fMRI of Prose Comprehension in High- and Low-Performing Older Adults

By

Clarice Wang, M.A.

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Chairperson David Johnson, Ph.D.

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Ruth Ann Atchley, Ph.D.

_____

Douglas Denney, Ph.D.

_____

Robert Fiorentino, Ph.D.

_____

Eric Vidoni, Ph.D.

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The Dissertation Committee for Clarice Wang

certifies that this is the approved version of the following dissertation:

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Chairperson David Johnson, Ph.D.

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Abstract

Characterization and clinical detection of early Alzheimer's disease is difficult due to significant neurocognitive variability present in both healthy and pathological aging. This poses a problem for memory and aging studies because individuals categorized as healthy may actually have an early or 'preclinical' AD, which may contaminate results. This study addressed these concerns by 1) using a novel prose recall task designed to elicit subtle changes in episodic memory that occur in early AD 2) examining neural activity of high- and low-performing older adults to reduce within-group variability and differentiate healthy from pathological brain activity. The prose recall task was extremely sensitive (81.8% sensitivity and 100% specificity for mean expository and narrative recall; 100% sensitivity and 100% specificity for expository stories alone) in differentiating healthy older adults from those with very mild AD. fMRI results showed evidence that high-performers retain the ability to recruit specialized regions of the brain during encoding of prose, while low-performers overrecruit nonspecific areas and strongly resemble adults with very mild AD. This suggests that high-performers engage in compensatory brain activity which may reflect a healthy aging process, while low-performers exhibit signs of dedifferentiation which may reflect a disease process.

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Differentiating healthy and pathological aging due to Alzheimer's disease (AD) has been a problem for researchers due to variability across cognitive, neural, and pathophysiological domains of older adult functioning. Studies find that cognitive change in older adults is largely dependent on individual differences rather than a progressive, developmental process (Wilson et al., 2002), and rates of change are highly variable among older adults (Bäckman, Small, & Fratiglioni, 2001; Christensen et al., 1999; Hedden & Gabrieli, 2004; Wilson et al., 2002). Functional neuroimaging studies report that older adults employ vastly different strategies to carry out tasks compared to younger adults; however, it is still unclear when these specific neural patterns occur and whether they serve a functional or dysfnctional purpose. Pathophysiological overlap between healthy older and AD individuals has also been observed: PET biomarker imaging studies show that cerebral amyloid, a well-known post-mortem indicator of AD pathology, can be present in some asymptomatic older adults (Aizenstein et al., 2008; Mintun et al., 2006).

The presence of this neurocognitive variability has led to difficulty diagnosing cognitive impairment in older adults. Clinicians and researchers have long been aware that clinically "healthy" samples of older adults often include minimally impaired individuals in a preclinical stage of dementia, despite screening procedures (Jacobs et al., 1995; La Rue & Jarvik, 1987; Rubin et al., 1998; Sliwinski, Lipton, Buschke, & Stewart, 1996). Sliwinski et al. (1996) reported a contamination rate as high as 20% in one sample. These individuals were unable to be detected using conventional screening measures for AD and were only able to be identified using longitudinal follow-up.

Mild Cognitive Impairment (MCI) represents another intermediate stage where individuals exhibit some symptoms of cognitive decline but do not meet full diagnostic criteria for AD (Albert et al., 2011; Petersen et al., 1999). MCI is highly linked to subsequent AD diagnosis; MCI to AD conversion rates range from 10 to 15% per year compared to a 1 to 2% conversion rate in healthy older adults (Bowen et al., 1997; Petersen et al., 2001; Tierney et al., 1996). Several neuropathological similarities between MCI and AD individuals predict future AD conversion, including decreased entorhinal cortex volume (deToledo-Morrell et al., 2004; Devanand et al., 2012; Dickerson et al., 2001; Killiany et al., 2000; Risacher et al., 2009; Stoub, Rogalski, Leurgans, Bennett, & deToledo-Morrell, 2010), elevated levels of amyloid (Albert et al., 2011; Vemuri et al., 2009), and elevated levels of tau protein (Albert et al., 2011; Hansson et al., 2006; Holtzman, 2011; Okonkwo et al., 2010; Vemuri et al., 2009). Increased neurofibrillary tangle density in MCI individuals is also associated with poorer memory performance (Guillozet, Weintraub, Mash, & Mesulam, 2003). Given these similarities, some have suggested that MCI may represent a transitional, prodromal stage of AD (Albert et al., 2011; Kelley & Petersen, 2007; Petersen et al., 2001; Wilson, Leurgans, Boyle, & Bennett, 2011). However, studies often use different definitions of MCI (Celone et al., 2006; Petersen et al., 2001) and rating scales for dementia can encompass individuals in both MCI and AD stages (Petersen et al., 1997). Though a definition of MCI exists, clinicians and researchers vary in their usage of the term. This further contributes to diagnostic overlap. Thus, the line between healthy aging and AD is not always clear.

The National Institute on Aging-Alzheimer's Association Workgroups (NIA-AA) has recognized the presence of this neurocognitive variability in older adults, and recently proposed a continuum model of AD that begins with a *preclinical AD* stage occurring several years before

MCI and subsequent AD diagnosis. This preclinical stage includes individuals who exhibit AD pathology and may have neurodegeneration and subtle cognitive decline, but have not yet displayed clinical symptoms (Sperling et al., 2011). This model is of particular interest to researchers studying prodromal stages of AD because it suggests that an upstream pathophysiological process occurring years before disease onset can be identified by the presence of specific, measurable biomarkers. This model provides a much-needed conceptual framework to describe the aging-AD continuum; however, the authors note that integration of biomarker research with additional measures, such as more sensitive imaging markers of functional and structural decline, is crucial for full characterization of AD progression and eventual development of early, amyloid-targeted therapies.

To facilitate integration of neuroimaging markers and improve characterization of this preclinical AD population, objective measures of early cognitive decline must be defined. Given the widespread neurocognitive variability present in older adults, examining sources of this variability is crucial to clarify which cognitive changes are specific to preclinical AD. One way to investigate variability is to segregate successful and unsuccessful performance on tasks of episodic memory, the earliest behavioral symptom of AD (American Psychological Association, 2000). Two methods in functional imaging have been used to distinguish successful from unsuccessful performance. Block designs show patterns of brain activation that are present in high- or low-performing older adults, while event-related designs show patterns of brain activation that are present during a discrete interval when older adults remember or forget an item.

Studies examining individual variability in older adults have suggested that successful and unsuccessful performers use different strategies during memory tasks. Neuroimaging

research typically finds three patterns of results in older adults: 1) overrecruitment of regions used by younger adults, 2) underrecruitment of regions used by younger adults, or 3) recruitment of alternate regions not used by younger adults. However, it is still unclear under what conditions each of these patterns is seen. Furthermore, behavioral studies of text recall indicate that older adults with higher comprehension abilities may allocate resources differently compared to those who do not perform as well (Stine-Morrow, Soederberg Miller, Gagne, & Hertzog, 2008). It seems that certain patterns of neural activity are associated with successful and unsuccessful memory performance, although it is still not known under what circumstances they occur. These findings are consistent with two predominant, conflicting theories of aging.

Dedifferentiation hypothesis

According to the *dedifferentiation hypothesis*, cognitive differentiation is responsible for generation of distinct cognitive abilities in early development. It is suggested that this differentiation is reversed in normal aging in a process called *dedifferentiation* (Baltes, Cornelius, Spiro, Nesselroade, & Willis, 1980; Cabeza, 2002; Reinert, 1970). Common causes such as declines in processing speed and sensory perception lead to changes in neural integrity that affect multiple domains (Lindenberger & Baltes, 1994; Park et al., 2002; Salthouse, 1991). As a result, older adults fail to recruit specialized areas generated for optimal task performance (Buckner & Logan, 2002; Cabeza et al., 2002; Logan et al., 2002; Wilson et al., 2012).

Results from functional neuroimaging studies support the dedifferentiation hypothesis. Activation patterns in cognitive and sensory domains show significantly greater correlation in older adults compared to younger adults, suggesting a common, age-related decrease in specialization (Baltes & Lindenberger, 1997). Other common phenomena in older adults include increased bilateral recruitment (Cabeza et al., 2002; Cabeza, 2002; Morcom, Good, Frackowiak,

& Rugg, 2003) and nonselective recruitment of alternate areas (Gutchess et al., 2005; Logan et al., 2002; McIntosh et al., 1999), both of which could be interpreted as disruptions in normal processes used by younger adults. Moreover, disruptions in the *default mode network* have been found in older adults. The default mode network refers to certain regions of the brain (medial frontal, lateral/medial parietal, posterior cingulate, and precuneus regions) that are more metabolically active during passive conditions and less active during task engagement (Raichle et al., 2001); thus, it is thought that successful task performance involves both simultaneous activation of specialized areas and deactivation of the default mode network. Studies have reported that older, MCI, and early AD adults either deactivate DMN regions to a lesser degree, or deactivate alternate areas to a greater degree compared to younger adults, suggesting a loss of ability to regulate this network (Celone et al., 2006; Davis, Dennis, Daselaar, Fleck, & Cabeza, 2008; Greicius, Srivastava, Reiss, & Menon, 2004; Lustig et al., 2003; Wang et al., 2010). Taken together, these results provide strong support for declining neural specialization and optimal functioning in older adults.

High- vs. low-performers: evidence for dedifferentation. Studies that examine performance outcome suggest that unsuccessful performers have a deficit in encoding strategy or ability. Low-performers show decreased activation in medial temporal lobe (MTL) ((Daselaar, Veltman, Rombouts, Raaijmakers, & Jonker, 2003), which is thought to be responsible for making associations that are necessary for successful encoding (Eichenbaum, Schoenbaum, Young, & Bunsey, 1996; Fernández et al., 1999; Henke, Buck, Weber, & Wieser, 1997; Henke, Weber, Kneifel, Wieser, & Buck, 1999; Strange, Otten, Josephs, Rugg, & Dolan, 2002). Older adults who subsequently forget items are also shown to overrecruit alternative areas, such as lingual, occipital, auditory, insula, supramarginal gyrus, and cerebellar areas (Daselaar et al.,

2003; Morcom et al., 2003; Stevens, Hasher, Chiew, & Grady, 2008). Some of these additional activations represent a shift to surface-level strategies; for example, (Morcom et al., 2003) found that both older and younger adults activated additional areas for subsequently remembered words. Younger adults upregulated left anterior inferior temporal cortex, a region involved in comprehension of complex words and sentences (Bottini et al., 1994; Fletcher et al., 1995; Mazoyer et al., 1993; Price, 2000). In contrast, older adults upregulated lingual cortex and occipital pole, suggesting that they relied on more basic visual and phonological properties during encoding. The authors interpreted this failure to activate specialized brain regions as support for the dedifferentiation hypothesis.

Finally, researchers suggest that differences in the DMN that are consistent with dedifferentiation are found in high- and low-performers as well. For example, some studies provide evidence for dedifferentiation by examining *functional connectivity,* which refers to spontaneous, inter-region correlations in blood oxygen level dependent (BOLD) signal observed during resting state. It is thought that these correlations represent the underlying functional architecture and connectivity of the brain (Biswal, Yetkin, Haughton, & Hyde, 1995; Vincent et al., 2007; Wang et al., 2010). Studies indicate that stronger intrinsic connectivity within the DMN predicts subsequent memory in both younger and older adults (Daselaar, Prince, & Cabeza, 2004; Wang et al., 2010). Stevens, Hasher, Chiew, & Grady (2008) found that older adults who subsequently forgot items activated auditory regions that are functionally connected to DMN regions, suggesting that unsuccessful performance is linked to disruptions in DMN. Another study found that low-performing older adults do not deactivate DMN regions at all (Miller et al., 2008), again suggesting that failure to regulate this system could be one potential reason for their poor performance.

Compensation Hypothesis

It is still unclear whether the nonselective recruitment or over-recruitment observed in older adults represents dedifferentiation rather than use of alternate strategies to compensate for age-related decline. The *compensation hypothesis* suggests that the alternate neural patterns observed in older adults do not represent brain damage or loss of cerebral specialization. Rather, they are employed with the specific purpose of compensating for age-related changes in neural efficiency and organization (Cabeza, McIntosh, Tulving, Nyberg, & Grady, 1997; Cabeza, 2002; Reuter-Lorenz, Stanczak, & Miller, 1999).

The compensation hypothesis is supported by evidence that healthy younger adults recruit additional bilateral brain regions under certain circumstances as well: as task difficulty increases, younger adults activate additional homologous regions to compensate for normal limitations in working memory resources (Just, Carpenter, Keller, Eddy, & Thulborn, 1996; Klingberg, O'Sullivan, & Roland, 1997; Reichle & Mason, 2007; Xu, Kemeny, Park, Frattali, & Braun, 2005). It is possible that a similar compensatory mechanism is used by older adults as age-related declines increase task difficulty and demand. Similar analogies can be drawn from research on brain damage recovery, which finds that homologous areas in an unaffected hemisphere can often be recruited to compensate for lesions or damage (Buckner, Corbetta, Schatz, Raichle, & Petersen, 1996; Cao, Vikingstad, George, Johnson, & Welch, 1999; Thulborn, Carpenter, & Just, 1999). This view is supported by evidence that increased bilaterality in older adults is associated with improved cognitive performance (Cabeza et al., 2002, 1997; Jonides et al., 1998; Rosen et al., 2002).

