significantly more frequent in the Declining group (p=0.01).

Summary of classifier performance. Aim 1. Examining solely stimulus-based activation (i.e., all participant data collapsed), MVPA was able to correctly classify famous and non-famous names stimuli with 90% accuracy, statistically greater than chance (p<0.01; Table 3). For examination of specific voxels of importance, see Figure 1.

Given the high classification accuracy rating, differences in accuracy for stimulus-based classification between the cognitively Stable and Declining group was examined. The analysis included the 34 Declining participants and 34 randomly selected Stable participants. There were no significant differences between the two groups on demographics, baseline neuropsychological performance, or fMRI task performance variables. Stimulus-based activation AUC was computed separately for each group, resulting in two separate parallel analyses. The remaining analysis was consistent with the Aim 1 methods described above. The MVPA of famous versus non-famous names within the Stable participants resulted in a mean classification accuracy of 83%; mean classification accuracy within the Declining group was also 83%. While both groups possessed a MVPA classification accuracy significantly above chance (p<0.01; see Table 3), the difference in classification accuracy between the two groups was not statistically significant (t=0.22, p=0.82).

Table 3. Summary of MVPA classification accuracy.

Regressor	Classification Accuracy	
	% accuracy (SD)	*p*
Aim 1: MVPA classification accuracy for stimulus		
Stimulus-based activation (Fam & NF)	89.72 (1.7)	<0.01
Stimulus-based activation separated by group		
Stable group	83.53 (1.7)	<0.01
Angular Gyrus	76.70 (2.0)	<0.01
Hippocampus	57.18 (1.9)	0.05
Superior Frontal Gyrus	77.06 (1.6)	<0.01
Posterior Cingulate	82.37 (2.0)*	<0.01
Declining group	83.43 (1.1)	<0.01
Angular Gyrus	77.29 (2.8)	<0.01
Hippocampus	55.59 (2.9)	0.07
Superior Frontal Gyrus	75.03 (2.4)	<0.01
Posterior Cingulate	74.79 (1.6)*	<0.01
Aim 2: MVPA classification accuracy for future cognitive status		
Stable & Declining group classification		
Famous stimulus activation	56.41 (3.4)	0.03
Angular Gyrus	40.01 (4.8)*	0.01
Hippocampus	60.46 (4.1)	<0.01
Superior Frontal Gyrus	63.84 (3.1)*	<0.01
Posterior Cingulate	55.56 (2.6)	0.03
Non-famous stimulus activation	54.85 (4.5)	0.05
Angular Gyrus	54.55 (3.0)*	0.05
Hippocampus	56.57 (3.0)	0.03
Superior Frontal Gyrus	55.76 (2.6)*	0.05
Posterior Cingulate	51.72 (4.2)	0.07

*Difference between groups for classification accuracy was statistically significant ($p<0.05$). P-values in right column represent if classification performance was greater than chance. Fam=famous name stimulus, NF=non-famous name stimulus; All analyses separated by region are bilateral.

Anatomical ROI's were created to examine region-based differences in Aim 1 classification accuracy. The selected regions have been previously shown to be vulnerable to AD and differentially active in individuals who go on to experience cognitive decline as compared to cognitively stable individuals (Woodard et al., 2010). The selected bilateral regions, as defined by Desikan and colleagues (2006), included poster cingulate cortex (PCC), superior frontal gyrus (SFG), hippocampus (Hipp), and the angular gyrus (AG; see Table 3). The MVPA process, as described in the Aim 1 methods, as repeated for each ROI, providing independent classification accuracy for each region. A significant group difference was only found in PCC, with the Stable group demonstrating higher classification accuracy for names than the Declining group ($t=5.93$, $p<0.01$).

