Neural Dedifferentiation in Relation to Risk for Alzheimer's Disease

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NEURAL DEDIFFERENTIATION IN RELATION TO RISK FOR ALZHEIMER'S DISEASE

By

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ABSTRACT
NEURAL DEDIFFERENTIATION IN RELATION TO RISK FOR ALZHEIMER'S DISEASE

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Functional magnetic resonance imaging (fMRI) research indicates that as an individual's age increases, the task-related spatial extent of neural activation increases. This decrease in neural specificity, or dedifferentiation, is often demonstrated by older adults during challenging cognitive tasks. Cognitively intact individuals at-risk for Alzheimer's disease (AD), as deemed by having an apolipoprotein-E ε4 allele or a family history of AD, demonstrate increased fMRI activation as compared to individuals at lower risk. Using a low effort, high accuracy event-related semantic memory task involving the presentation of famous and non-famous names, we examined spatial neural specificity through a measure of dedifferentiation using fMRI. In particular, the goal was to look at degree of dedifferentiation between older healthy subjects with or without risk factors for AD. Our results indicated that while there was not a significant difference between the two groups on the total amount of neural dedifferentiation, there was a significant interaction between stimulus type and risk group. Individuals at-risk for AD displayed greater dedifferentiation for non-famous names yet greater differentiation (i.e., less dedifferentiation) for famous names as compared to the low-risk group. These findings may reflect disturbances in memory formation for individuals at-risk for AD.

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Neural Dedifferentiation In Relation To Risk For Alzheimer's Disease

Previous studies using functional magnetic resonance imaging (fMRI) indicate that as age increases, the task-related spatial extent of neural activation increases (Cabeza, 2002; Langenecker, Nielson, & Rao, 2004). This decrease in neural specificity, or "dedifferentiation," is seen in older adults during challenging cognitive tasks, as evidenced by greater contralateral activation in older adults as compared to young adults (Cabeza, 2002). Specifically, older adults use more of their brain to successfully complete a task than do young adults (Nielson et al., 2002). Dedifferentiation has been shown to occur across a variety of tasks and systems including working memory (Reuter-Lorenz et al., 2000), episodic memory (Cabeza et al., 1997) and visual semantic category discriminations (Park et al. 2004).

There are three central theories to explain the reason for dedifferentiation: (1) compensation, (2) inefficiency, or (3) Scaffolding (Park & Reuter Lorenz, 2009). The theory of compensation posits that the increased activation seen in older adults enhances cognitive performance and counter-balances neurological decline (Cabaza, 2002). The extra activation, also known as hyperactivation or recruitment, allows individuals to compensate for declining neural networks, thereby performing at a cognitively normal level (Nielson et al., 2002). Reuter-Lorenz (2000) reported that older adults who displayed bilateral patterns of activation in the prefrontal cortex (PFC) were faster performing a verbal working memory task than those who did not, suggesting hyperactivation is serving a beneficial role in these individuals. This compensatory activation is also found in areas other than the frontal lobes. For example, Fera et al. (2005) found bilateral parietal activation in healthy older adults during a visual probabilistic learning task. This pattern of activation was not seen in the younger adults despite equivalent performance between the two groups. This result suggests that older adults need more of their

brain in order to perform at the same level as younger adults (Nielson et al., 2002). Task difficulty may also play a role in the necessity for recruitment as older adults display increased bilateral activation as task difficulty increases, implying that more neural resources are necessary to maintain performance as the brain is stressed (Anderson et al., 2002).

The second theory, dedifferentiation through inefficient neural networks, states that the increase of spatial activation in aging is simply a by-product of neural degradation that occurs with aging (Li & Lindenberger, 1999). In contrast to the theory of compensation, hyperactivation does not play a beneficial role in this theory. Instead, the neural connections in older adults break down, which is thought to cause hyperactivation in a non-selective manner (Logan et al., 2002). A decrease in dopaminergic modulation causes the brain to function less efficiently, interferes with neural connectivity, and results in the pattern of decline in cognitive performance characteristic of older adults (Li et al., 2001).

In a third theory, Park & Reuter-Lorenz (2009) propose a new model to explain the hyperactivation that occurs with aging, named the Scaffolding Model of Aging and Cognition. The Scaffolding Model posits that as the brain experiences the hallmarks of aging (e.g., atrophy, neural degradation), it undergoes reorganization and creates new compensatory connections. A constant adaptive recruitment process occurs, mending networks that have become inefficient and increasing the amount of spatial activation. By adapting, individuals undergo minimal cognitive decline despite their compromised neurological integrity. The strain of aging eventually becomes too much and the brain runs out of cognitive resources to reorganize. It is at this point we see the cognitive decline that characterizes aging.

Regardless of the underlying theory, dedifferentiation is a common phenomenon in the aging population. However, the amount of spatial activation varies between individuals (Voss et

al., 2008) and Alzheimer's disease (AD) has been demonstrated to play a role in the level of activation seen in aging adults (Buckner, 2004; Grady, 2003; Nielson et al., 2002; Nielson et al., 2006; Twamley, 2006).

fMRI and AD. AD is a progressive neurodegenerative disorder characterized by the gradual degeneration of an assortment of cognitive abilities and activities of daily living due to the death of neurons in a variety of brain areas (Buckner, 2004). Declines in episodic and semantic memory, attention, naming, executive functioning, and spatial ability are all early clinical hallmarks of AD (Johnson et al., 2008). Pathologically, AD is characterized by the presence of amyloid plaques, neurofibrillary tangles, and atrophy of several areas of the brain (Arnold et al., 1991). There is increasing evidence that the process of AD begins long before its clinical onset (Braak & Braak, 1991; Ghebremedhin et al., 1998). Preclinical AD is characterized by two phases. The first phase is a latent period in which individuals do not show cognitive impairment. During this phase, despite a lack of clinical symptoms, individuals may display hyperactivation to a greater extent than what is often seen in normal aging (Seidenberg et al., 2009). The second prodomal phase, referred to as Mild Cognitive Impairment (MCI), is characterized by slight impairment in cognitive processing, most especially in the domain of memory (Petersen et al., 2001).