Additionally, there are some studies that report reversal of underrecruitment if older adults are given a task-specific strategy, and the magnitude of this reversed activity can approach

that of younger adults (Grady et al., 1995; Grady, McIntosh, Rajah, Beig, & Craik, 1999; Logan et al., 2002; Stebbins et al., 2002). This is inconsistent with dedifferentiation because it indicates that unactivated brain areas are still preserved; they are simply not recruited. In summary, these studies show that additional activations can be beneficial to performance and that some underrecruitment can be reversed. This provides evidence that different activation patterns in older adults may represent alternate strategies that specifically serve to compensate for age-related decline.

High- vs. low-performers: evidence for compensation. Increased activation of brain areas is commonly seen in functional neuroimaging studies of older adults and provides strong evidence for a compensation model. For example, high-performing older adults show reduced lateralization in PFC compared to low-performing older adults (Cabeza et al., 2002; Rosen et al., 2002) and young adults (Cabeza et al., 2002; Daselaar et al., 2003; Morcom et al., 2003), or upregulation of contralateral areas of PFC compared to young adults (Rosen et al., 2002). Activation of alternate areas is also seen in older adults who successfully remember items; (Gutchess et al., 2005) found that older adults upregulated left dorsolateral prefrontal cortex (DLPFC) and left parietal areas for subsequently remembered items, while younger adults did not.

Though there is strong evidence to support the compensation hypothesis, two important caveats must be noted. Compensation is most often described as overrecruitment or increased bilaterality, but there may be other examples of compensation. Older adults can also activate contralateral areas, activate alternate areas, or even deactivate additional areas. Theoretically, any over- or under-recruitment beyond what healthy young adults use could be considered consistent with compensation. This broad definition presents a major problem when

distinguishing between dedifferentiation and compensation: many of the aforementioned trends can be explained by both hypotheses. For example, increased bilaterality could be a byproduct of decreased specialization in one hemisphere, leading to nonselective activity in the opposite hemisphere. It could also represent a strategy to compensate for normal age-related decline by recruiting supplemental areas for support (Cabeza, 2002; Reuter-Lorenz et al., 1999). Some authors propose that both explanations may simultaneously occur; that aging involves both reversible, compensatory underrecruitments and nonspecific overrecruitments (Logan et al., 2002). However, this still does not explain under what circumstances each pattern occurs. More specific definitions of compensation are necessary to fully encompass the nature of this hypothesis.

One key element of compensatory activity that is often not addressed by imaging studies is the outcome of compensatory activity. Studies suggest that not all compensation is beneficial. Low-performing older adults frequently upregulate additional areas compared to high-performers and younger adults. Low-performing older adults typically overrecruit right PFC (Cabeza et al., 2002; Duverne, Motamedinia, & Rugg, 2009; Grossman et al., 2002; Persson et al., 2006), and one study also reported overrecruitment in left PFC (Rosen et al., 2002). Since these additional recruitments were used by low-performers, they ultimately provided no benefit in performance. Similarly, subsequent forgetting effects in older adults are often associated with upregulation of alternate areas, yet this does not lead to successful memory for an item (Daselaar et al., 2003; Morcom et al., 2003; Stevens et al., 2008). Further, studies that describe compensatory overrecruitment in PFC are inconsistent, with some studies finding overrecruitment and others finding underrecruitment in the same areas for low-performing older adults (Cabeza et al., 2002; Duverne et al., 2009; Rosen et al., 2002). Thus, while the compensation hypothesis may explain

brain activity in high-performers, it does not adequately describe the neural patterns observed in low-performers. Given these inconsistencies, the compensation hypothesis is not sufficient to explain neural activation patterns in older adults because it lacks information on the beneficial or non-beneficial outcome of compensatory activity.

Dedifferentiation and Compensation as Complementary Processes

There is substantial evidence for both dedifferentiation and compensation when examining performance variability in older adults. Age-related cognitive decline is normative and requires compensation for maintenance of task performance. Studies of successful and unsuccessful memory performance suggest that an unhealthy trajectory of aging also exists and may be driven by dedifferentiation of specialized processes in the brain, leading to use of alternate strategies that ultimately do not aid performance. Researchers are still unclear on which hypothesis provides the most effective explanation for brain activity in older adults.

The present study argues that current definitions of compensation do not address the outcome of compensatory activity. Determining whether compensation is beneficial or non-beneficial to performance is crucial resolve the debate between compensation and dedifferentiation. Using a performance-based framework, this paper suggests that compensation and dedifferentiation are complementary age-related processes that occur under different circumstances: high-performing older adults may represent healthy individuals who are able to use beneficial compensatory neural strategies, while low-performing older adults may represent individuals in the disease continuum who use non-beneficial neural strategies due to dedifferentiation. Both compensation and dedifferentiation may occur as complementary age-related processes, and each presents under different circumstances. Thus, categorizing

participants based on memory performance rather than diagnosis may reduce one source of variability and improve consistency of neuroimaging findings.

High- and Low-Performers on the AD Continuum

If high- and low-performing older adults exhibit significantly different neural patterns of activation, it is likely that these two populations will follow different temporal trajectories as they age further. Studies consistently indicate that MCI and AD exist on a continuum rather than as discrete diagnostic categories. This is evidenced by the multiple pathophysiological similarities between MCI and early AD individuals (Albert et al., 2011; deToledo-Morrell et al., 2004; Dickerson et al., 2001; Guillozet et al., 2003; Killiany et al., 2000; Small, Nava, Perera, Delapaz, & Stern, 2000; Small, Tsai, DeLaPaz, Mayeux, & Stern, 2002; Sunderland et al., 1999) and high MCI to AD conversion rates (Bowen et al., 1997; Friedrich, 1999; Petersen et al., 2001). This study hypothesizes that low-performing older adults may represent a very early stage of the AD continuum and possess a similar relationship to preclinical AD or MCI populations; they may be at much higher risk to follow a preclinical AD or MCI trajectory compared to their high-performing counterparts.

Studies of the DMN provide support for this hypothesis. Healthy older, MCI, and AD individuals show disrupted patterns in DMN deactivations compared to younger adults (Celone et al., 2006; Greicius et al., 2004; Lustig et al., 2003; Sperling et al., 2009). Disruptions in the DMN have also been linked to amyloidosis in asymptomatic and mildly impaired individuals (Sperling et al., 2009). Additionally, coactivation between hippocampus and the DMN is found in healthy older and young adults but lacking in AD patients. Thus, it appears that one mechanism by which episodic memory declines in early AD is via dysfunction of DMN areas (i.e., hippocampus) that support memory function.

In summary, disruptions in the DMN are consistently observed across various stages of the AD continuum, from asymptomatic amyloid-positive older adults, to adults diagnosed with AD. This suggests that there are specific, measurable cognitive changes associated with an AD trajectory. Given the evidence for disrupted DMN in low-performing older adults and subsequently forgotten items in older adults (Miller et al., 2008; Stevens et al., 2008), it is likely that low-performing older adults could represent individuals on the AD trajectory as well. Low-performers may be in or at high risk for the preclinical AD stage.

It is worth nothing that this hypothesis is consistent with the concept of Cognitive Reserve (CR), which is one explanation for the commonly observed variability in clinical expression of AD. CR describes that brain resiliency due to individual differences in education and IQ may serve a protective factor against pathology, leading to significant variability in dementia diagnosis (Birren & Schaie, 2001). Stern (2006) suggests that these individuals may cope with disease-related neurodegeneration in one of two ways: first, they may possess greater *neural reserve*, which is defined as a preexisting neural network characterized by greater efficiency or capacity. These networks are the same ones used by healthy individuals to cope with increased task load. Second, individuals with high CR may engage in *neural compensation* by developing alternate networks not used by healthy adults. Stern (2006) describes several studies in which neural compensation leads to improvement in performance (Cabeza et al., 2002; Grady et al., 2003; Rosen et al., 2002). However, CR does not address situations in which compensatory activity is not beneficial. While individual variability in CR may delay disease pathology, it is ultimately not preventive. Thus, it is possible that CR has a moderating effect on disease pathology: beneficial compensatory activity may reflect 1) a healthy aging process, or 2) greater CR. Non-beneficial compensatory activity reflects disease pathology, which may present

as 1) less severe in those individuals who have lower CR, or 2) more severe in those individuals with greater CR. If this is true, performance-based approach is still beneficial because all low-performers would have neural patterns consistent with preclinical AD, regardless of CR. CR would simply dictate when the preclinical AD symptomology manifests, such that individuals with high CR may progress more slowly than individuals with low CR.

Prose Recall Paradigm

In order to study a preclinical AD population, researchers need a task that is sensitive enough to detect the earliest cognitive changes in AD. However, this has continued to be an area of difficulty for researchers. In AD, initial changes in episodic memory are minimal and individuals can remain relatively stable for up to 7 years prior to diagnosis. Accelerated decline only occurs when disease pathology has worsened significantly near diagnosis (Bäckman et al., 2001; Rubin et al., 1998; Sliwinski, Hofer, Hall, Buschke, & Lipton, 2003). Thus, many neuropsychological tests lack the sensitivity to detect subtle cognitive changes associated with a preclinical AD population. This methodological problem may further contribute to the variability observed when assessing older adult episodic memory.

While list-learning tasks have traditionally been used by researchers to measure episodic memory decline, Storandt & Hill (1989) reported that the Logical Memory subtest of the Wechsler Memory Scale (WMS) (Wechsler, 2009), a prose recall task, is actually more sensitive in differentiating adults with very mild, mild, and no AD. Other studies indicate that prose recall and generation ability is specifically altered in AD individuals (Ellis, 1996; Haut, Demarest, Keefover, & Rankin, 1994; Johnson, Storandt, & Balota, 2003; Kemper et al., 1993; Lyons et al., 1994). A longitudinal study of older adults found that declines in performance on the Logical Memory subtest actually precede clinical detection of AD (Rubin et al., 1998). Given the

sensitivity of this task, prose comprehension could potentially be a valuable tool to improve understanding of early, subtle declines associated with preclinical AD.

Psycholinguistic theories describe prose comprehension on three levels of processing: first, individual words in a text must be disambiguated into propositions, or idea units. Second, propositions must be integrated with meaning to form a *textbase representation*, a mental representation of a text based on its organizational structure. Finally, inferences based on prior knowledge are integrated into the textbase representation to deepen meaning. It is proposed that integration and inference occur in an iterative cycle known as construction-integration: inferences are constructed, and those that are semantically relevant are selectively integrated into the textbase representation. This cycle continues until a coherent and stable textbase is formed (Kintsch & van Dijk, 1978; Kintsch, 1988, 1998; Mason & Just, 2006).

These levels of processing have been linked to specific patterns of neural activity in healthy younger adults: surface-level processing of syntax and idea units occurs in left temporal areas, integration of text elements and ideas occurs in right temporal areas, and inference based on prior knowledge occurs in frontal, parietal, and precuneus areas (Bottini et al., 1994; Caplan & Dapretto, 2001; Just et al., 1996; Mason & Just, 2004; Mazoyer et al., 1993; Nichelli et al., 1995; Robertson et al., 2000; St George, Kutas, Martinez, & Sereno, 1999; Tomitch, Newman, Carpenter, & Just, 2008; Xu et al., 2005). Prose comprehension is a highly specialized task in which neural resources are allocated very specifically to each level of processing.

This specialization is particularly useful for functional neuroimaging because it means that neural activation patterns are extremely sensitive to task manipulations. Previous studies in this laboratory have found that manipulation of story structure via genre elicits age- and disease-specific patterns of activity that may reflect the earliest declines in episodic memory. Genres

included expository (factual information about the basic structure, functioning, or sequence of events commonly learned about in school) and narrative (a sequence of causally and temporally related events, with a main protagonist who engages in an action to fulfill a goal) text. Compared to younger adults, healthy older adults showed overactivation in areas involved in episodic retrieval and inference (left posterior cingulate) during expository prose comprehension. Compared to healthy older adults, AD adults showed deactivation in areas involved in inference and integration (right anterior cingulate, right superior temporal) during narrative prose comprehension (Wang, 2011). These preliminary findings suggest that a prose comprehension task that manipulates discourse structure via genre type may be sensitive enough to detect the earliest episodic memory declines in AD.

In summary, it seems that the earliest episodic memory declines in AD may stem from disturbances in ability to organize, integrate, and infer during discourse processing. One method to examine these differences is via manipulation of story genres with distinct organizational structures, and preliminary studies indicate that this method is effective at eliciting age- and disease-specific differences in brain activation. The sensitivity of this task may be particularly useful when attempting to detect very subtle declines in preclinical AD that are otherwise undetectable using conventional memory tasks.

Current Study

The goal of this study was to improve understanding of the AD continuum by examining sources of variability among older adults. This investigation aimed to resolve two major sources of variability:

1) Errors in diagnostic overlap were addressed by using a performance-based approach. An older adult sample of “healthy” and “very mild AD” individuals were re-

categorized into high- and low-performers. It was also suggested that this approach will reconcile the roles of compensation and dedifferentiation in aging.

2) Methodological errors related to task sensitivity were addressed by using a novel, diagnostically sensitive prose recall paradigm to identify and elicit subtle neural differences among high- and low-performing older adults. fMRI was used to measure brain activity during prose comprehension, and a post-scan behavioral task was used to measure prose recall.