Aim 2. The second aim examined the ability of MVPA the correctly delineate the Stable and Declining groups using task-related BOLD activation. In other words, participant declining status was the independent variable and task activation separated by stimulus type was the dependent variable. Using solely famous names activation, MVPA was able to correctly delineate participants into their respective groups with an accuracy statistically greater than chance (56%; $p=0.03$). MVPA utilizing non-famous name activation was trending towards significance with 55% classification accuracy ($p=0.05$; Table 2). There was no statistical difference between MVPA classification accuracy utilizing famous names and non-famous names activation ($t=1.38$, $p=0.18$). Results of the feature selection process are provided in Figures 1. Again, anatomical ROIs were utilized to examine region-based differences in classification accuracy (PCC, Hipp, SFG, and AG). MVPA group classification accuracy in the famous name condition was greater

than chance in four all regions (see Table 3). For non-famous names, activation in the Hipp was statistically greater than chance for differentiating group membership; AG and SFG were both trending towards significance (see Table 3). Classification of group membership utilizing famous names was significantly lower than non-famous names in AG (t=5.93, p=0.01), but higher in SFG (t=3.73, p=0.02).

Discussion

The present study consisted of two aims. The first, examine the ability of MVPA, a multivariate classification technique, to discriminate between famous and non-famous name fMRI task-activation in healthy older adults. The second aim examined the ability of baseline fMRI task-related activation to predict cognitive decline in healthy older adults over an 18-month retest interval through the use of MVPA.

With regard to the first aim, previous fMRI research suggests that examination of the neural networks underlying semantic memory, specifically activation for famous minus non-famous names, reveals early activation differences between older adults who go on to experience cognitive decline and those who are cognitively stable (Woodard et al,. 2010). Previous studies aimed at predicting cognitive decline have relied exclusively on traditional univariate fMRI analysis. MVPA, given its ability to assess stimulus-driven pattern of activation without relying on cluster thresholds, has potential for revealing early changes in task activation heretofore unrevealed by univariate analysis. Yet, the technique had not before been applied towards distinguishing voxels by stimulus fame. The first aim of this study set out to evaluate the efficacy of MVPA for making that distinction as a first step toward applying it to distinguishing patterns of activation.

In Aim 1, the MVPA classifier differentiated activity patterns associated with famous and non-famous names with 90% accuracy, significantly greater than chance. These findings suggest that the FNDT stimulus has potential for unique contribution in classification of fMRI data. This 90% accuracy rating is consistent with similar MVPA findings examining stimulus-based classification (Haxby et al., 2001). For example, a

recent study by Akama and collegues (2012) using MVPA and integrating feature selection of living and non-living concepts achieved 80-90% accuracy.

The different patterns of activation between famous and non-famous names, despite their similarity in nature, suggest disparate neural networks and common overlapping constellations of neural networks within each stimulus type. Previous research using univariate methodology indicates that fame recognition and discrimination involve a complex system of interrelated bilateral networks, including substantial frontal and parietal activation (Douville et al., 2005; Nielson et al., 2010). The current study similarly found fairly widespread clusters of task activation (Figure 1), including in traditional name discrimination regions (Douville et al., 2005). Portions of the cerebellum, superior frontal gyrus, the left and right insula cortex, and the posterior cingulate cortex (PCC) contained voxels deemed important in differentiating conditions. Univariate fMRI research indicates increased fame-related activation in all of these regions (Leveroni et al., 2000; Nielson et al., 2010) and suggests these regions may be important in both attention and processing emotionally salient information (Nielson et al., 2010; Maddock, 1999).

The stimulus-based analysis was then performed separately for the Stable and Declining groups. Mean MVPA classification accuracy for famous and non-famous names was 83% for both the Stable and Declining groups. This finding is comparable, but significantly less than the collapsed stimulus-based analysis described above. The drop in classification accuracy may be attributable to the reduction in total data points. Providing a classifier with as much data as possible lends to more efficient and robust classification (Pereira et al., 2009). While the collapsed stimulus-based analysis

contained 99 participants, the number of participants for each MVPA in the post-hoc analysis was reduced to 68 in order to evenly separate participants by group status.