Genetic studies indicate an association between late-onset AD (i.e., symptom onset after age 60) and the possession of one or both copies the ε4 allele of the apolipoprotein-E (APOE) gene on chromosome 19. Individuals with an ε4 allele are three to four times more likely to develop AD than those without ε4 (Saunders, 1993). The presence of APOE ε4 has been linked to both plaques and neurofibrillary tangles (Namba et al., 1991). AD-related neuropathology has been found in individuals possessing the APOE ε4 even during middle age (Ghebremedhin et

al., 1998). These findings suggest that AD has a gradual progression and is present long before it clinically manifests. Findings suggest the neuropathological changes associated with AD may go back as far as 50 years before a formal diagnosis of AD can be made (Ohm et al., 1995).

Similarly, a first-degree family history (FH) of AD is a risk factor for late-onset of the disease (Devi et al., 2000; Johnson et al., 2006; Saunders et al., 1993). At-risk asymptomatic offspring of late-onset familial AD (unrelated to APOE status) showed differences in activation during both encoding and recall when compared to healthy subjects without a family history of AD (Basset et al., 2006). Assessing for both a family history of AD and the presence of an APOE ε4 allele is important when predicting risk for AD as having both risk factors exert a stronger influence on brain activation than one risk factor alone (Johnson et al., 2006; Seidenberg et al., 2009). However, both APOE ε4 and FH are imperfect predictors of who will progress to AD and a more reliable prediction model is needed.

fMRI appears to be particularly sensitive to identifying pre-clinical changes in activation for individuals at-risk for AD (Sperling, 2007). Individuals with a family history of AD and/or carriers of the APOE ε4 allele show an increased magnitude and spatial extent of activation in specific regions (hippocampus, precuneus/posterior cingulate, frontal and temporoparietal regions) when compared to individuals who do not show these risk-factors (Bassett et al., 2006; Bondi et al., 2005; Burggren et al., 2002; Houston et al., 2005; Jacobson et al., 2005). These changes in activation occur before the presence of clinical symptoms and even before atrophy or structural changes (Seidenberg et al., 2009, Woodard et al., 2009). These changes in activation are thought to be of a compensatory nature, just like in healthy aging, despite a lack of obvious pathology. In a seminal study, Bookheimer et al. (2000) found a greater magnitude and extent of activation in cognitively normal individuals with APOE ε4 as compared to individuals with the

ε3 allele during a verbal memory task. The increased activation was in areas affected by AD (hippocampus, parietal, and prefrontal regions). In the study, individuals with high activation demonstrated the largest decline in performance in a one-year follow-up. The results suggest the increased activation is compensatory in nature with subjects showing increased neuronal recruitment in what could be the preclinical stage of AD. Specifically, hyperactivation might be caused by very subtle initial neuropathological changes in relation to preclinical AD. In response, extra neuronal recruitment is needed to successfully complete the task. Secondly, the results imply a trajectory of increased activation eventually leading towards decreased cognitive performance. Unfortunately, the follow-up did not include neuroimaging so the association of hyperactivation leading to hypoactivation and decreased performance cannot be confirmed within this particular study.

Task-activated fMRI studies of subjects with MCI indicate hyperactivation converting to hypoactivation as the disease progress (Dickerson et al., 2005; Machulda et al., 2003; Small et al., 1999). The progression from hyperactivation to hypoactivation may represent the brain's initial attempt to compensate for neuropathological changes followed by eventually succumbing to the severe neuropathological burden of AD (Buckner, 2004). Further demonstrating this, the degree of hyperactivation in the hippocampus of subjects diagnosed with MCI has been shown to be predictive of a greater degree of cognitive decline when followed up 5 years later (Miller et al., 2008). The cognitive decline characteristic of AD is correlated with hypoactivation and atrophy. However, hyperactivation has also been found in bilateral dorsalateral prefrontal cortex in patients with mild AD when compared to healthy controls (Grady et al., 2003). This might indicate that even in the mild stages of AD, individuals may still be able to use compensatory recruitment to make up for a loss of cognitive resources. The parietal lobe may also be an area

used for compensatory recruitment when there is a loss of functional integrity in the hippocampal-based memory system, an area affected early in AD (Celone et al., 2006). Examining changes in neural activation within individuals at-risk for AD may play an integral role in early intervention and coupled with other biomarkers, possibly allow for prediction of who will convert from asymptomatic to MCI to AD (Woodard et al., 2009).