It was hypothesized that these two changes would reduce within-group variability in older adult samples. It was further hypothesized that they would differentiate two categories of older adults who exhibit neural patterns consistent with a complementary view of compensation and dedifferentiation: high-performers who represent a healthy aging population undergoing normal age-related decline and use beneficial, compensatory strategies; and low-performers who represent a preclinical AD population undergoing dedifferentiation and breakdowns in neural circuitry and use non-beneficial strategies. Individual differences in CR may additionally serve a moderating effect with respect to high- and low-performers: for individuals with greater CR, compensatory activity may eventually become non-beneficial as disease pathology worsens and CR can no longer serve a protective function.

The following results were predicted:

1) AD and older adults diagnosed as “healthy” will consist of both high- and low-performers, supporting the hypothesis that diagnostic overlap is a major contributor to older adult variability.
2) fMRI will confirm previous findings with more robust results, and support a complementary dedifferentiation and compensation model:

a. Low-performers will exhibit the previously found "disease effect" of deactivation in ACC and right temporal lobe during comprehension of narrative prose, suggesting that low-performing older adults are on a pathological disease trajectory that involves dedifferentiation and breakdown of specialized neural systems.
b. High-performers will exhibit the previously found "age effect" of increased activation of PCC during comprehension of expository prose, suggesting that high-performing older adults are on a healthy aging trajectory that involves additional, compensatory activation of brain areas to maintain performance.

Method

Participants

All participants were right-handed, monolingual, native English-speaking adults. Older adult participants with (n=11) and without dementia (n=10) were recruited from the University of Kansas Alzheimer's Disease Center. The presence or absence and severity of dementia were obtained by a medical clinician trained in AD diagnostic issues using the Clinical Dementia Rating (CDR; Morris, 1993). Healthy older adults **(HOA)** met inclusion criteria that included cognitively intact subjects aged 60 and above, and a CDR rating of 0 (no AD). Demented older adults **(AD)** met inclusion criteria that included a CDR rating of 0.5 (Very Mild AD). All healthy younger adult **(YA)** participants (n=10) were recruited through local area advertisements and met the same health exclusion criteria as older adult participants.

Stimulus Materials

Two story genres were presented: expository stories, which were didactic and factual in nature, and narrative stories, which involved a protagonist who underwent a sequence of events

to fulfill a goal. All stories were adopted from Wolfe (2005), who examined differences in underlying organizational structure of narrative and expository prose and its effects on prose recall.

All stories were decomposed using a technique known as *propositional analysis*. Propositional analysis models and decomposes text into *propositions*, which are defined as the smallest idea unit in discourse (Turner & Greene, 1977). While propositions may often take the form of individual words (i.e., "Becky," "lived"), it should be noted that some propositions may be comprised of multiple words that form a single concept (i.e., "best friend," "second floor"). Propositional analysis is based on the construction-integration theory of discourse processing; propositions are derived by analyzing the degree of semantic relatedness and connectedness of different text elements. This technique yields a model of prose that is rich in semantic meaning and it has been shown to effectively predict prose recall and comprehension (Kintsch & van Dijk, 1978; Kintsch, 1994; Ratcliff & McKoon, 1978; Zwaan & Radvansky, 1998).

Experimental Task

The experimental task consisted of two components: fMRI during stimulus presentation, and an immediate post-scan recall task.

fMRI task. All participants were auditorally presented with 18 sensical stories (9 expository, 9 narrative) and 6 nonsensical, scrambled (3 expository, 3 narrative). Nonsensical stories were not analyzed for the purposes of this experiment. Stories were presented binaurally using scanner-safe, noise-attenuating headphones to minimize competing scanner noise. Stories were presented in blocks containing baseline, countdown, story presentation, and rehearsal conditions. First a 15 second baseline condition consisting of a Korean translation of identical story content was presented. The baseline condition was followed by a 7 second

delay/countdown, which was then followed by a 60 second story presentation. Each story was followed by 2.5 seconds of instructions in which subjects were asked to mentally rehearse the story they previously heard; this was done to encourage further semantic elaboration and encoding of the story in preparation for the post-scan recall task. After instructions were presented, participants were given 15 seconds of rehearsal time. These blocks were repeated for all 18 stories.

Recall task. Immediately following scanning, participants were read the same story segments that they heard in the scanner and instructed to remember the story for a recall test afterwards. Thus, intentional recall ability was measured. Presentation of stories was randomized for each participant. After presentation of all stories, participants performed a free recall task in which they were cued with the title of the story and asked to recall as much detail as they could. All free recall was audiotaped and transcribed for scoring purposes.

fMRI Procedure

Data acquisition. Functional data was acquired on a head-only Siemens 3.0 Tesla Allegra MRI scanner as gradient echo blood oxygen level dependent (BOLD) scans in 45 contiguous axial slices (TR=3000ms, TE=30ms, flip angle=90˚, FOV=192mm, 64 x 64 matrix, slice thickness=3mm, in-plane resolution=3x3mm). Prior to functional imaging, high-resolution T1 weighted anatomical images were collected for anatomical localization and coregistration of the functional images (magnetization-prepared rapid gradient echo [MPRAGE]; TR=2300ms, TE=3.05ms, TI= 1100ms flip angle=8˚, FOV=240mm, 267x185 matrix, slice thickness=1mm, in-plane resolution 1.3x0.9mm).

All data analysis was performed on SPM8 (Wellcome Department of Cognitive Neurology, London, UK) running under MATLAB r2010b (The MathWorks, Natick, MA, USA)

on Windows 7. Anatomical and functional images were first manually reoriented along the anterior commissure and posterior commissure (AC-PC) line. Functional images were realigned to the first image of the run to account for subject motion. Anatomical and functional data were spatially normalized to a standard Montreal Neurological Institute (MNI) template using parameters generated under the unified segmentation procedure. Functional images were smoothed using a 6mm FWHM Gaussian filter. The experiment was modeled using a boxcar function of Korean Fixation and Sensical Story conditions convolved with a canonical hemodynamic response function. Individual participant motion parameters were entered into the model as regressors of no interest. All conditions required sustained vigilance to stimuli, therefore the contrast of condition effects was designed to capture activity specific to story comprehension. Contrasts of Story conditions (Sensical > Korean) were applied in a second level analysis using a 2x2 ANOVA with group (High-HOA, Low-HOA) as a between-subjects independent variable and contrast (Expository vs. Korean, Narrative vs. Korean) as the within-subjects independent variable. In SPM, these analyses are equivalent to conducting a second level random-effects analysis using a two-sample t-test.

Between-group fMRI analyses between younger and older adults can be problematic due to age-related changes in vasculature, metabolism, brain morphology, and signal to noise ratio (Buckner, Snyder, Sanders, Raichle, & Morris, 2000; D'Esposito, Deouell, & Gazzaley, 2003; Fotenos, Snyder, Girton, Morris, & Buckner, 2005; Huettel, Singerman, & McCarthy, 2001; Raz et al., 2005; Samanez-Larkin & D'Esposito, 2008). Younger adult BOLD responses and brain structure may not serve as an adequate comparison group for older adult brains. This study attempted to overcome this problem by segregating subjects into high- and low-performers for between-group comparison.

fMRI of older adults is also a challenge because of the *partial voluming problem*. This occurs when one voxel mistakenly contains two different tissue types due to loss of contrast between adjacent tissue types. Partial voluming causes further problems when smoothing is applied (which is commonly used in preprocessing to correct for intersubject variability); non-gray voxels are coded as false positive "activations," leading to overestimation of activation (Momenan, Rawlings, Fong, Knutson, & Hommer, 2004). To ensure our clusters were localized to gray matter, gray matter probability maps were created (see Momenan et al., 2004 for details on calculation) for HOA and AD groups by averaging individual gray matter maps created in the unified segmentation process and creating binary group masks with a lower boundary of p=.25. These maps were used as inclusive masks in our second level analyses; any voxel that had a 25% or greater probability of being gray matter was included in analysis, while any voxel that had less than a 25% probability of being gray matter was not included in analysis. Thus, we accounted for the partial voluming problem by using a more conservative analysis. Anatomic localization was then determined using the computerized Talairach Client (Lancaster et al., 1997) within the Wake Forest University (WFU) Pickatlas (Maldjian, Laurienti, Kraft, & Burdette, 2003), and confirmed by visual inspection.

Behavioral Procedure

Data analysis. Scoring followed procedures outlined by (Johnson et al., 2003), who reported that veridical scoring of the Logical Memory subtest of the WMS (Wechsler, 2009) using propositions rather than the standard criteria had greater predictive validity for AD severity. The WMS standard scoring criteria requires recall of certain phrases, many of which contain several propositions. Scoring based on propositions allows for more units of measurement, which removes a significant amount of ambiguity compared to scoring phrases

that contain multiple idea units. This scoring technique also allows for greater flexibility in capturing variability in prose recall responses (Johnson et al., 2003).

Using this method, propositions were scored based on *veridical* or *nonveridical* recall. Veridical recall includes reproduction of the exact proposition as well as different tenses of that proposition. Nonveridical recall includes 1) *gist* recall, reproduction of the proposition's general meaning that is not veridical, and 2) *distorted* recall, reproduction of an unrelated proposition. Aging is associated with decreased veridical recall ability and increased reliance on gist (Balota et al., 1999; Tun, Wingfield, Rosen, & Blanchard, 1998; Watson, Balota, & Sergent-Marshall, 2001); therefore, gist recall will be included in scoring to increase the range of possible items. Veridical and gist responses were given a score of 1. Distorted recall and unrecalled propositions were given a score of 0. The total number of veridical and gist reproduced propositions were summed to yield a total recall score for each story.

High- and low-performers. High- and low- performers were segregated by median split on total propositional recall score (i.e., high-performers perform above the 50^{th} percentile and low-performers perform below the 50^{th} percentile). This method has been successfully used in previous studies to segregate high- and low-performers (Duarte, Ranganath, Trujillo, & Knight, 2006; Duverne et al., 2009; Miller et al., 2008; Stevens et al., 2008). However, when the median split was performed, all HOA were categorized as high-performers and all but one AD participant was categorized as a low-performer. Discussion on why this was the case follows. To gather preliminary results on neural patterns in high- and low-performers, each group was segregated by median split into high-and low-performers. The between-group contrasts examined included High-HOA only, Low-HOA only, High-HOA vs. Low-HOA, High-HOA vs. Low-YA, and Low-HOA vs. High-AD.

Results

Demographics

The older adult groups were similar in age (two-tailed *t*-test, $t = 1.06$, $p \leq .30$) but not in gender distribution due to recruitment difficulties. The 10 YA included 6 men and 4 women who ranged in age from 22 to 29 years (M=25.6, SD=2.37). The 10 HOA (CDR=0) included 6 men and 4 women who ranged in age from 65 to 83 years (M=73.5, SD =5.46). The 11 AD adults (CDR=0.5) included 7 men and 4 women who ranged in age from 61 to 81 years (M=71, SD=5.35). All individuals identified their primary race as white, non- Hispanic (N=31).

Prose Recall Task

Discriminant analysis was used to determine if healthy and AD adults would differ significantly on a linear combination of two variables: mean narrative story recall, and mean expository story recall. Univariate analyses showed that both variables produced significant differences between diagnostic groups (Table 1). Multivariate analysis showed that there was a significant difference between mean narrative and expository recall (λ=.24, $X^2(2)$=25.71, p<.001, R^2 canonical=.76). Results showed that both variables contributed to the multivariate effect, though expository story recall had greater predictive capability (Table 2). Reclassification of diagnosis based on the new canonical variables resulted in 90.5% correct classification, with a 81.8% sensitivity and 100% specificity. A receiver-operating characteristic curve indicated that both mean expository recall (area under the curve=1.00, 95% confidence interval 1.00-1.00) and mean narrative recall (area under the curve=.93, 95% confidence interval .80-1.00) reliably distinguished healthy older from AD adults (see Figure 1).

Given the sensitivity of the expository story recall task, discriminant analysis was again used to determine which specific stories had the highest loadings on prediction of diagnosis.

When all expository stories were included as variables to predict diagnosis, univariate analysis showed that all stories produced significant differences between healthy and AD adults (Table 3). Multivariate analysis demonstrated that there was a significant difference between recall on all expository stories (λ=.065, $X^2(9)$=39.54, p<.001, R^2 canonical=.94). Results indicated that the stories with the greatest predictive capability were "Matter" and "Government." There was some inconsistency between the standardized canonical function coefficients and their structure weights (Table 4), which may have been a result of multicollinearity of recall of the different stories. Reclassification of diagnosis using these 9 expository stories as new canonical variables resulted in 100% correct classification, with a 100% sensitivity and 100% specificity.

Johnson et al. (2003) previously reported that inclusion of gist recall in propositional analysis of the Logical Memory subtest actually decreases diagnostic sensitivity to dementia status, compared to using veridical recall alone. Our results did not consistently support these previous findings. For example, when gist recall was removed from the discriminant analysis that used mean expository and mean narrative recall as predictor variables, this yielded a model with the improved sensitivity (90.2%) and specificity (100%) compared to the original (gist and veridical) model, consistent with Johnson et al. (2003). However, when gist recall was removed from the discriminant analysis using individual expository stories as predictor variables, this yielded a model with decreased sensitivity (81.8%) and specificity (100%) compared to the original (gist and veridical) model. These findings do not support Johnson et al.'s (2003) previous reports; however, it should be noted that the genre of story in the Logical Memory subtest is narrative. Thus, our results suggest that inclusion of gist recall may improve diagnostic sensitivity for expository prose recall, but not narrative prose recall.