Regardless, classification for both groups (Stable & Declining) was significantly above chance with 83% accuracy, suggesting little difference in the level of "noisy activation" between the two groups and comparable group-based neural specificity. Previous research indicates differential activation in individuals who go on to experience cognitive decline and those who remain stable (Miller et al., 2008). More specifically, increased fMRI task activation during the FNDT was associated with cognitive stability over an 18-month period (Woodard et al., 2010). When integrated with these univariate findings, the current results suggests that while stimulus-related neural networks may initially remain structurally intact and comparable between groups, compensatory activation may be occurring on a participant-dependent level that is not easily captured when examined on an stimulus-driven, individual voxel basis (Cabeza et al., 2004; Machulda et al., 2003).

A secondary analysis examined classification accuracy for names in regions implicated in early AD (PCC, SFG, Hipp, and AG; Table 3). Significantly greater classification accuracy was found for names in the PCC for the Stable as compared to the Declining group. This finding suggests that individuals who go on to experience cognitive decline are demonstrating less differentiated activation specifically in the PCC, a region preferentially impacted by AD, important in semantic processing, and frequently involved in compensatory activation (Hedden & Gabrieli, 2004). Recent studies indicate that the PCC, an integral part of the DMN, is often disrupted in individuals who carry a

diagnosis of MCI or early AD, suggestive of early AD pathology and inefficient cognitive processing (Pihlajamaki & Sperling, 2009; Supekar et al., 2010).

Stimulus-based activation classification accuracy in the hippocampus was significantly lower than all other examined regions, a finding consistent across both groups (56% and 57% respectively). However, previous research indicates that the hippocampus is integral in the discrimination of fame and memory retrieval, a basic process inherent to the FNDT and across both stimulus types, which may explain MVPA's failure in this specific region (Douville et al., 2005).

The purpose of Aim 2 was to expand upon Aim 1's proof-of-concept and investigate the ability of MVPA of fame and non-famous names related baseline fMRI activation to correctly classify individuals who go on to experience future cognitive decline. When comparing the activation seen in the stimulus-based analysis (Aim 1) and the group-based analysis (Aim 2), the Aim 1 MVPA demonstrated more condition differentiating voxels. The finding is understandable given its higher classification rate and more defined classifier (stimulus versus group membership). Famous-name related fMRI activation correctly classified 56% of participants as Stable or Declining while non-famous name activation correctly classified 55%.

Further region-specific analysis indicates higher classification accuracy for differentiating Declining versus Stable group membership in the angular gyrus and the superior frontal gyrus. Specifically, in the angular gyrus, MVPA of non-famous name activation possessed higher accuracy than famous names for differentiating future cognitive decline status, as classification accuracy was nearly 15% lower than the general classification rate for famous names across all other regions. In other words, famous

name activation in the angular gyrus is especially uninformative in determining cognitive decline. This finding is somewhat surprising given the role of the angular gyrus in the DMN and in semantic processing, both processes which previous studies indicate are compromised in MCI and AD (Pihlajamaki & Sperling, 2009; Woodard et al., 2009). The angular gyrus is believed to be important in a variety of cognitive processes, including memory retrieval and detection of expected versus unexpected information (Park et al., 2008). The current findings suggest that in both cognitively stable and cognitively declining participants, the angular gyrus is utilized uniformly in the detection of novelty and in searching of fame-related memory networks, understandable given the high accuracy rate of both groups in the FNDT.

However, SFG activation demonstrated an opposite effect as compared to the angular gyrus, with famous name activation accuracy classifying significantly better than non-famous names, and 7% better than the general classification accuracy. This finding is consistent with previous research, which indicates differential frontal activation in individuals at greater risk for AD (Bondi et al., 2005) and may reflect increased semantic activation in cognitively stable older adults (Woodard et al., 2010).

Further examination of the group-based analysis indicates a cluster of voxels within the thalamus as important in differentiating group membership regardless of stimulus type in Aim 1 & 2. The thalamus, important in alertness and cortical connectivity, is directly functionally connected to the hippocampus and may play a role in recollective and familiarity memory (Stein et al., 2000). Its importance in differentiating future cognitive decline in the current study may suggest subtle white

matter changes in hippocampal memory processes and early AD pathology (Jacobs et al., 2012).