Differentiation Index. Studies investigating age-related spatial activation have primarily focused on activation differences. In contrast, Voss et al. (2008) proposed a technique to quantitatively measure age-related (group) and individual variance in magnitude of spatial activation. This was done by creating a "differentiation index" to examine the spatial specificity of a neural response in order to measure the amount of dedifferentiation. Specifically, they computed a standardized score of differentiation for each individual by comparing the amount of activation that would be expected in a given region during a task with the amount of activation that actually occurred. Greater unexpected activation indicated greater dedifferentiation (i.e., larger task-related spatial activation). The intent of the study was to measure neural dedifferentiation in the ventral visual cortex, an area chosen for its spatially well-defined, stimulus-dependent areas of activation (Park et al., 2004).

While the study by Voss et al. (2008) found varying degrees of dedifferentiation between stimuli, the authors used only healthy subjects who were not characterized regarding AD risks and they focused strictly on the ventral visual cortex. Previous research showed that individuals who are both APOE ε4 and FH-positive demonstrate significantly greater activation during a famous name recognition task (i.e., semantic memory) as compared to those without risk factors, despite comparable cognitive abilities between the two groups (Seidenberg et al., 2009). The event-related task was designed to activate the networks that typically show the earliest

neuropathological changes in AD (Douville et al., 2005; Nielson et al., 2006; Woodard et al., 2007). In particular, hyperactivation occurs in AD in the posterior cingulate and lateral posterior temporoparietal regions, important areas in semantic processing and memory retrieval (Seidenberg et al., 2009). Indeed, a decline in semantic memory occurs in normal aging but is especially pronounced in AD (Hodges & Patterson, 1995; Semenza et al., 2003; Werheid & Clare, 2007). In particular, individuals with AD struggle with the semantic task of identification and categorization of famous names, even early on in the progression of the disease (Seidenberg et al., 2009; Semenza et al., 2000; Thompson et al., 2002). Further, a recent study reported that poor performance on a famous face recognition task was predictive of individuals converting to AD at a two-year follow-up (Esevez-Gonzalez et al., 2004).

The current study used an extrapolation of the model presented by Voss et al. (2008) applied to a comparison of the level of spatial activation in individuals at-risk for AD (APOE ε4 and FH positive) versus those without AD risk during the semantic memory task used by Seidenberg et al. (2009). We expected to detect a difference in the magnitude and degree of spatial activation between the two groups. In particular, we hypothesized that participants at risk for AD would show a greater amount of dedifferentiation during a semantic task (fame discrimination) than the non-risk group.

Method

Participants

Participants included 44 healthy adults between the ages of 65-79 years recruited from newspaper advertisements. The initial 459 potential participants were screened with a telephone interview in regards to the exclusion criteria described below, narrowing the possible pool to 109. Any participants with family history of Alzheimer's disease but who did not have at least

one APOE4 allele were excluded from this analysis. Similarly, participants with at least one APOE ε4 allele but no family history of Alzheimer's disease were excluded. The remaining 64 participants were then demographically matched for age, gender, and education to form even groups. The at-risk group was defined by the presence of at least one APOE ε4 allele and a family history of AD (n=22; 1 ε2/ε4; 20 ε3/ε4; 1 ε4/ε4). The low-risk group was defined by the lack of both an APOE ε4 allele and family history of AD (n=22; 1 ε2/ε3; 21 ε3/ε3). A family history of AD was defined as a clear clinical diagnosis of AD or a history of gradual decline in cognition and judgment or increased confusion in a first-degree relative (i.e., parent, sibling).

Exclusion Criteria. Participants were excluded if they reported a history of neurological disease, medical illness that may affect brain functioning (e.g. hypertension), a psychiatric disturbance or substance abuse meeting DSM-IV Axis I criteria, a Geriatric Depression Scale score greater than 10 (falling in the depressed range), neuropsychological scores falling in the cognitively intact range (see cognitive battery) or the current use of psychoactive medication. Genotyping was determined using PCR method (Mayeux et al., 1998; Saunders et al., 1996) and DNA was isolated with Gentra Systems Autopure LS for Large Sample Nucleic Acid Purification. Exclusion criteria related to the fMRI included pregnancy, weight appropriate for height, ferrous objects within the body, an inability to see the stimuli in the scanner, and claustrophobia. Only right-handed participants were included based on the Edinburgh Handedness Inventory (Oldfield, 1971).

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

2001; Mattis, 1988), the Rey Auditory Verbal Learning Test (RAVLT; Rey, 1958), the Geriatric Depression Scale (GDS), and the Lawton Activities of Daily Living Scale (ADLs; Lawton & Brody, 1969). Cut-off scores for being included in the study were: a score less than 28 on the MMSE, a score of more than 1.5 standard deviations below the mean for the participants age and gender on the RAVLT Delayed Recall and Long Term Percentage Retention measures, an age and education corrected MOANS on the DRS-2 that fall in the non-demented range (Lucas et al., 1998), and ADLs scores in the normal range.

fMRI Acquisition. Whole brain, event-related fMRI was conducted on a GE Signa Excite 3.0 Tesla short-bore scanner equipped with a split quadrature head coil (Froedert Hospital,Wauwatosa, WI). Echoplanner imaging was collected using gradiant-echo echoplanar pulse sequence (TE=25 ms; flip angle = 77 degrees; field of view (FOV) = 24 mm; matrix size = 64 x 64). Thirty-six contiguous axial 4 mm thick slices were selected to provide coverage of the entire brain (voxel size = 3.75 x 3.75 x 4mm). The interscan interval (TR) was 2 seconds. Anatomical scans, high-resolution three-dimensional spoiled gradient-recalled at steady state (SPGR) were obtained (TE = 3.9 ms; TR = 9.5 ms; inversion recovery (IR) preparation time = 450 ms; flip angle = 12 degrees; number of excitations (NEX) = 2; slice thickness = 1.0 mm; FOV = 24 cm; resolution = 256 x 224). Participants' heads were stabilized in the scanner with foam padding in order to reduce head movement.