Imaging Results

Voxel-wise examination of gray matter volumes was performed for all group analyses. To isolate the activation specific to story comprehension, all contrasts involved comparison of stories to their Korean translations. Korean was chosen because it is not comprehendible to English speakers, yet is still perceived as a language because it has some phonemic overlap with English and has a relatively simple syllabic structure (Wang, Park, & Lee, 2006). Thus, the Korean translated stories provided baseline activation for audition of phonemes lacking semantic content. This method has previously been used successfully in this laboratory to isolate brain activation during story encoding (Wang, 2011).

To segregate older adults into high- and low-performers, a median split was performed on all older adult participants (HOA and AD). Median split showed that all but one AD participant was categorized as a low-performer, and all HOA participants were categorized as high-performers. There are two likely explanations for these results. First, previous studies of high- and low-performers included only apparently healthy older adults. It is very likely that even our CDR=0.5 AD participants were too impaired and therefore an inappropriate population to use to study earlier, subtle changes in AD. Second, using a performance-based approach to recategorize our older adult participants may have been unsuccessful due to the sensitivity of our prose recall paradigm. High- and low-performers were no different than our diagnostic categories, contrary to our original predictions. Thus, we were unable to examine unique, performance-based differences.

To examine the hypothesis that neural activation patterns may be indicative of a disease or healthy aging trajectory, the 10 HOA participants were divided using median split into high- and low-performers for neuroimaging analysis. High-HOA were significantly different than

Low-HOA in mean prose recall task performance ($t(8)=-3.55$, $p<.008$). High-HOA were also contrasted with Low-YA, though these two groups were not significantly different from each other in mean task performance ($t(8)=-.56$, $p<.59$). Finally, Low-HOA were contrasted with High-AD, and these groups were significantly different in mean task performance ($t(8)=-3.14$, $p<.014$). It should be noted that results from these analyses should be interpreted cautiously due to small sample size. See Tables 5 and 6 for a summary of all peak activation regions.

High performers only. Expository stories (vs. Korean) were associated with peak activation in R postcentral gyrus/somatosensory cortex (BA 3) (see Appendix, Figure A1) and L middle temporal gyrus (BA 21), $p<.0001$ (uncorrected), k=5 voxels. Narrative stories (vs. Korean) were associated with peak activation in L superior temporal (BA 22) and bilateral middle temporal gyrus (BA 21), $p<.001$ (uncorrected), k=5 voxels (Figure 2).

Low performers only. Expository stories (vs. Korean) were associated with activation in L middle temporal/parietal regions (BA 21/39), $p<.0001$, k=5. Narrative stories (vs. Korean) were associated with activation in L superior temporal (BA 22), bilateral middle temporal gyrus (BA 21/22), and bilateral insula (BA 13), $p<.0001$, k=5 (Figures 3, 4).

High- and low-HOA. To examine areas of activation specific to High-HOA, a contrast of High-HOA vs. Low-HOA was analyzed. Expository stories (vs. Korean) were associated with activation in R anterior cingulate (BA 24), $p<.001$, k=5 (Figure 3). Narrative stories (vs. Korean) were associated with activation in L cerebellum, $p<.05$, k=5.

To examine areas specific to low-HOA, a contrast of Low-HOA vs. High-HOA was analyzed. Expository stories (vs. Korean) were associated with activation in L cerebellum and L middle/inferior frontal areas that corresponded to dorsolateral prefrontal cortex (DLPFC) (BA 46), $p<.001$, k=5) (Figure 4). Narrative stories (vs. Korean) were associated with activation in L

cerebellum, R inferior parietal (BA 40) (see Appendix, Figure A2), and R superior frontal/DLPFC (BA 9) regions, $p<.0005$, k=7) (Figure 4).

High-HOA vs. Low-YA. We also wanted to determine whether there were age-specific differences between high-performing HOA and younger adults (High-HOA vs. Low-YA contrast). Compared to Low-YA, High-HOA showed greater activation for expository stories (vs. Korean) in L superior temporal (BA 38), L middle temporal (BA 21), R posterolateral temporal (BA 21), and L lingual gyrus (BA 18), $p<.001$, k=5. High-HOA also showed greater activation for narrative stories (vs. Korean) in bilateral ventral inferior frontal gyrus (BA 47), $p<.01$, k=5) (Figure 3).

Low-HOA vs. High-AD. To determine the differences between low-performing HOA and individuals with the mildest AD, we contrasted Low-HOA vs. High-AD. There were few differences between these two groups. For expository stories (vs. Korean), Low-HOA showed greater activation in R precentral gyrus (BA 6) (see Appendix, Figure A3) and R parahippocampus (BA 36), $p<.001$, k=5). For narrative stories (vs. Korean), Low-HOA showed greater activation in only R parahippocampus (BA 28), $p<.01$, k=6 (Figure 5).

Discussion

Prose Recall Task

One aim of this study was to use a novel, sensitive prose recall paradigm to elicit subtle changes in early AD. Results of the discriminant analysis showed that our prose recall task was extremely sensitive to subtle changes in early AD. Mean expository and narrative story recall reliably differentiated healthy adults from those diagnosed with very mild AD (CDR=0.5), with 81.8% sensitivity and 100% specificity. Mean expository recall had greater predictive power compared to narrative recall, and when individual expository stories were analyzed as predictors

using discriminant analysis, this produced a model with 100% sensitivity and 100% specificity. These results are comparable to or even more robust than many commonly used neuropsychological assessments. For example, the Mattis Dementia Rating Scale was found to have 98% sensitivity (for individuals already diagnosed with AD) and 97% specificity (Monsch et al., 1995). The Logical Memory subtest of the WMS-R has been shown to have 58% sensitivity for a very mildly demented group and 95% specificity for healthy older adult controls (Brown & Storandt, 2000). A study on the Montreal Cognitive Assessment (MoCA) showed that it had greater sensitivity for mild AD (100%) and greater specificity (87%) compared to the MMSE (78% sensitivity, 100% specificity) (Nasreddine et al., 2005).

Many researchers have examined the utility of combining subtests to detect AD. Our prose recall task demonstrates comparable sensitivity and specificity to these batteries as well. For example, Welsh, Butters, Hughes, Mohs, & Heyman (1991) tested the sensitivity and specificity of a word-list learning task from the Consortion to Establish a Registry for Alzheimer's Disease (CERAD) battery. The authors found that delayed recall was the best discriminator between healthy adults and those with mild, moderate, or severe AD, with 86% sensitivity for mild AD and 96% specificity. Salmon et al. (2002) determined that a combination of delayed recall, verbal fluency, and global cognitive status tests (i.e., the Mattis Dementia Rating Scale) had 96% sensitivity and 93% specificity for a very mild AD group. It should also be noted that several of the aforementioned studies measured diagnostic sensitivity for a mild AD group, while our study examined very mild AD individuals in even earlier stage of AD. This further supports the sensitivity of our task. Our prose recall task not only demonstrates comparable sensitivity and specificity, but has the added benefit of being a less complex and time-consuming task compared to these multi-test batteries.

Finally, previous studies in this laboratory found that scoring the Logical Memory subtest of the WMS using the same propositional scoring technique employed in this study greatly improved its sensitivity for detecting very mild AD (84%) and specificity (87%) (Johnson et al., 2003). The current results indicate that use of specific story genres, particularly expository, further improves the sensitivity of a prose recall task.

These findings provide strong preliminary evidence that our novel prose recall task is a highly sensitive diagnostic test for very mild AD. The task is inexpensive and does not require extensive training to administer, unlike many neuropsychological batteries. Moreover, since each story is only presented for 60 seconds, the task is short in duration and could be easily administered at a routine medical appointment. This would greatly reduce fatigue effects which may lead to inaccurate conclusions or diagnosis. The task's overall practicality and sensitivity to subtle episodic memory changes makes it a potentially useful tool to study early cognitive changes in preclinical AD.

Neuroimaging: Prose Comprehension

We found that both high- and low-performers recruited areas of the brain consistent with previous neuroimaging studies of prose comprehension. High-HOA alone showed increased activation in bilateral middle temporal and L superior temporal regions during comprehension of both story types (see Figure 2). Compared to Low-YA, High-HOA also overrecruited areas of L superior/middle temporal lobe. There regions are thought to be responsible for disambiguation and integration of story propositions (Just et al., 1996; Mazoyer et al., 1993; Robertson et al., 2000; St George et al., 1999; Tomitch et al., 2008; Xu et al., 2005). Low-HOA alone activated L middle temporal areas during expository story comprehension, and L superior temporal and bilateral middle temporal areas during narrative story comprehension. These were the same areas

that High-HOA recruited, though Low-HOA recruited them to a greater degree (Figure 1). Thus, both high- and low-performers activated prose comprehension regions. However, Low-HOA also showed noncompensatory overrecruitment of several regions that were inappropriate for a prose comprehension task, suggesting that dedifferentiation led to a decrease in optimal performance. These findings are discussed below.

High Performers

Although neuroimaging results did not support our original hypothesis that high-performers would exhibit an age effect seen as activation of PCC regions, results were consistent with research on discourse processes and supportive of a compensation hypothesis.

Evidence for compensation. Our results showed that high-performing HOA exhibited increased activation in several areas compared to both Low-YA and Low-HOA. Because High-HOA achieved high performance, these additional activations likely served a beneficial function, thus supporting the compensation hypothesis. These areas include posterolateral temporal, ventral inferior frontal, anterior cingulate, and lingual gyrus regions (see Figure 3).

Posterolateral temporal and ventral inferior frontal areas. Compared to Low-YA, High-HOA exhibited greater activation in a posterolateral region of R temporal lobe during encoding of expository prose, and greater bilateral activation in bilateral ventral inferior frontal gyrus (IFG) during encoding of narrative prose. These areas are consistent with the results found in a similar study conducted by Grossman et al. (2002) that investigated sentence comprehension in high- and low-performing older adults. The authors identified that sentence processing involves left perisylvian regions (posterolateral temporal and ventral IFG) as well as an extrasylvian support network (right homologues of perisylvian regions, bilateral DLPFC, bilateral dorsal IFG) that engages working memory when sentences become long or grammatically complex (Caplan,

Alpert, Waters, & Olivieri, 2000; Friederici, 2002; Luke, Liu, Wai, Wan, & Tan, 2002; Reuter-Lorenz et al., 2000; Rypma & D'Esposito, 2000). Grossman et al. (2002) found that high-performing older adults recruit these perisylvian and extrasylvian regions during sentence comprehension, while low-performers do not and instead overrecruit alternate areas of left prefrontal cortex, left dorsal IFG, and bilateral striatum. Our findings parallel these results and indicate that High-HOA maintain the ability to engage L perisylvian sentence processing areas (L ventral IFG), as well as extrasylvian support areas (R posterolateral temporal, R ventral IFG) for comprehension of prose. Grossman et al. (2002) posited that the ability to use L perisylvian regions is crucial to maintain successful performance. Moreover, the presence of R ventral IFG activation specifically during narrative prose comprehension is consistent with Grossman et al.'s hypothesis that these extrasylvian support regions are utilized when a task becomes more difficult. Additional activity in R/bilateral IFG has also been linked to successful performance in older adults in studies on verbal encoding (Rosen et al., 2002) and subsequent memory effects for words (Morcom et al., 2003). Taken together, these results indicate that High-HOA require additional activation to comprehend prose compared to YA. However, they are able to achieve successful performance by recruiting specific L perisylvian sentence processing regions and extrasylvian support networks. Because they retain the ability to recruit these specialized networks, these findings support a compensation rather than a dedifferentiation hypothesis.

Anterior cingulate. When compared to Low-HOA, High-HOA recruited a posterior region of R anterior cingulate (ACC) during expository story comprehension. There is evidence that ACC functions within a larger top-down attentional control system such that it evaluates the need for attentional allocation (Botvinick, Cohen, & Carter, 2004; Milham et al., 2002). For example, ACC activation is consistently found in younger adults who perform the Stroop task

(Barch et al., 2001; Bush et al., 1998; Carter et al., 2000; Kerns et al., 2004; Pardo, Pardo, Janer, & Raichle, 1990). Milham et al. (2002) found increased ACC activation when older adults performed the Stroop task, and the authors suggest this may be indicative of a failing attentional control system. However, Stevens et al. (2008) found increased ACC activation when older adults subsequently remembered items, suggesting that additional ACC activation may be beneficial. Our findings that High-HOA showed greater ACC activation compared to Low-HOA are similarly indicative of a beneficial effect. Thus, it is possible that 1) High-HOA recruited ACC to compensate for age-related cognitive declines, or 2) that Low-HOA underrecruited ACC, which may represent earliest stages of attentional dyscontrol that is often seen in AD (Baddeley, Baddeley, Bucks, & Wilcock, 2001; Balota & Duchek, 1991; D.A. Balota et al., 1999; David A Balota & Faust, 2001; Spieler, Balota, & Faust, 1996).

Lingual gyrus. Results also showed that High-HOA had greater activation in L lingual gyrus compared to Low-YA. Though lingual gyrus activity is commonly observed in studies of visual encoding (Beason-Held, Golski, Kraut, Esposito, & Resnick, 2005; Grön et al., 2003; Schiavetto, Köhler, Grady, Winocur, & Moscovitch, 2002; Schwindt & Black, 2009; Stern et al., 1994), researchers have also found bilateral lingual gyrus activity in verbal encoding tasks (Kalpouzos et al., 2009). Increased lingual gyrus activation has been associated with greater accuracy in performance (Springer, McIntosh, Winocur, & Grady, 2005; van der Veen, Nijhuis, Tisserand, Backes, & Jolles, 2006) and with subsequently remembered items (Morcom et al., 2003). It has been suggested that these additional activations could represent an age-related reliance on more surface-level, visual encoding strategies to carry out verbal tasks (Morcom et al., 2003). Our findings that High-HOA recruited lingual gyrus support the notion that these additional activations serve a compensatory purpose in older adults. Though lingual gyrus is a

less specialized area, it appears that using this region is still an effective, beneficial strategy for High-HOA.