Broader examination and contextualization of the current findings shows consistency with both univariate fMRI findings and the larger body of aging literature. Traditional univariate analysis of fMRI data in older adults indicates increased task activation as age increases, especially in individuals at-risk for future cognitive decline (Bondi et al., 2005; Cabeza, 2002). These techniques depend on ROIs and examine large increases or decreases in BOLD response. The current findings suggest that even on a stimulus level (i.e., not dependent on large fluctuations in BOLD response), stable and declining participants demonstrate somewhat different spatial patterns of activation. This finding is compatible with the CRUNCH or STAC models, which propose neural recruitment and reorganization in the face of cognitive decline (Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008). Specifically, individuals in the future declining group appear to be employing different neural networks, as compared to cognitively stable participants, in order to maintain performance. Presumably, over time the brain is unable to employ adequate scaffolding, which results in cognitive decline at follow-up in those individuals (Park & Reuter-Lorenz, 2009). Scattered voxels in the frontal lobe, particularly prefrontal/superior frontal gyrus, in both famous and non-famous names uniquely contributed to differentiating future cognitive decline. Furthermore, selective MVPA of the superior frontal gyrus found that famous name activation correctly classified future cognitive decline with 64% accuracy, significantly higher than all other regions, excluding the hippocampus. This is also consistent with prior research that suggests that frontal regions in particular are actively recruited to maintain cognitive

performance and occurs more prominently in the Stable group as compared the Declining group (Cabeza, 2002; Park & Reuter-Lorenz, 2009; Reuter-Lorenz & Cappell, 2008; Woodard et al., 2010).

This increase in frontal activation may also represent a subtle change in cognitive processing among these older adults. One theory of aging posits that as the integrity of the hippocampus weakens through the aging process, older adults employ a more frontally mediated top-down approach to memory, relying more on familiarity as compared to explicit recall (Reuter-Lorenz et al., 2008). Previous univariate fMRI research examining individuals at-risk for AD reports similar findings of increased prefrontal activation during episodic and semantic memory tasks, presumably to compensate for very early AD pathology (Grady et al., 2003; Han et al., 2007).

To my knowledge, this is the first paper examining the ability of MVPA to classify future cognitive decline using fMRI data. Nevertheless, a peripherally related study, which utilized support vector machine of MR images, classified MCI versus healthy controls with 67-72% accuracy (Yang et al., 2011). The 55-56% classification accuracy of the current study is somewhat lower. There are several key differences between the studies. Yang and colleagues utilized MR images of over 800 subjects, as compared to the 99 of the current study. Because a larger training set is preferable and generally leads to higher mean classification accuracy (Pereira et al., 2009; Yang et al., 2011), their larger data set may have allowed for more accurate classification. Secondly, Yang and colleagues utilized MRI, while the current study utilized an fMRI task. High level cognitive tasks, such as the FNDT used in the present study, are often associated with distributed activation and individual variability (Etzel et al., 2013). While spatial

smoothing alleviates some of these concerns, MVPA is predisposed to errors within tasks that have higher variability between subjects, given the functional and organizational differences in individual activation patterns to different stimulus (Etzel et al., 2013).

Previous research utilizing MVPA to examine age-related changes in activation found increased neural dedifferentiation in early visual cortex, inferior parietal cortex and areas of the prefrontal cortex when comparing young and older adults (Carp et al., 2011). Interestingly, Carp and colleagues did not find a strong relationship for neural distinctiveness between regions, as determined by the ability of MVPA to accurately classify stimuli. For example, dedifferentiation in the visual cortex did not correlate with dedifferentiation in other areas of the brain, suggesting that compensatory activation does not occur uniformly throughout the brain, nor predictably incorporate other regions. While inconsistent with PASA (Davis et al., 2008) and other theories of compensatory activation that presume frontal recruitment in the face of posterior neural degeneration (Cabeza, 2002), the finding of individual and region variability in compensatory activation is compatible with the findings of the current study. In the present study, the hippocampus and frontal regions contained a relatively focused portion of voxels that preferentially differentiated the Stable and Declining groups, particularly with famous name activation, despite being regions that are preferentially impacted in early cognitive decline (Raz & Rodrigue, 2006). Individual and regional variability may account for the lack of strong classification accuracy. In other words, while functional neural recruitment may be occurring on a region-based level, variance in specific voxel recruitment may hurt MVPA classification accuracy (Seidenberg et al., 2009; Cabeza, 2002).