fMRI Task. All participants were presented a semantic memory task composed of 30 famous and 30 non-famous names (60 total) using E-Prime programming software while in the scanner. Stimuli were selected from a pool of 784 names based on participants' ability to correctly classify the stimuli as famous or non-famous. All selected stimuli demonstrated a >90% successful classification rate in healthy older adults (Douville et al., 2005). Famous

stimuli were selected from three different time epochs (10 each): remote (e.g., Tab Hunter), enduring (e.g., Frank Sinatra), and recent (e.g., Barack Obama). A trial consisted of a visual presentation of a single name for a duration of 4 seconds. Participants were instructed to press a button with their right index finger if they believe the name is of a famous individual or their right middle finger if the name is non-famous. Accuracy, response time in milliseconds, and any response bias were recorded. Among the trials, 20 fixation cross-hairs were presented for a duration of 4 seconds to introduce jitter into the fMRI time-series, thereby allowing improved deconvolution of the individual response trials in time. During this time, participants were asked to fixate on the cross-hair; no response was to be given. The study began and ended with a 12-second fixation. The total time for a single imaging run for the semantic task was 5 minutes and 24 seconds. The order of the stimuli was counter-balanced among groups.

Image Analysis. Functional images were generated using the Analysis of Functional Neuroimages (AFNI) software package (Cox, 1996). Each voxel time series was temporally shifted to the beginning of the TR to account for time differences in slice acquisition and spatially registered to account for head motion using the AFNI 3dRegistration algorithm. A deconvolution analysis was conducted with AFNI's 3dDeconvolve in order to analyze the event-related design (famous and not-famous), extracting hemodynamic response functions (HRF). Estimation of HRFs was restricted to correct responses only. The area under the curve (AUC) was conducted by summing the HRF at time points 4, 6, and 8 seconds post-trial onset. The anatomical and functional scans were transformed into standard Talairach space (Talairach, 1988). A 6mm Gassuian full-width half-maximum blur was used to account for anatomical variability between subjects.

Spatial Extent of Activation Analysis. In order to account for differences between groups, we generated famous and not famous maps for each group using the 3d voxel-wise t-test. Voxels that were activated in the same spatial regions for both groups during each stimulus were considered common areas of activation and used as preferred regions. Specifically, regions that demonstrate significantly greater activation for famous as compared to not famous stimuli were considered regions of famous processing that are common between groups. The statistical threshold was established using a Monte-Carlo simulation technique using the AlphaSim program with a *p*-value of .001 and cluster size threshold of 100 microliters. The same procedure was done to establish non-famous name regions of interest (ROIs). Next, we computed the average level of activation for each subject within each preferred region per condition. This provided famous task activation in famous ROIs, famous task activation in non-famous ROIs, non-famous task activation in non-famous ROIs, and non-famous task activation in famous ROIs.

Differentiation Index. For each participant, a differentiation index was computed as an average percent signal change during the presentation of the preferred stimuli within the established preferred stimulus ROI minus the percent signal change within the preferred ROI that occurred during the presentation of non-preferred stimuli. This total was then divided by square root of the average standard deviation of the response amplitude for famous names and non-famous names within the preferred ROI divided by the number of conditions (Figure 1). This computation created a z-score where positive numbers mean greater differentiation and negative numbers equaled greater dedifferentiation (adapted from Afraz et al., 2006; Grill-Spector et al., 2007; and Voss et al., 2008). For each participant, the z-scores of each condition was added together then divided the total number of preferred ROIs for each condition, creating an average

Figure 1. **The differentiation index formula**

$$\text{ROI Z-Score} = \frac{\text{Average Preferred Activation} - \text{Average Non-Preferred Activation}}{\sqrt{\left(\frac{\text{Pref. Activation } \sigma \ + \text{Non-Pref. Activation } \sigma}{2}\right)}}$$

z-score per stimulus. Overall differentiation differences were examined using between-subjects Analysis of Variance (ANOVA).

Results

Demographic and Neuropsychological Performance. There were no significant differences between groups on age, gender, education, or performance on neuropsychological measures (Table 1).

fMRI Task Performance. All groups performed above 73.3% on the task with no significant group differences in percent correct for either famous or non-famous names. There were no significant group differences in reaction time for either famous or non-famous names (Table 1). There was a significant difference between conditions for reaction time with non-famous names requiring significantly longer response time than famous names ($t(42)=4.458$, $p<.001$).