Other areas of activation.

Cerebellum. High-HOA showed greater activation in R and L cerebellum compared to both Low-YA and Low-HOA (respectively) during comprehension of expository prose. There is a growing body of literature that supports a cerebellar role in various areas of cognition, including working memory, language, and attention (Cabeza & Nyberg, 2000; Chen & Desmond, 2005; Desmond & Fiez, 1998; Hogan et al., 2011; Paul et al., 2009; Schmahmann, 2004). It has been suggested that cerebellum works in conjunction with frontal areas to facilitate executive control (Cabeza & Nyberg, 2000; Hogan et al., 2011). Some studies have found increased cerebellar activity in older adults during encoding and retrieval of episodic memory (Beason-Held et al., 2005; Daselaar et al., 2003; Kalpouzos et al., 2009; van der Veen et al., 2006), which is consistent with our findings. It is possible that this additional cerebellar activity represents a strategy used by High-HOA used to compensate for age-related decline.

Studies also suggest that cerebellum plays a role in motor and perceptual timing (Ivry, Spencer, Zelaznik, & Diedrichsen, 2002; Penhune, Zattore, & Evans, 1998). For example, cerebellum activity has been found during tasks involving rhythm (Grahn & Brett, 2007) and temporal discrimination (Coull, Vidal, Nazarian, & Macar, 2004; Pastor, Day, Macaluso, Friston, & Frackowiak, 2004). Thus, one possible interpretation of our results is that our participants were tracking the temporal sequence of events during story presentation.

Somatosensory Cortex. High-HOA alone and compared to Low-HOA had significant activation in postcentral gyrus. Further inspection of this area showed that this region is the portion of somatosensory cortex responsible for sensations in the hands and fingers. Some

researchers have found that presentation of action words elicits activation in areas of somatosensory or primary motor cortex that are responsible for the body parts involved in those action words (Hauk, Johnsrude, & Pulvermüller, 2004; Raposo, Moss, Stamatakis, & Tyler, 2009). For example, presentation of an action word involving the legs elicits activation in sensorimotor regions that corresponds to foot movement (Hauk et al., 2004). Thus, it is possible that High-HOA detected action words in our story stimuli, leading to corresponding activations in somatosensory regions. However, if this is the case, it is unclear why High-HOA would detect these action words to a greater degree than Low-HOA. Perhaps this represents another compensatory strategy to improve story comprehension. Further studies must be conducted to expand on these findings.

Low Performers

We did find evidence that low-performers did not activate ACC to the degree that high-performers did (see previous discussion), consistent with one of our hypotheses. We did not observe decreased activation in right temporal lobe as originally hypothesized. However, results were still consistent with a dedifferentiation hypothesis.

Evidence for dedifferentiation. Results showed that Low-HOA overrecruited regions that were not recruited by High-HOA, including DLPFC and bilateral insula (see Figure 4). Since these overrecruitments were associated with lower performance, it is likely they represent a decreased ability to effectively recruit networks for specific tasks, consistent with a dedifferentiation hypothesis. Moreover, neural activity in Low-HOA was highly comparable to that of High-AD (see Figure 5), which supports the hypothesis that Low-HOA may be on a disease trajectory while High-HOA are not.

DLPFC. Low-HOA displayed greater activity in L inferior/middle portions of DLPFC compared to High-HOA when comprehending expository stories. Bilateral DLPFC is part of the extrasylvian support network that Grossman et al. (2002) identified for sentence comprehension, which is typically activated when a task increases in difficulty. Recall that High-HOA also activated portions of this extrasylvian support network (bilateral ventral IFG) during comprehension of narrative stories, which is consistent with Grossman et al.'s hypothesis because narrative stories require more inference and as a result are more difficult. However, Low-HOA recruited L DLPFC during comprehension of expository stories, which are easier to comprehend. Similarly, Grossman et al. (2002) found that low-performing older adults overrecruited L prefrontal regions during comprehension of easier sentences while high-performers did not. Thus, although Low-HOA still retain the ability to activate these extrasylvian support networks, they do not activate them under typical (i.e., difficult) circumstances. This may indicate that the underlying sentence comprehension network is disrupted. Moreover, activation of DLPFC does not have a beneficial effect on Low-HOA overall performance, indicating that using these specialized networks for this purpose is ineffective.

Low-HOA also activated superior portions of R DLPFC to a greater degree than High-HOA during narrative story comprehension, which is part of the extrasylvian support network discussed above. It has been established that bilateral prefrontal regions are active when encoding stories that involve inferences (Bottini et al., 1994; Caplan & Dapretto, 2001; Mason & Just, 2004; Nichelli et al., 1995), such as narratives, and right hemispheric "spillover" activation is often observed when language tasks become more difficult (Beeman et al., 1994; Ferstl, Rinck, & von Cramon, 2005; Xu et al., 2005). Given that narrative stories require inference and are relatively difficult, it is not entirely unexpected that Low-HOA would activate R DLPFC.

However, High-HOA did not overrecruit these areas, indicating that inference-making may have been more taxing on Low-HOA than High-HOA. Again, it appears that Low-HOA are still able to activate specialized language support networks that are typically used during difficult tasks. However, they are using these networks under conditions that may not be considered "difficult" for High-HOA.

Insula. When we examined the activity present in low-HOA alone, there was further evidence supporting a dedifferentiation hypothesis. Low-HOA alone showed additional activation in bilateral insula, which was not seen in High-HOA. Although insula is associated with emotional and sensorimotor processing, there is also evidence that it is involved in goal-directed cognition and switching between networks (Chang, Yarkoni, Khaw, & Sanfey, 2013). Insula activity has previously been found in tasks of verbal encoding in younger (Blumenfeld, Parks, Yonelinas, & Ranganath, 2011; Fletcher et al., 1995) and older adults (Dannhauser et al., 2008; Rosen et al., 2002). In many cases, insula activity has been associated with negative performance. For example, increased insula activity has been associated with subsequent forgetting effects in younger adults (Daselaar et al., 2004; Reynolds, Donaldson, Wagner, & Braver, 2004; Wagner & Davachi, 2001). Cabeza et al. (1997) similarly found that older adults showed greater bilateral insula activity compared to younger adults on a word pair recall task. In both older and younger adults, R insula activity was found to be negatively correlated with delayed test recall. Cabeza et al. (1997) concluded that increased insula activation may reflect an inability to inhibit detrimental processes in older age. Our results are consistent with these findings and overall support the dedifferentiation hypothesis: overrecruitment of bilateral insula by Low-HOA may represent a non-beneficial strategy that is employed due to cognitive

disruptions. Since these non-beneficial overrecruitments were not observed in High-HOA, it is likely these disruptions are not age-specific and may be an early indicator of a disease process.

Low-HOA and High-AD. Patterns of neural activity in Low-HOA were remarkably similar to High-AD. Compared to High-AD, Low-HOA had greater activation in R phg during comprehension of both story types. This is consistent with well-documented evidence of changes in hippocampal volume (Apostolova et al., 2006; Csernansky et al., 2005; Dickerson et al., 2001; Jack et al., 1999; Schuff et al., 2009) connectivity (Allen et al., 2007; Scheff, Price, Schmitt, & Mufson, 2006; Sheline et al., 2010; Wang et al., 2010), and pathology (Braak & Braak, 1991; Burton et al., 2009; Dubois et al., 2007; Mirra et al., 1991; Sheline et al., 2010) in early AD.

Low-HOA also showed greater activations in the supplementary motor area (SMA) of R precentral gyrus. There is evidence that SMA is part of a larger network responsible for word production and planning (Indefrey, 2011; Smith & Jonides, 1997). Researchers have proposed that SMA may be involved in speech encoding (Indefrey & Levelt, 2004) or execution (Alario, Chainay, Lehericy, & Cohen, 2006). Thus, it is possible that our Low-HOA were more successful at encoding the stories compared to High-AD. It is also possible that our Low-HOA were subvocally rehearsing as they attempted to encode the stories for future recall.

Although they are diagnostically categorized as different, our results reveal that Low-HOA and High-AD are cognitively similar and may simply fall on different ends of the AD continuum. Patterns of brain activity in our Low-HOA largely paralleled those of High-AD, suggesting that they either failed to activate task-specific networks or activated them under inappropriate circumstances, leading to their poor performance.

Other areas of activation.

Cerebellum. Compared to High-HOA, Low-HOA showed greater activation in L cerebellum for both expository and narrative story comprehension. As discussed previously, there is some evidence for increased activity in cerebellum in older adults during episodic memory encoding and retrieval (Beason-Held et al., 2005; Daselaar et al., 2003; Kalpouzos et al., 2009; van der Veen et al., 2006). Daselaar et al. (2003) found that older individuals who had a decline in cognitive functioning displayed greater cerebellar activity compared to older adults who had not experienced a decline in cognitive functioning. However, this additional activity was not only present in Low-HOA because we also observed that High-HOA overrecruited R cerebellum (compared to Low-YA). Thus, it is possible that the activity observed in cerebellum simply reflects an age difference in episodic memory processing. Further research needs to be done to clarify the role of cerebellum in episodic memory encoding.

R inferior parietal areas. Compared to High-HOA, Low-HOA additionally overrecruited R inferior parietal areas during narrative story comprehension. R inferior parietal regions are widely seen in neuroimaging studies of working memory in younger adults, and some researchers have proposed that this area mediates phonological storage (Braver et al., 1997; Grossman et al., 2002; Jonides et al., 1998, 1998; Paulesu, Frith, & Frackowiak, 1993). In an fMRI study of sentence comprehension in older adults, Grossman et al. (2002) found that both high- and low-performing older adults overrecruited R inferior parietal regions. It is still unclear why we found this pattern in low-performers, but not in high-performers.

Some studies of working memory have found a relationship between inferior parietal activation and cognitive load that follows an inverse U shape: activity in inferior parietal areas increases as a function of cognitive load, then levels off as cognitive load has reached its capacity. This *capacity-constrained* response has been observed in in younger (Callicott et al.,

1999; Linden et al., 2003) and older adults (Nyberg, Dahlin, Stigsdotter Neely, & Bäckman, 2009). It is possible that our Low-HOA experienced greater cognitive load during narrative story comprehension compared to High-HOA. However, Nyberg et al. (2009) proposed that increases in inferior parietal regions are accompanied by compensatory frontal activations, which we did not observe. Additionally, although declines in working memory have been observed in normal aging (Balota, Dolan, & Duchek, 2000; Bopp & Verhaeghen, 2005; Borella, Carretti, & De Beni, 2008; McCabe, Roediger, McDaniel, Balota, & Hambrick, 2010; Rypma, Prabhakaran, Desmond, Glover, & Gabrieli, 1999), MCI (Economou, Papageorgiou, Karageorgiou, & Vassilopoulos, 2007; Gagnon & Belleville, 2011; Nordahl et al., 2005; Saunders & Summers, 2010), and AD (Economou et al., 2007; Gagnon & Belleville, 2011; Johnson, Storandt, Morris, & Galvin, 2009; Lim et al., 2008), it has been proposed that these declines are not a direct effect of disrupted working memory but rather a result of disruption of other processes such as attention (Balota et al., 2000; Germano & Kinsella, 2005; McCabe et al., 2010) or processing speed (Rypma & D'Esposito, 2000; Salthouse, 1991). Thus, the overrecruitments in R inferior parietal areas still remains unclear and further studies must be conducted before conclusions can be drawn about the role of this region in prose comprehension.

Future Directions

Preliminary results of our prose recall task strongly suggest that this is a sensitive test for very mild AD. Future research should be conducted to determine replicability, to ascertain which specific stories have the greatest predictive capability, and to develop norms for standardization. Given the sensitivity of this task, future studies examining its ability to diagnose MCI or preclinical AD are warranted.

Due to the discriminatory ability of our prose recall task, there was too little variability remaining in our sample to test the hypothesis that using a performance-based approach would more accurately categorize individuals in a preclinical AD stage. Although we were unable to divide HOA two significantly different groups of high- and low-performers, small sample size (n=5) suggests that these results are preliminary and should be interpreted with caution. This may explain why we were unable to replicate the age and disease effects as originally hypothesized, or why we found some unclear patterns of activation in areas such as sensorimotor and inferior parietal cortex. To improve validity of results, future studies should examine a larger sample of healthy older adults such that there is a sufficient amount of variability to examine high- and low-performers.

We used a whole-brain analysis to demonstrate that, overall, that high- and low-performers engage in different patterns of brain activity. Future studies should focus on region of interest (ROI) analyses to specify which brain regions are consistently correlated with successful performance. Additionally, using a regression based approach may reveal regions of the brain that lead to better performance if activated to a greater degree.

Conclusion

Early diagnosis of AD continues to be a struggle for aging and dementia researchers due to significant overlap in pathology, cognitive ability, and neural activity in older adults. Multiple stages of pathology in between healthy aging and AD have been found, such as MCI and amyloidosis in asymptomatic older adults, suggesting that the disease trajectory begins years before our ability to detect it. As such, there has been a shift towards studying an earlier, preclinical stage of AD. Although advancements are being made in biomarker research, a coherent description of cognitive change in preclinical AD is still lacking. Unless sources of

variability are clarified, studies of older adults will continue to be contaminated with preclinical individuals who are undetectable using conventional screening methods.