When discussing the comparison of findings across studies, it should be noted that there are a multitude of different ways to utilize MVPA. The goal of the current study was to examine the ability of MVPA to correctly classify a dichotomous variable (stimulus-type or cognitive status) based on fMRI activation, modeled after the research of Haxby and colleagues (2001). However, the above discussed study by Carp et al (2011) utilized a searchlight analysis followed by the creation of a correlation index to examine neural distinctiveness based on age. The searchlight was focused within defined regions of the ventral visual cortex, prefrontal cortex, and inferior parietal cortex. Searchlight analysis (not utilized in the current study) examines the activation-based activity of each voxel and the neighboring cluster of voxels by employing a spherical spotlight (Etzel et al., 2013; Kriegeskorte et al., 2006). This analysis results in individual subject information maps which are then aggregated into a group level analysis (Etzel et al., 2013). While similar to the MVPA utilized in the current study, there is a key difference. The current study compared individual activation against the group activation test data using a leave-one-out method, resulting in a predicted classification. This predicted classification was then compared against the participant's actual group membership, resulting in a direct examination of the ability of fMRI data to predict future cognitive status. Searchlight analysis takes an alternative approach of examining activation patterns on an individual level, then aggregating the data group level analysis to look at correlations within groups. While a powerful tool, searchlight analysis answers a fundamentally different question and does not directly examine the ability of MVPA to classify group membership. Finally, the study by Carp and colleagues (2011) focused on examining activation differences between young and old adults, while the current study

looked at AD-risk in same aged participants. Future research examining the ability of searchlight analysis to examine correlations between AD risk status or other variables may prove informative, providing perspective on the spectrum of aging and cognitive decline, as compared to the current study's dichotomous approach. A combination of searchlight and ROI-based MVPA may prove informative in examining likelihood of cognitive decline and provide a complementary approach.

Previous univariate fMRI studies have demonstrated potential for predicting future cognitive decline in older adults (O'Brien et al., 2010; Woodard et al., 2010). In the current study, famous name activation was able to correctly classify future cognitive decline at a rate greater than chance, but the findings suggest that MVPA performance is less accurate than traditional univariate fMRI analysis. Using the same fame discrimination task, Woodard and colleagues (2010) achieved a 71% classification accuracy using traditional univariate cortical and hippocampal fMRI activation indices, which was superior to 55-56% by MVPA, despite the utilization of restrictive ROIs and secondary ANOVA during feature selection with MVPA.

There are several potential reasons for the poorer performance of MVPA in the current study as compared to other MVPA and univariate studies (e.g., Woodard et al., 2010). Traditional univariate analysis focuses on cluster-based regions of activation. In contrast, MVPA measures patterns of voxels that are more strongly associated with one regressor as compared to another (e.g., stable cognitive status or cognitive decline). It is feasible that univariate analysis, by using a more gross measure of semantic activation, may better capture the "noisy" nature of compensatory activation across large groups of individuals. Concordantly, a recent study by Jimura et al. (2012) suggests that when

directly compared, univariate ROI analysis may better capture global task engagement (i.e., compensatory activation), while MVPA is more sensitive in differentiating content and the distributed coding of information. Furthermore, while the two methods demonstrated some overlapping regions of activation, effect sizes estimates were found to be uncorrelated between the two regions. Jimura and colleagues (2012) suggest that MVPA and univariate analysis may best serve as complimentary methodologies to understanding cognitive processes.