Localization of Famous and Non-famous Name Regions of Interest. The Differentiation Index yielded 3 famous name ROIs and 12 non-famous name condition-specific ROIs that activated across both the low-risk and at-risk groups (Table 2, Figure 2). Both name conditions showed unique activation solely in frontal and occipital regions. The non-famous ROIs tended

Table 1. **Group demographics, neuropsychological test results, and fMRI task performance**

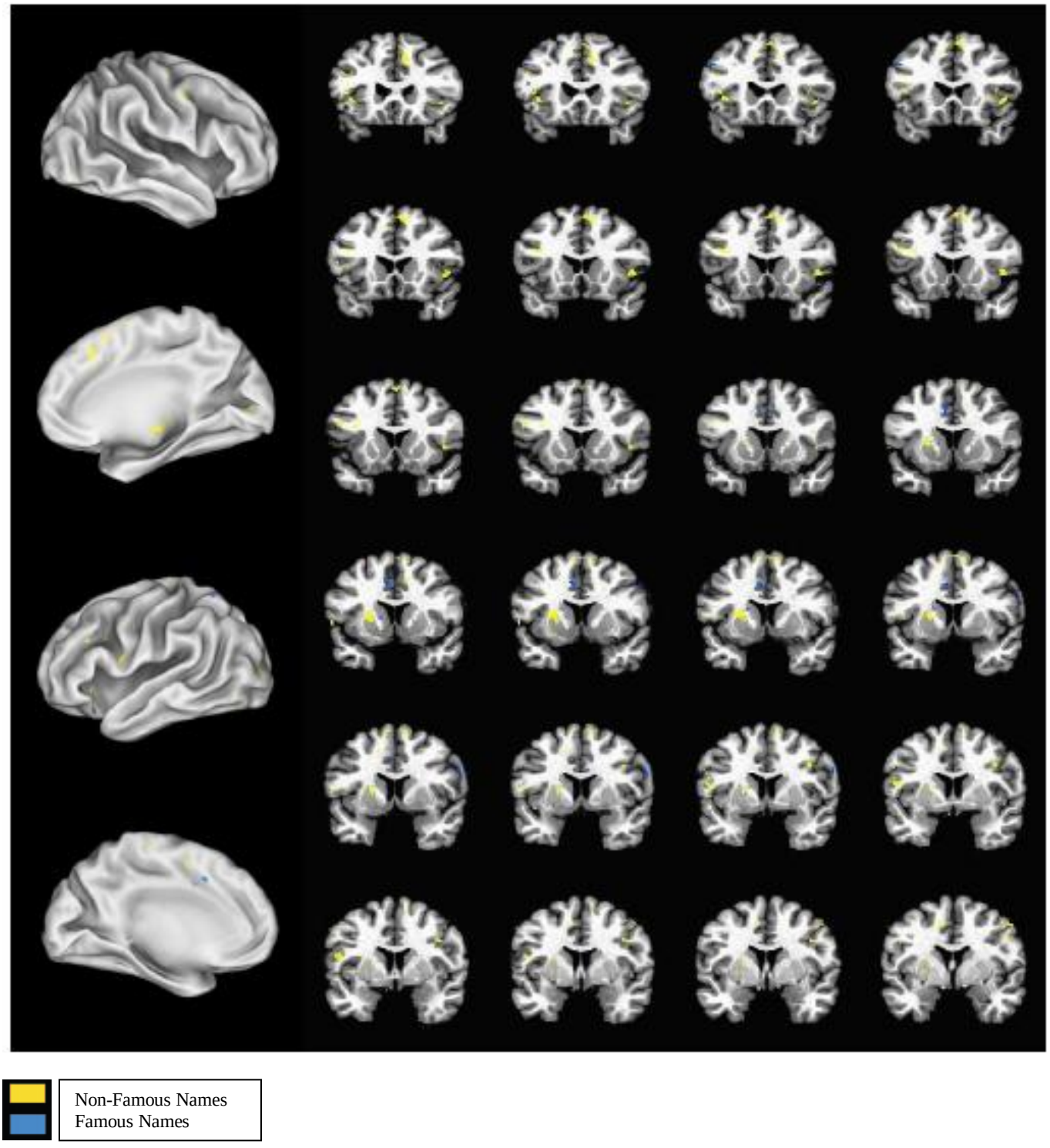
Variables	Low-risk	High risk	*p*
Demographics			
No. enrolled (No. female)	22 (16)	22 (16)	NS
Mean age (range)	71.5 (65-79)	70.8 (65-77)	.616
Mean education (range)	14.2 (11-22)	15.9 (12-23)	.060
Neuropsychological Tests (Mean +/- SD)			
Mini-Mental State Exam	29.3 (0.8)	29.1 (1.3)	.391
DRS-2 total score	140.7 (2.1)	141.1 (2.6)	.655
RAVLT trials 1-5	48.3 (8.0)	50.0 (7.6)	.489
RAVLT delayed recall	9.6 (2.4)	9.5 (3.0)	.913
GDS Total	1.6 (2.0)	2.5 (2.5)	.239
ADL-Lawton	5 (0)	5 (0)	NS
fMRI Task Performance (Mean +/- SD)			
Famous names percent correct	91.5 (7.0)	93.2 (8.1)	.472
Famous names reaction time (ms)	1316.8 (179.0)	1267.8 (232.0)	.437
Non-famous names percent correct	97.6 (3.7)	96.6 (7.5)	.553
Non-famous names reaction time (ms)	1638.0 (252.8)	1603.8 (305.2)	.688

***Table 2*. Unique activation foci for the famous and non-famous name discrimination task.**

				Both Groups							
				Famous				**Non-famous**			
#	**Side**	**Region**	**BA**	**x**	**y**	**z**	**vol**	**x**	**y**	**z**	**vol**
	Frontal Lobes										
1	L	Middle Cingulate	24	6	-7	37	115				
2	R	Superior/Medial Frontal Gyrus	6,8					-6	-15	50	774
3	L	Inferior Frontal Gyrus	45					36	-25	7	670
4	L	Putamen						21	-2	9	496
5	L	Middle Frontal Gyrus	32					40	-17	25	360
6	R	Insula	45					-42	-17	2	350
7	R	Precentral Gyrus	6					-45	3	38	320
8	L	Inferior Frontal Gyrus	44					48	-2	15	147
9	L	Paracentral Lobule	4					9	21	53	107
	Occipital Lobes										
10	L	Calcarine Gyrus	17	13	85	-3	212				
11	R	Lingual Gyrus	18,19	-24	83	-16	120				
12	R	Calcarine Gyrus	18					-14	75	6	185
13	R	Inferior Occipital Gyrus	19					-35	75	-11	168
14	R	Middle Occiptal Gyrus	17					-28	95	-4	134
15	L	Middle Occipital Gyrus	18					32	83	5	129

All areas are greater than 100 microliters.