This study aimed to understand variability in older adult episodic memory by using two approaches. First, a novel, sensitive prose recall task was used to elicit the earliest changes in cognitive ability. Second, healthy older adults were divided into high- and low-performers to decrease within-group variability and determine the neural signatures of successful and unsuccessful performers.

Results demonstrated the sensitivity of our novel prose recall task in segregating healthy older adults from those with very mild AD. Using task performance as a between-groups comparison, we were able to parse out the variability in our healthy older adult sample into two groups of high- and low-performers. fMRI showed that all older adults recruited bilateral temporal and frontal regions during story comprehension, consistent with the literature on discourse processing. This suggests that regardless of performance, older adults still maintain some ability to recruit specialized prose comprehension regions of the brain. However, examining patterns of activation in high- and low-performers revealed that each group overrecruited different areas to carry out the task. These findings have implications for the specific circumstances in which compensation and dedifferentiation occur in older adults.

High-HOA activated specialized areas for sentence processing (R posterolateral temporal and bilateral ventral IFG) and attentional control (ACC). These temporal/frontal networks were the same ones observed in a previous study by Grossman et al. (2002) which examined sentence comprehension in high- and low-performing older adults. We additionally observed increased activation of lingual gyrus. Though this is not a higher-order processing area, it has been linked to successful memory performance in older adults and may reflect a shift towards more surface-

level encoding strategies. Thus, the neural activity exhibited by High-HOA suggests that specialized, compensatory brain regions are used to achieve successful performance.

In contrast, neural activity in Low-HOA was characterized by noncompensatory overrecruitment of language support areas that are typically used when tasks are more difficult (bilateral DLPFC). These regions were not activated in High-HOA. Again, consistent with Grossman et al. (2002), we found that Low-HOA are characterized by an inability to effectively use specialized language processing networks. Low-HOA alone also evidenced nonselective overrecruitment of areas linked to unsuccessful verbal encoding (insula), which further supports the dedifferentiation hypothesis. Moreover, Low-HOA resembled High-AD except for additional activations in R parahippocampal gyrus, suggesting that these two groups may be on a similar disease trajectory.

Overall, these results provide compelling evidence that examining performance variability on a prose recall task may be an effective way to differentiate healthy aging from AD at early, asymptomatic stages. High-performers may represent individuals undergoing a healthy aging process. This healthy aging process is characterized by a preserved ability to recruit specialized areas that aid their performance; it is ultimately compensatory in nature. In contrast, low-performers may represent individuals undergoing a disease-related dedifferentiation process. This process involves noncompensatory overrecruitment of areas that are inappropriate to carry out the task at hand, contributing to their poor performance.

Results from this study demonstrate that there is a clear link between episodic memory task performance, neural activity, and AD status. This has significant implications for researchers studying preclinical AD because we have identified that different trajectories of aging exist and that they can be detected by examining patterns of brain activity. These neural

changes occur early in the disease process and are so subtle that they manifest as variation in task performance. Thus, neural activity patterns may be a new, promising biomarker to study. Examining the neural signatures of performance variability can allow us to distinguish healthy and unhealthy trajectories of aging. In conjunction with research on pathophysiological and cognitive changes, this will continue to improve our definitions of preclinical AD.

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Table 1
Means (standard deviations) and ANOVA results

	Healthy	**AD**	**F, *p***
Mean Expository Recall	18.48 (1.90)	9.45 (3.39)	55.07, $p<.001$
Mean Narrative Recall	25.28 (2.21)	14.66 (6.73)	22.61, $p<.001$

Table 2
Standardized canonical coefficients and structure weights from the discriminant model

	Standardized Coefficients	**Structure Weights**
Mean Expository Recall	1.37	.96
Mean Narrative Recall	-.51	.61

Table 3
Means (standard deviations) and ANOVA results: expository stories

Story	Healthy	AD	F, *p*
Behaviorism	15.00 (3.43)	6.64 (2.80)	37.72, $p<.001$
Circulatory System	22.20 (4.26)	12.63 (6.52)	15.48, $p=.001$
Civil War	19.50 (2.88)	10.91 (5.07)	22.16, $p<.001$
Forest Fires	21.40 (3.37)	9.09 (5.05)	42.20, $p<.001$
Government	23.10 (4.07)	12.55 (5.05)	27.47, $p<.001$
Matter	13.70 (4.16)	5.36 (1.57)	38.29, $p<.001$
Nervous System	15.10 (3.73)	6.55 (2.73)	36.48, $p<.001$
Tornadoes	20.20 (4.13)	13.45 (6.77)	7.40, $p=.014$
Volcanoes	16.10 (4.01)	7.91 (3.99)	21.98, $p<.001$

Table 4
Standardized canonical coefficients and structure weights: expository stories

Story	Standardized Coefficients	Structure Weights
Behaviorism	.95	.37
Circulatory System	.90	.24
Civil War	.81	.29
Forest Fires	.57	.39
Government	-1.61	.32
Matter	1.22	.38
Nervous System	.70	.37
Tornadoes	-1.01	.17
Volcanoes	-.22	.29

Table 5
Coordinates for significant clusters of gray matter during prose comprehension in high-performing healthy older adults

Region (Brodmann Areas)	Peak MNI Coordinate				
	k	***x***	***y***	***z***	***t***
High-HOA Only					
Expository vs. Korean					
R postcentral gyrus (BA3)	12	45	-25	55	9.72[a]
L middle temporal gyrus (BA21)	6	-57	-7	-11	8.90[a]
Narrative vs. Korean					
L superior temporal gyrus (BA22)	64	-63	-22	4	8.88[c]
L superior temporal gyrus (BA21)	With above	-60	-10	-2	7.28[c]
L middle temporal gyrus (BA21)	With above	-54	-1	-17	6.92[c]
R middle temporal gyrus (BA21)	7	57	-19	-5	6.25[c]
High-HOA vs. Low-HOA					
Expository vs. Korean					
R anterior cingulate gyrus (BA24)	6	12	-13	40	7.06[d]
R postcentral gyrus (BA3)	5	45	-25	55	5.78[d]
Narrative vs. Korean					
L cerebellum	6	-15	-40	-14	2.54[f]
High-HOA vs. Low-YA					
Expository vs. Korean					
L superior temporal gyrus (BA38)	11	-42	14	-32	6.90[b]
L middle temporal gyrus (BA21)	With above	-48	8	-32	6.19[b]
L lingual gyrus (BA18)	9	-15	-79	-2	6.81[b]
R cerebellum	7	15	-49	-23	6.56[b]
R posterolateral temporal gyrus (BA21)	5	54	-46	7	5.66[b]
Narrative vs. Korean					
L ventral inferior frontal gyrus (BA47)	19	-51	29	-5	4.18[e]
L ventral inferior frontal gyrus (BA47)	With above	-42	23	-11	3.81[e]
R ventral inferior frontal gyrus (BA47)	5	42	23	-14	3.77[e]

[a]Contrast significant at the $p<.0001$ level (uncorrected), cluster threshold k=5 voxels
[b]Contrast significant at the $p<.0005$ level (uncorrected), cluster threshold k=5 voxels
[c]Contrast significant at the $p<.001$ level (uncorrected), cluster threshold k=5 voxels
[d]Contrast significant at the $p<.002$ level (uncorrected), cluster threshold k=5 voxels
[e]Contrast significant at the $p<.01$ level (uncorrected), cluster threshold k=5 voxels
[f]Contrast significant at the $p<.05$ level (uncorrected), cluster threshold k=7 voxels
Peak voxels associated with significantly activated clusters. Only peak voxels are listed. Region labels are derived from Talairach atlas within the Wake Forest PickAtlas and confirmed with visual inspection on an average structural HOA image.

Table 6
Coordinates for significant clusters of gray matter during prose comprehension in low-performing healthy older adults.

Region (Brodmann Areas)	k	Peak MNI Coordinate *x*	*y*	*z*	*t*
Low-HOA Only					
Expository vs. Korean					
L middle temporal gyrus (BA21)	35	-57	-10	-14	13.75[a]
L middle temporal gyrus (BA21)	With above	-51	-13	-5	8.35[a]
L temporal/parietal gyrus (BA39)	6	-45	-67	22	8.10[a]
Narrative vs. Korean					
L superior temporal gyrus (BA22)	16	-63	-22	4	14.10[a]
L superior temporal gyrus	With above	-60	-13	1	10.10[a]
L middle temporal gyrus (BA21)	31	-51	-19	-14	10.80[a]
L middle temporal gyrus (BA21)	With above	-54	-10	-11	9.19[a]
L superior temporal gyrus (BA21)	With above	-48	-28	-8	7.29[a]
R insula (BA13)	6	39	-22	4	9.83[a]
L middle temporal gyrus (BA21)	6	57	-19	-8	8.65[a]
L insula (BA13)	6	-45	-16	1	7.57[a]
Low-HOA vs. High-HOA					
Expository vs. Korean					
L cerebellum	12	-3	-58	-4	8.34[c]
L middle frontal/DLPFC (BA46)	7	-45	32	25	7.25[c]
L inferior frontal/DLPFC (BA46)	5	-45	44	7	6.85[c]
L middle frontal/DLPFC (BA10)	11	-36	53	7	6.26[c]
Narrative vs. Korean					
R inferior parietal lobe (BA40)	9	51	-58	46	8.06[b]
L cerebellum	10	-36	-55	-44	7.12[b]
R superior frontal gyrus/DLPFC (BA9)	7	15	47	37	6.66[b]
R superior frontal gyrus/DLPFC (BA9)	12	33	47	34	6.57[b]
R superior frontal gyrus/DLPFC (BA9)	With above	39	41	34	3.62[b]
R superior frontal gyrus/DLPFC (BA9)	With above	24	44	34	3.60[b]
Low-HOA vs. High-AD					
Expository vs. Korean					
R precentral gyrus (BA6)	5	3	-25	52	6.26[c]
R precentral gyrus (BA6)	With above	6	-34	55	6.12[c]
R parahippocampal gyrus (BA36)	6	24	-43	-11	5.95[c]
Narrative vs. Korean					
R parahippocampal gyrus (BA28)	6	21	-10	-23	3.96[d]

[a]Contrast significant at the $p<.0001$ level (uncorrected), cluster threshold k=5 voxels
[b]Contrast significant at the $p<.0005$ level (uncorrected), cluster threshold k=7 voxels
[c]Contrast significant at the $p<.001$ level (uncorrected), cluster threshold k=5 voxels
[d]Contrast significant at the $p<.01$ level (uncorrected), cluster threshold k=6 voxels
Peak voxels associated with significantly activated clusters. Only peak voxels are listed. Region labels are derived from Talairach atlas within the Wake Forest PickAtlas and confirmed with visual inspection on an average structural HOA image. DLPFC=dorsolateral prefrontal cortex.

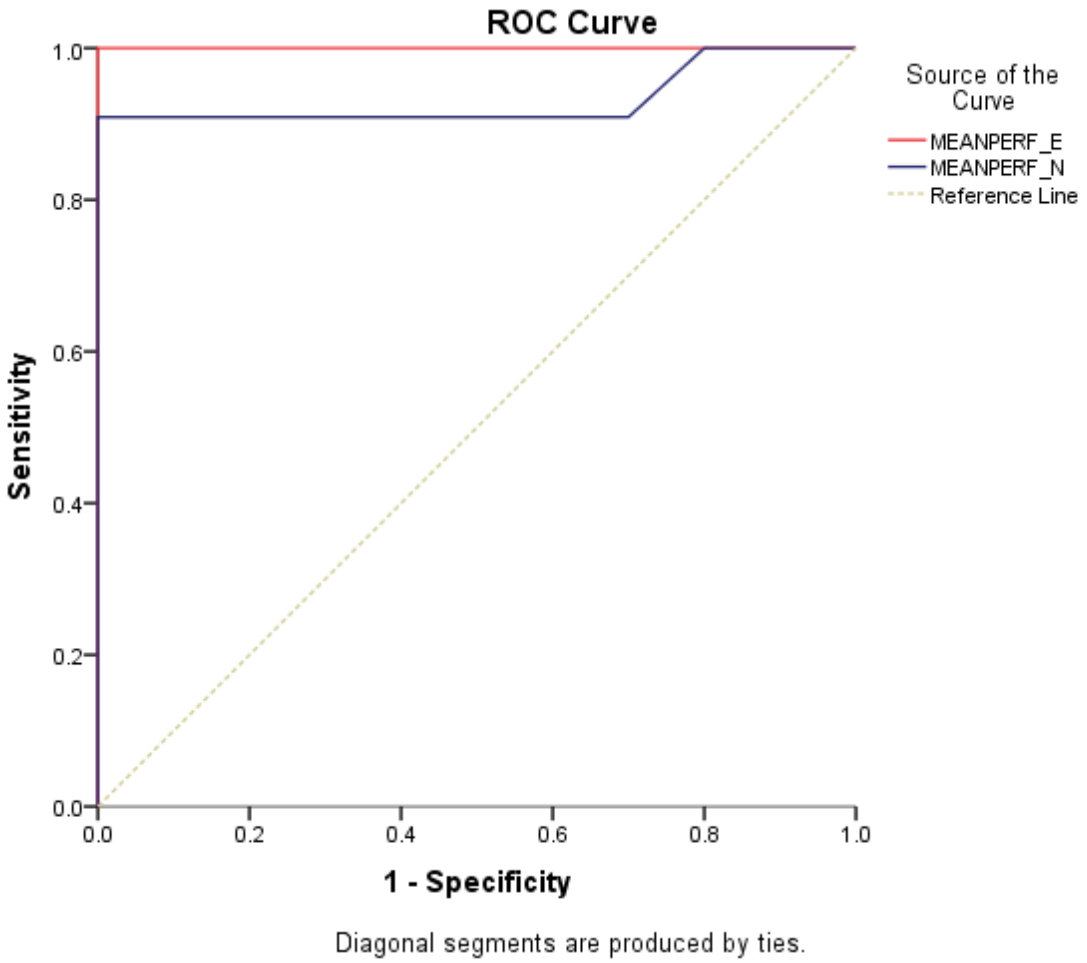

Figure 1. Receiver-operating characteristic curve for mean expository and narrative recall.