Secondly, univariate analysis allows for direct analysis of increases/decreases in fMRI activation, which may better capture the increases in task-related BOLD response seen in cognitive aging and often seen in those with increased risk for AD (Seidenberg et al., 2009b). MVPA does not directly capture increases or decreases in BOLD response, as there is no control task for comparison. Therefore, activation patterns witnessed in MVPA demonstrate stimulus-based networks and not subtraction-based analysis of region activation (e.g., semantic networks) that are susceptible in AD (Woodard et al., 2009).

Thirdly, it should be noted that the term "classification" is defined fundamentally differently between the two studies. The study by Woodard and colleagues utilized principal component analysis coupled with a logistic regression to test the ability of specific variables (fMRI activation within specific regions) to discriminate between cognitively stable and declining participants. This results in a predicted probability out of all possible pairings for each participant to be correctly paired as either declining or stable. This model is then validated with bootstrapping. In contrast, the current study created an exemplar "declining" and "stable" pattern of neural activation and compared

the ability of these exemplars to be representative of each individual's future cognitive grouping via a decision boundary. Therefore, MVPA is not directly testing multiple statistical "models" but instead an fMRI data-driven support vector machine. Also, MVPA utilizes cross-validation via leave-one-out methods, not bootstrapping, allowing for an unbiased analysis (Pereira et al., 2009).

There are several limitations of the study worth noting. The goal of the study was to examine baseline fMRI correlates of future cognitive decline using MVPA. The study purposely used the fairly liberal criterion of 1 SD to represent cognitive decline, as compared to a more formal criterion such as diagnosis of MCI or AD, etc. The purpose of the study was to examine the very early stages of possible cognitive decline, examining subtle yet meaningful changes in fMRI activation. Previous work using the same fame discrimination task, criteria for cognitive decline, and test-retest interval suggests this degree of decline is meaningful and robust (Hantke et al., 2013; Woodard et al., 2010). That being said, given the short test-retest interval of 18-months, a longer follow-up interval is necessary to draw definitive conclusions on the ability of MVPA to predict conversion to MCI or AD.

Secondly, the current sample was selectively recruited to contain a high number of older adults who possess the APOE ε4 allele, a known risk factor AD. Therefore, the findings of the study may not necessarily generalize to the general population. However, the high presence of risk factors within the study sample allows for a focused analysis of how cognitive decline may interact with fMRI activation and expounds upon the large body of literature examining genetic factors and AD (Bookheimer & Burggren, 2009).

Thirdly, the primary function of MVPA is to examine differences between regressors by using pattern-based classification. As MPVA focuses on patterns instead of cluster-based ROIs, extrapolating the current study's findings to compensatory activation models (e.g., STAC) is tenuous. The activation patterns reported in the current study (Table 3) do not represent increased neural activity related to semantic networks nor does it represent that a voxel is integral in semantic processing. Rather, it indicates that a voxel is informative in classifying the regressors (e.g., cognitive decline).

The analysis of fMRI activation holds promise as a method to identify at-risk individuals for interventions designed to prevent or delay cognitive decline. Future research directions include utilizing MVPA to examine functional activation in individuals with increased genetic risk for AD, as previous research indicates that individuals who possess genetic risk factors for AD demonstrate different patterns of activation than those at lower risk (Seidenberg et al., 2009b). Also, given the high accuracy of MVPA for classifying famous and non-famous names, other possible directions include utilization of MVPA to delineate fame epoch in older adults. Recent research indicates that the temporal gradient of fame may serve as an early preclinical cognitive marker for cognitive decline (Seidenberg et al., 2013). Furthermore, neocortical activation varies for memories of different temporal periods, lending itself well to MVPA (Woodard et al., 2007).

In summary, the current findings indicate that famous and non-famous names invoke differential patterns of fMRI activation in older adults. When utilizing this activation, individuals who go to on to experience even a relatively mild decline on cognitive measures display differential patterns of famous name fMRI activation as

compared to those who do not. MVPA of fMRI data may be useful in determining which individuals may be at a higher risk for future cognitive decline, guiding early intervention.

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