Figure 2. **The location of famous and non-famous specific ROIs**



to be larger in size than the famous names ROIs with means of 320 ml and 149 ml respectively ($t(13)=-1.281$, $p=.222$).

Neural Dedifferentiation Differences Between Groups. There was not a significant difference between groups on the total degree of dedifferentiation ($t(42)=-.808$, $p=.424$). However, the groups displayed significant differences in the degree of dedifferentiation in two regions. The at-risk group showed increased dedifferentiation for non-famous names as compared to the at-risk group in the left paracentral lobule and the right inferior occipital gyrus (Table 2).

There was a significant main effect for fame, with the low-risk groups displaying greater dedifferentiation for famous names ($F(1, 42)=7.038$, $p=.011$), while the at-risk group showed greater dedifferentiation for non-famous names ($F(1, 42)=4.237$, $p=.046$). There was a significant interaction between condition and risk group ($F(1, 42)=6.971$, $p=.012$) with the at-risk group showing greater dedifferentiation for non-famous names yet greater differentiation (i.e., less dedifferentiation) for famous names (Table 3, Figure 3).

Discussion

In contrast to our prediction, there was no significant difference on the general amount of dedifferentiation between participants at-risk for Alzheimer's disease and those at lower risk on a semantic memory task. However, the findings indicated that group dedifferentiation levels vary based on stimulus type. The at-risk group demonstrated significantly more dedifferentiation for non-famous names yet greater differentiation (i.e., less dedifferentiation) for famous names. The interaction may represent manifestations of very early neuropathology in individuals at-risk for AD.

***Table 3*. Differentiation index scores by group using the famous and non-famous name discrimination task.**

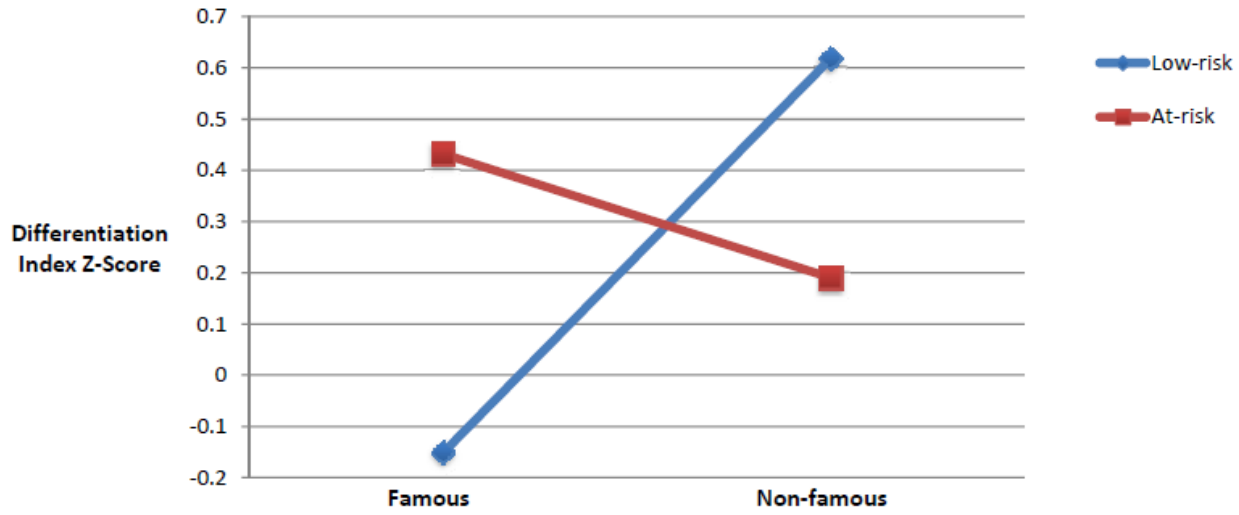
				Famous & Non-famous				Group Z-scores		
#	**Side**	**Region**	**BA**	**x**	**y**	**z**	**vol**	**Low-risk**	**At-Risk**	**Risk p**
	Frontal Lobes									
1F	L	Middle Cingulate	24	6	-7	37	115	-.0822	.3785	.407
2N	R	Superior/Medial Frontal Gyrus	6,8	-6	-15	50	774	.5776	.3303	.271
3N	L	Inferior Frontal Gyrus	45	36	-25	7	670	.3307	.2875	.870
4N	L	Putamen		21	-2	9	496	.6926	.2000	.229
5N	L	Middle Frontal Gyrus	32	40	-17	25	360	.5663	.2088	.137
6N	R	Insula	45	-42	-17	2	350	.6017	.4781	.661
7N	R	Precentral Gyrus	6	-45	3	38	320	.5503	.2805	.223
8N	L	Inferior Frontal Gyrus	44	48	-2	15	147	.8287	.3363	.175
9N	L	Paracentral Lobule	4	9	21	53	107	.8749	-.0624	**.032**
	Occipital Lobes									
10F	L	Calcarine Gyrus	17	13	85	-3	212	-.0654	.1856	.300
11F	R	Lingual Gyrus	18,19	-24	83	-16	120	-.0962	.6537	.094
12N	R	Calcarine Gyrus	18	-14	75	6	185	.8450	-.0367	.079
13N	R	Inferior Occipital Gyrus	19	-35	75	-11	168	.5192	-.0063	**.048**
14N	R	Middle Occipital Gyrus	17	-28	95	-4	134	.3943	.2894	.797
15N	L	Middle Occipital Gyrus	18	32	83	5	129	.6469	.4101	.448