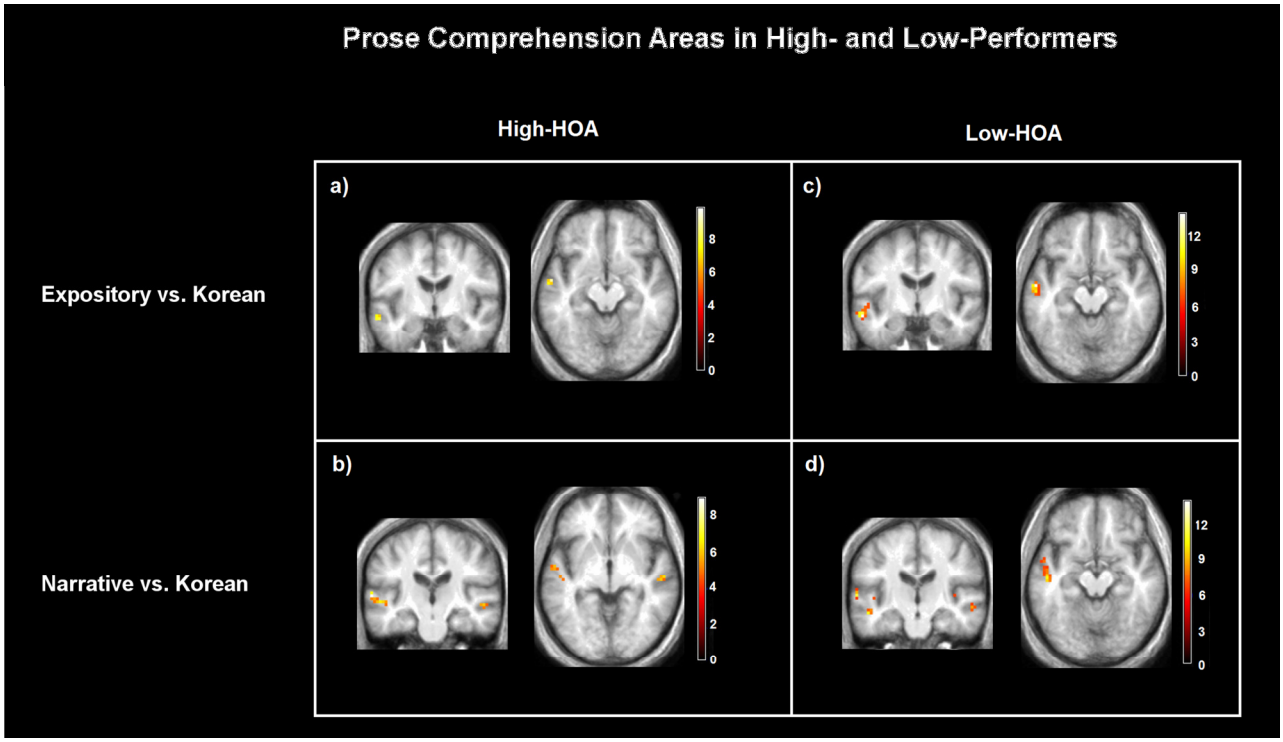

Figure 2. Prose comprehension regions activated in High-HOA during a) Expository vs. Korean task (p<.0001 (uncorrected), k=5) b) Narrative vs. Korean task (p<.001 (uncorrected), k=5), and Low-HOA during c) Expository vs. Korean task (p<.0001 (uncorrected), k=5) d) Narrative vs. Korean task (p<.0001 (uncorrected), k=5). Thresholded images were transformed into MNI stereotaxic space and converted into t-scores, which were projected onto an averaged T1-weighted anatomical images of subjects in the HOA group. Images are displayed using neurological convention (left hemisphere is on left). The range of t-scores is indicated in the accompanying color table.

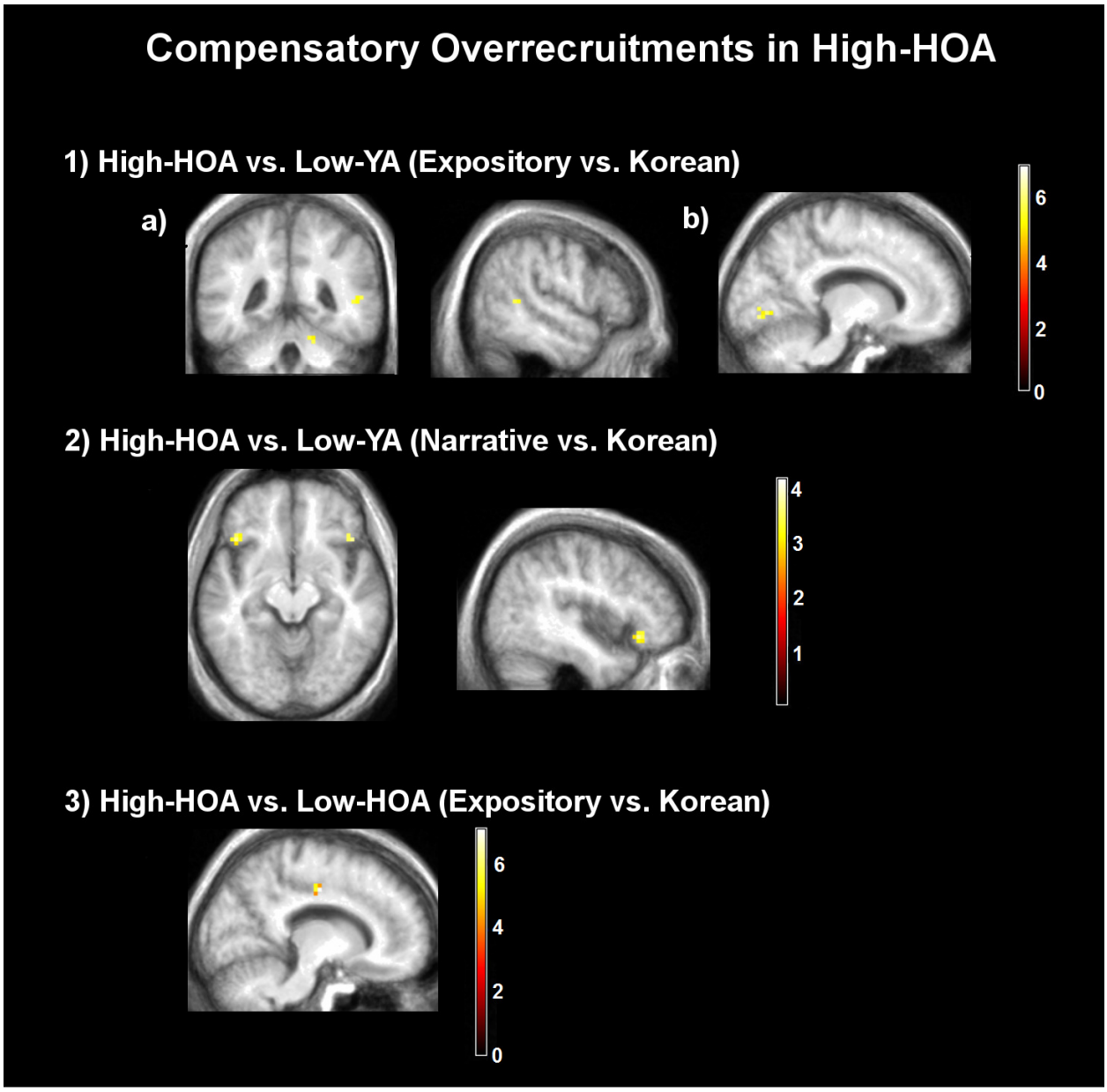

Figure 3. Regional activation patterns demonstrating compensatory overrecruitment in High-HOA versus 1) Low-YA during Expository vs. Korean task (p<.0005 (uncorrected), k=5) 2) Low-YA during Narrative vs. Korean task (p<.01 (uncorrected), k=5) 3) Low-HOA during Expository vs. Korean task (p<.002 (uncorrected), k=5). Regions of activation include 1a) R posterolateral temporal lobe 1b) L lingual gyrus 2) bilateral ventral inferior frontal gyrus 3) posterior portion of anterior cingulate cortex. Thresholded images were transformed into MNI stereotaxic space and converted into t-scores, which were projected onto an averaged T1-weighted anatomical images of subjects in the HOA group. Images are displayed using neurological convention (left hemisphere is on left). The range of t-scores is indicated in the accompanying color table.

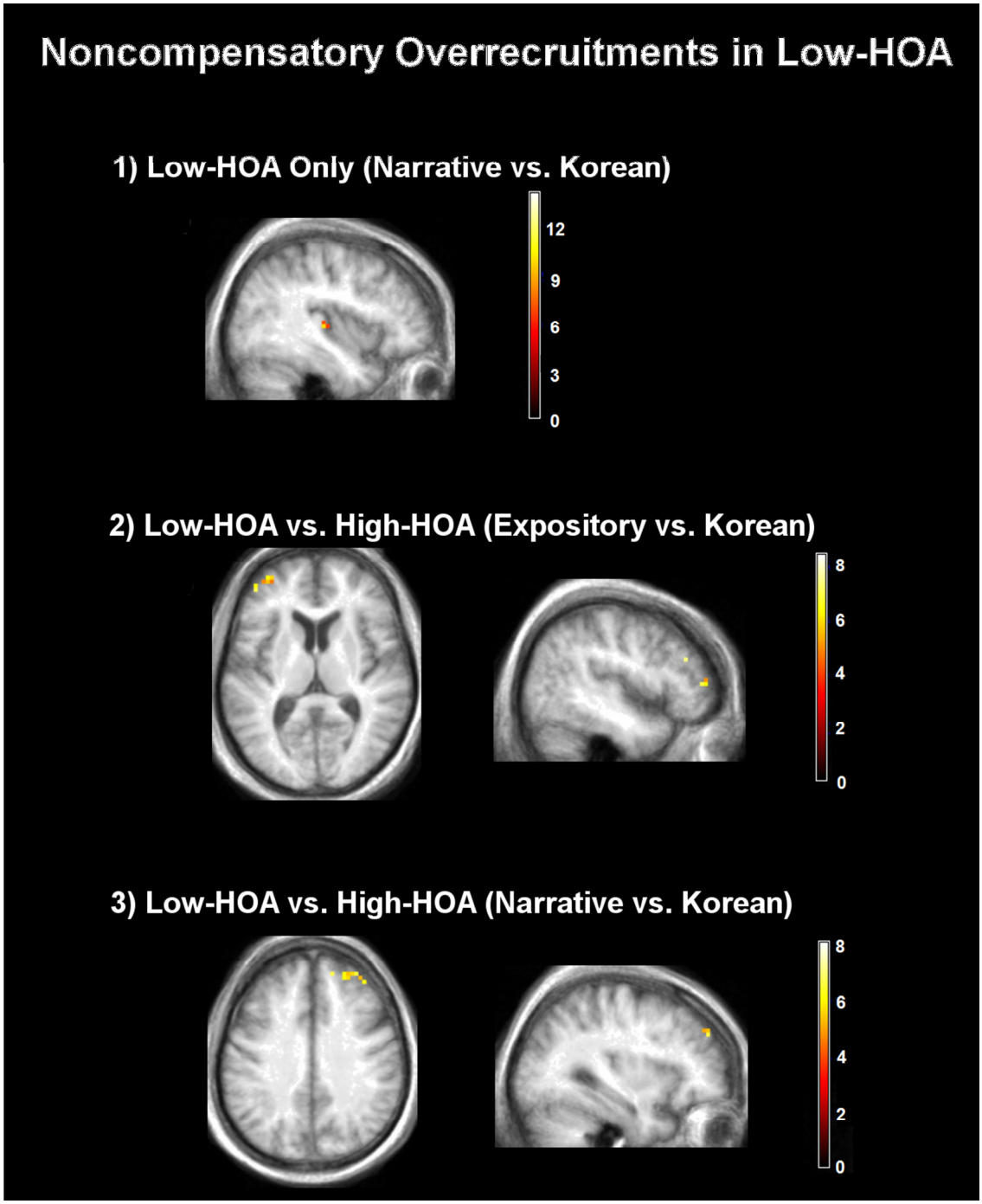

Figure 4. Regional activation patterns demonstrating noncompensatory overrecruitment in 1) Low-HOA only during Narrative vs. Korean task (p<.0001 (uncorrected), k=5) 2) Low-HOA vs. High-HOA during Expository vs. Korean task (p<.001 (uncorrected), k=5) 3) Low-HOA vs. High-HOA during Narrative vs. Korean task (p<.0005 (uncorrected), k=7). Regions of activation include 1) insula 2) L inferior/middle DLPFC 3) R superior DLPFC. Thresholded images were transformed into MNI stereotaxic space and converted into t-scores, which were projected onto an averaged T1-weighted anatomical images of subjects in the HOA group. Images are displayed using neurological convention (left hemisphere is on left). The range of t-scores is indicated in the accompanying color table.