	Stimulus Condition (all regions)	**Low-risk**	**At-risk**	**F-value**	**p**
	Famous	-.1508	.4316	7.038	**.011**
	Non-famous	.6186	.1903	4.237	**.046**
	Stimulus*Risk			6.971	**.012**
	Total Index		t = -.808		.424

The Brodman areas (BA), Talairach coordinates at the center of the region, and tissue volume (microliters) are shown for those regions that indicated significant activation during one condition but not the other across both groups. For group z-scores, higher values indicate increased spatial specificity.

F = Famous ROIs; N = Non-famous ROI

Figure 3. **The interaction of dedifferentiation based on stimulus type and risk for AD.**



The current finding of stimulus dependent levels of spatial activation is consistent with previous research using the differentiation formula. Voss et al. (2008) found that while older adults demonstrated uniformly greater dedifferentiation within the visual cortex, it was not ubiquitous across stimulus conditions. Also, different stimuli evoked different levels of dedifferentiation between young and older adults. Specifically, stimuli theorized to cause primarily right lateralized activation (e.g., faces and places) demonstrated the greatest age-related dedifferentiation, a finding supported by previous literature (Dolcos et al., 2002). As the current study used only older participants, the lack of lateralization in the present findings is not surprising as it may reflect age-related bilateral hemispheric compensatory activation (Cabeza, 2002), consistent with the Voss et al. (2008) study. Interestingly, one of the two regions that demonstrated significant dedifferentiation for the at-risk group was in the right inferior occipital gyrus (Table 3), consistent with a region that displayed significantly greater dedifferentiation in the older adult group for the Voss et al. (2008) study. The inferior occipital gyrus is an area believed to be important for processing faces. The findings of the current study indicate that the at-risk group recruited this region while processing famous names, perhaps needing

compensatory activation to process through their semantic network regarding famous faces. Perhaps increased dedifferentiation (i.e., compensatory activation) occurs in the at-risk group in various regions, but the similarity of the networks underlying the famous v. unfamiliar name distinction prevents the appearance of group differences. That is, while the current study used a task known to activate networks believed to vulnerable to early AD-related pathology, it also involved a whole brain analysis of two very similar tasks (Seidenberg et al., 2009). In contrast, Voss et al. (2008) used tasks that were more regionally distinguishable. This fundamental distinction in methodology may account for the lack of demonstrated difference in total dedifferentiation between the low-risk and at-risk group. However, the interaction of AD-risk and stimulus familiarity is a novel finding. Both pertinent effects in the interaction suggest there may be predictive value in the dedifferentiation index for preclinical AD.

Examining first the increased differentiation (i.e., less dedifferentiation) for famous names in the at-risk group, one possible explanation is that very early AD-related pathology is interfering with the individual's ability to properly encode semantic information regarding famous individuals. Despite a lack of symptoms indicative of pathology, some individuals in the at-risk group may be developing early accumulation of the plaques and tangles associated with AD, functionally disrupting semantic networks (Braak & Braak, 1991; Ghebremedhin et al., 1998). Supportive of this interpretation, individuals with aMCI produce less semantic information about famous names than do healthy controls, presumably due to an inability of individuals to integrate new semantic information with previously stored information (Seidenberg et al., 2009). Temporo-frontal pathways are believed to be crucial in memory retrieval and searching memory traces (Kroll et al., 1997), and importantly are susceptible to AD-related pathology (Maguire et al., 2000; Seidenberg et al., 2009). The net result of such

pathology would be reduced spatial extent of networks. Thus, the at-risk participants in the present study may have had greater differentiation because of greater spatial specificity of semantic networks, owing to poorer integration of new encoding experiences with existing relevant information. Due to the designed simplicity of the semantic task, individuals performed the task at a high rate of accuracy. However, if the individuals at-risk for AD had less breadth of knowledge for the famous names, greater differentiation could have result (as we found). Activation for both older adult groups is most likely more dedifferentiated than young, healthy adults (Nielson et al., 2006; Voss et al., 2008). However, the low-risk group is perhaps expressing an age-appropriate amount of spatial activation by showing increased spatial activation for famous names. The larger spatial activation may reflect a larger, more easily accessed semantic network as compared to the at-risk group. Future studies examining differences in the breadth of semantic knowledge between individuals at-risk and those at low-risk for AD may help in understanding the findings of this study and the progression of AD.