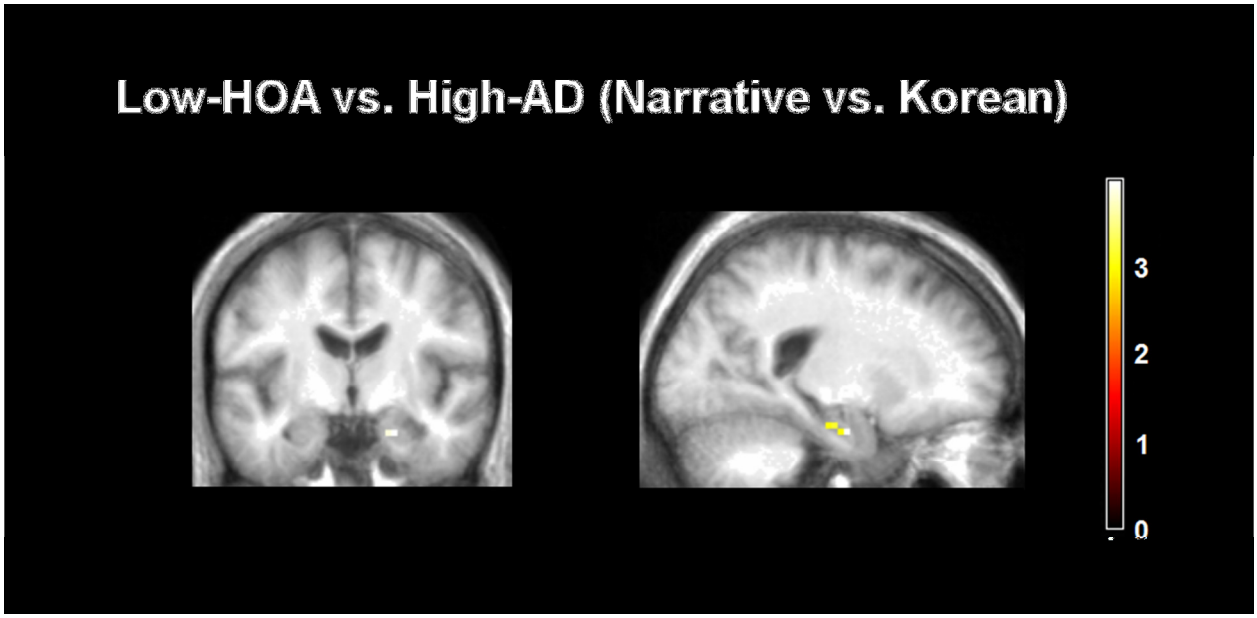

Figure 5. Regional activation in R parahippocampal gyrus demonstrating differences between Low-HOA and High-AD during Narrative vs. Korean task (p<.01 (uncorrected), k=6). Thresholded images were transformed into MNI stereotaxic space and converted into t-scores, which were projected onto an averaged T1-weighted anatomical images of subjects in the HOA group. Images are displayed using neurological convention (left hemisphere is on left). The range of t-scores is indicated in the accompanying color table.

Appendix

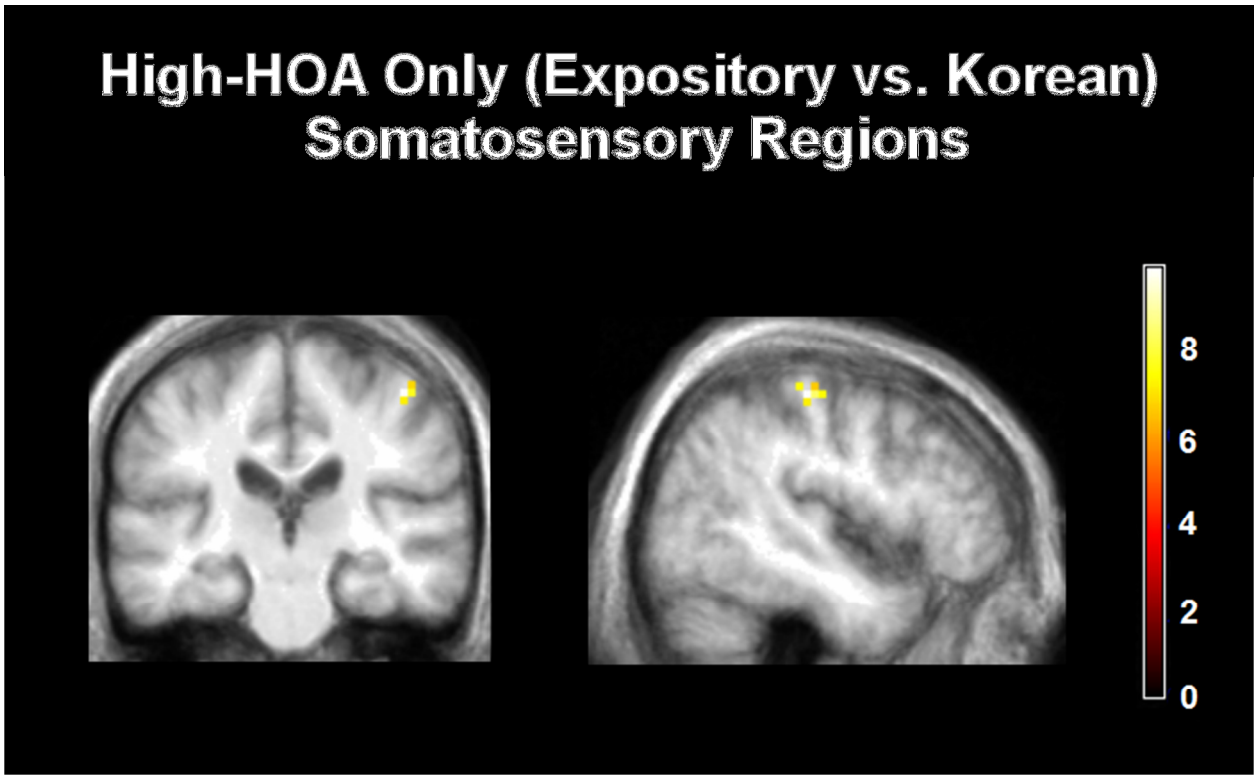

Figure A1. Somatosensory activations in High-HOA only during Expository vs. Korean task ($p<$ .0001 (uncorrected), k=5) in regions controlling sensation in the hands/fingers. Thresholded images were transformed into MNI stereotaxic space and converted into t-scores, which were projected onto an averaged T1-weighted anatomical images of subjects in the HOA group. Images are displayed using neurological convention (left hemisphere is on left). The range of t-scores is indicated in the accompanying color table.

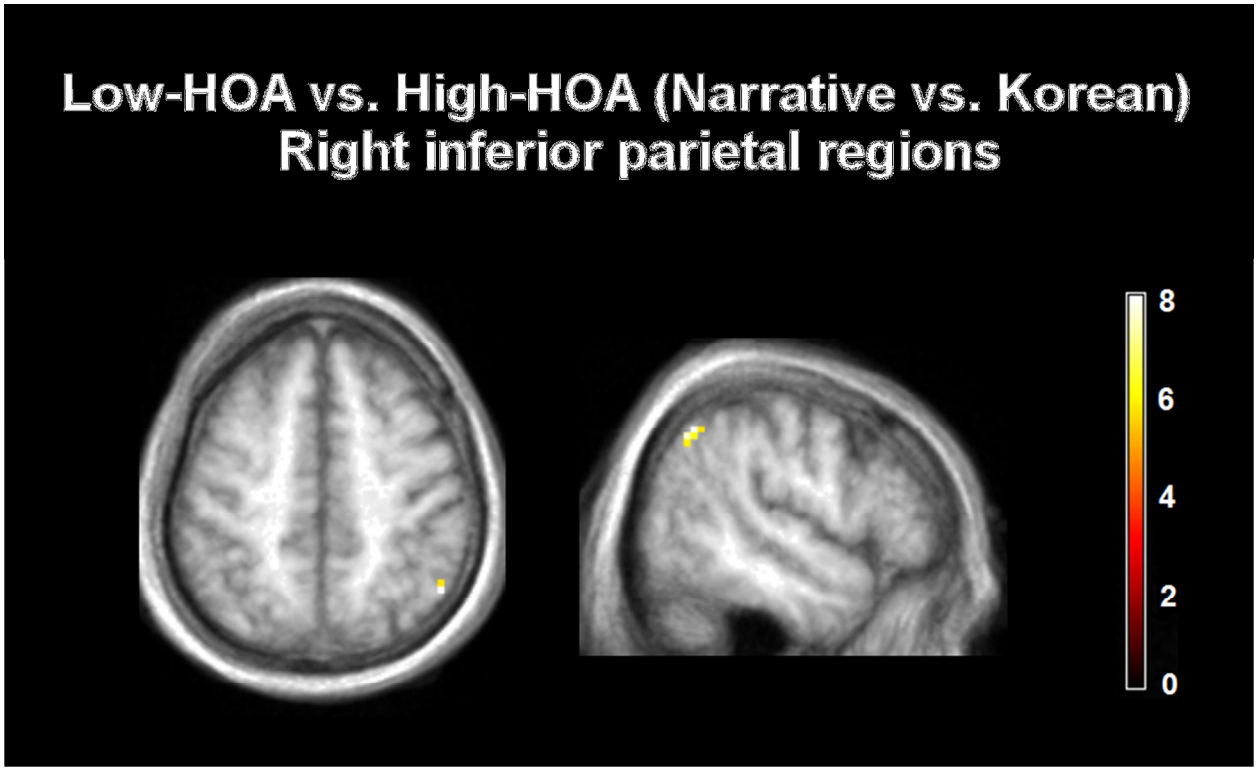

Figure A2. Activation in R inferior parietal regions in Low-HOA compared to High-HOA, during Narrative vs. Korean task ($p < .0005$ (uncorrected), k=7). Thresholded images were transformed into MNI stereotaxic space and converted into t-scores, which were projected onto an averaged T1-weighted anatomical images of subjects in the HOA group. Images are displayed using neurological convention (left hemisphere is on left). The range of t-scores is indicated in the accompanying color table.

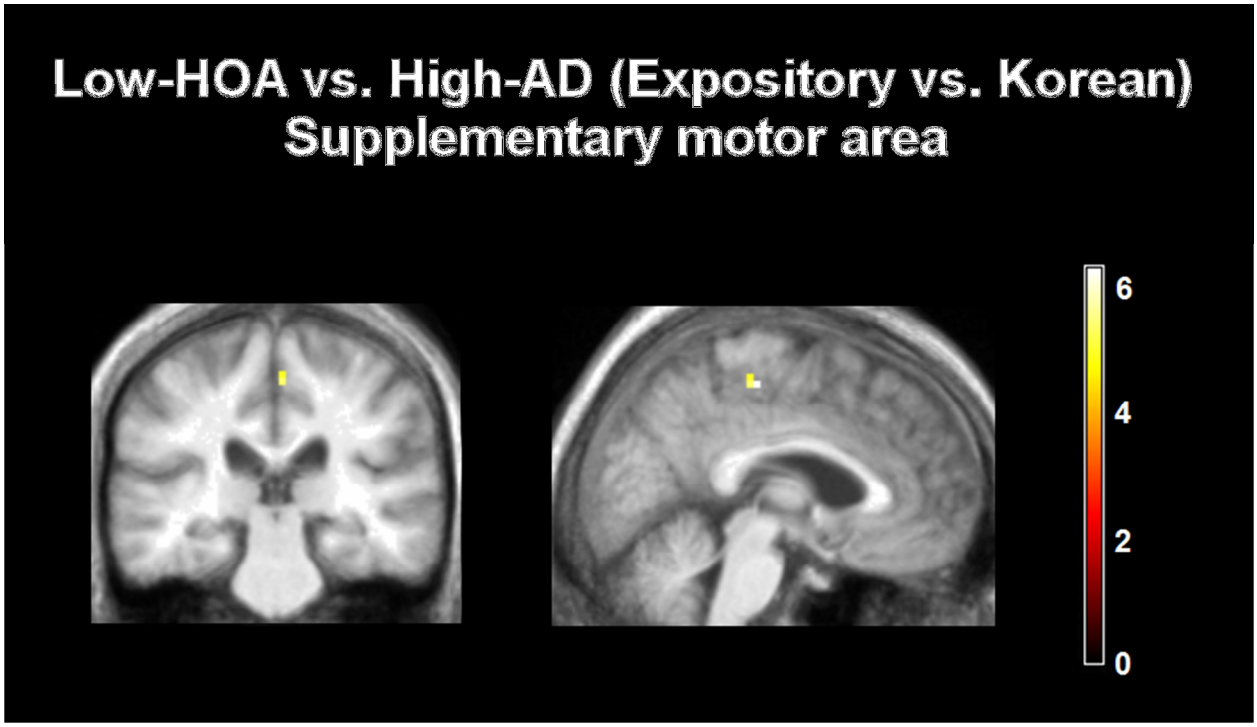

Figure A3. Supplementary motor area activations in Low-HOA compared to High-HOA, during Expository vs. Korean task ($p < .001$ (uncorrected), k=5). Thresholded images were transformed into MNI stereotaxic space and converted into t-scores, which were projected onto an averaged T1-weighted anatomical images of subjects in the HOA group. Images are displayed using neurological convention (left hemisphere is on left). The range of t-scores is indicated in the accompanying color table.