The increased dedifferentiation for non-famous names displayed by individuals at-risk for AD may also have reflected very early pathology of the disease. This finding is consistent with previous literature indicating individuals at-risk for AD display increased activation (Bookheimer et al., 2000). Non-famous names may have caused increased dedifferentiation compared with famous names because of the cognitive effort required to make the non-famous decision. This finding is supported by the longer overall reaction time displayed by participants when making a familiarity decision on non-famous names as compared to famous names. Non-famous and famous names inherently induce different levels of activation because deciding if a non-famous name is familiar requires more cognitive resources than performing the same semantic decision for a familiar name (Nielson et al., 2010). Thus, to perform the task with high

accuracy, the at-risk group demonstrated increased spatial activation, which is believed to reflect compensation for task difficulty. Specifically, the increased dedifferentiation by the at-risk group in the paracentral lobule may reflect compensatory recruitment as the parietal lobe has been previously theorized to play a compensatory role during AD-related dysfunction (Celone et al., 2006). In contrast, the low-risk group more efficiently searched semantic networks to make the fame discrimination, which resulted in more differentiated neural activation for non-famous names.

Findings in this study point to network efficacy mediating activation, which supports the presence of a compensatory mechanism as compared to neural inefficiency. The increased dedifferentiation exhibited by the at-risk group during the presentation of non-famous names may represent neural recruitment during the inherently more "difficult" task. That is, the recruitment may have allowed the at-risk group to perform the task at the same level as the low-risk group despite early AD-related pathology. Alternatively, the findings may be interpreted in terms of the Scaffolding Model (Park & Reuter-Lorenz, 2009). Very early AD-related neuropathology may have compromised existing networks, causing the brain to then undergo reorganization and create new compensatory connections, resulting in increased spatial activation. The brain may have to allocate more neural resources to this type of task because of the comparative difficulty of making a semantic decision about a novel stimulus as compared to a familiar stimulus. Novel stimuli tax semantic networks more because of the need to check the stimulus against all names in the semantic network despite not finding a match. Thus, when confronted with this task, participants at-risk for AD with very early AD-related neuropathology displayed greater spatial extent of activation due to reorganized networks. Further studies need to be conducted to look at the specificity of scaffolding reorganization (e.g., semantic network

vs. task specific). Overall, the findings indicate task difficulty and specificity within network activation mediating the need for compensatory recruitment.

Study limitations. Previous findings in individuals at-risk for AD indicate hyperactivation in semantic networks including the hippocampus, precuneus, posterior cingulate, frontal and temporoparietal regions when compared to individuals who do not show these risk-factors (Bassett et al., 2006; Bondi et al., 2005; Burggren et al., 2002; Houston et al., 2005; Jacobson et al., 2005). These findings were not replicated in the current study as only the left paracentral lobule and the right inferior occipital gyrus demonstrated significant differences in dedifferentiation. One possible explanation for this involves the specific methodology of the study. In order to examine dedifferentiation, selected ROIs must be predominantly activated by one stimulus but not by the other stimulus. While famous and non-famous names demonstrated some unique areas of activation, general networks contained significant overlap, including frontal, parietal, and temporal regions. Therefore, most regions that previously demonstrated significant differences between at-risk and low-risk groups were removed due to common activation (Seidenberg et al., 2009). Future studies using stimuli with less spatial overlap yet activating semantic networks may provide more insight into neural spatial specificity in the individuals at-risk for AD.

Secondly, the progression of at-risk individuals toward MCI (and eventually, AD) is slow and indeterminate process. Risk factors alone are an imperfect predictor of who will decline (Ohm et al., 1995; Woodard et al., in press). A longitudinal study examining changes in dedifferentiation over the progression of the disease from healthy but at-risk to impaired would provide insight into predictive biomarkers. Similarly, the presence of early AD-related pathology in the at-risk group in this study is speculative and unable to be confirmed.

Due to limitations of the number of stimuli, analysis of the influence of the time epoch of the famous names on spatial activation was impractical. Research indicates that activation levels vary in specific regions in response to the age of the memory (Woodard et al., 2007). Additionally, patients with AD show a temporal gradient in their recognition of famous faces and famous names, with better performance for stimuli from more remote time epochs as compared to more recent time epochs (Beatty et al., 1988, Greene & Hodges, 1996; cf. Nadel & Moscovitch, 1997; Seidenberg et al., 2009). Thus, it is also possible that the at-risk and low-risk group displayed different levels of dedifferentiation depending on the time epoch of the stimuli, which varied in the current study from recent to remote. Future studies should address the role of the temporal gradient in semantic memory with respect to AD risk and dedifferentiation.

In summary, the at-risk group demonstrated significantly more dedifferentiation for non-famous names yet greater differentiation (i.e., less dedifferentiation) for famous names as compared to the low-risk group. Differences in spatial activity between groups may have been due to early-AD related pathology in the at-risk group. Specifically, early AD-related disruption of temporo-frontal pathways may have resulted in less effective encoding and access to newly experienced semantic information regarding familiar individuals (Seidenberg et al., 2009). This would result in smaller semantic networks and greater neural differentiation (i.e., less dedifferentiation). Also, pre-AD-related network inefficiency may have been responsible for the increased dedifferentiation during the presentation of non-famous names. Deciding if a name is famous or not famous requires more cognitive resources (i.e., compensatory recruitment), as it is inherently more "difficult" for the at-risk group due to problems efficiently searching networks (Nielson et al., 2010). Future studies examining depth of semantic knowledge with respect to AD risk and dedifferentiation may provide more insight into the early progression of AD.

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