

A FUNCTIONAL AND STRUCTURAL MRI MODEL OF NAMING IN ALZHEIMER'S
DISEASE

By

AMANDA GARCIA

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To my loving family

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Abstract of Thesis Presented to the Graduate School
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Amanda Garcia

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Anomia in Alzheimer's Disease (AD) may result from impaired semantic and/or lexical functioning normally mediated by the inferior temporal (ITL) and posterior perisylvian cortices (PPS), respectively. The current study utilized functional magnetic resonance imaging (fMRI) during picture naming and voxel-based morphometry (VBM) to determine the relationship between activity (fMRI) and structural changes (VBM) in these language areas and semantic and lexical performance in early AD and healthy controls (HC). The functional activity of 10 participants with mild AD or multi-modality amnesic mild cognitive impairment (MCI) and 12 age-and-education matched controls was extracted from regions of interest (ROIs) (right and left ITL, PPS, and frontal lobe). Magnitude of functional activity was then correlated with a semantic composite score (Animal Fluency, Pyramids and Palm Trees) and a lexical composite score (Letter Fluency, Phonological Blocking). T-tests of cortical density between AD and HCs were also conducted. Average grey matter densities within areas of group difference within the ROIs were correlated with lexical and semantic scores. There was a significant negative correlation between the both lexical and semantic measures and functional activity in right PPS, $r_s(19) = -.564$, $p = .048$, $r_s(20) = -.625$, $p = .012$, respectively. There

was also a significant positive correlation between the cortical density in the right PPS and semantic composite score, $r_s(20) = .577, p = .03$. These results do not support our a-priori hypotheses; however, they may suggest that the increase in right PPS activity reflects an extension of healthy aging processes that is aggravated by AD pathology. Cortical density reductions in the same area may be accompanied by loss of inhibitory functions, such that the increased activity in this area interferes with semantic functions.

CHAPTER 1 INTRODUCTION

Although cognitive decline in Alzheimer's disease (AD) is most commonly associated with degraded explicit memory, these patients also experience impaired communication. One common language deficit in Alzheimer's disease, anomia, is most often identified clinically by diminished picture naming ability. Anomia presentation is not homogenous across patients, however, possibly due to the distinct cognitive processes involved in the task. This study specifically focused on the contributions of semantic processing and lexical retrieval to anomia. That is, it focused on patients' ability to understand the meaning of the picture they were being asked to name (semantic processing) and choose the correct word for that object (lexical retrieval). It further examined the neural correlates of these cognitive substrates to elucidate the variable nature of naming deficits.

Language Production

Language production, while highly complex, can be more readily understood when broken down into distinct but interactive cognitive components (e.g. semantic, lexical, phonemic components). The modular model put forth by Ellis and Young (1988) emphasizes the importance of the semantic system in the language production process (Figure 1-1). In this model, multiple lexicons feed into the semantic system. Spoken and written words enter the model through the phonological and orthographic input lexicons, which recognize the words forms as familiar. Visual objects similarly enter the model through the structural description system, which acts like an input lexicon to recognize the visual form as familiar. These familiar forms then enter the semantic system, where they are assigned meaning. Meaningful concepts are next prepared to be spoken or

written: the proper word form is retrieved from the phonologic or orthographic output lexicons, allowing the concept to be expressed out loud or on paper. In this way, a centralized semantic system is integral to both assigning meaning to concepts/objects that are encountered and generating the words used to represent those concepts.

Though this model is by no means all-encompassing, its relative simplicity is especially useful for the discussion of picture naming and the brain. The distinct cognitive processes it outlines (i.e. recognition, lexical retrieval, and semantic processing) are associated with functional neuroanatomical regions. For instance, lesion studies suggest that lexical and associated phonological processes are supported by posterior perisylvian cortices in the language-dominant hemisphere (Nadeau, 2000; Ojemann, 1983). A similarly discrete area that supports semantic processes is more difficult to pinpoint given the distributed nature of the semantic system. However, when considering the semantic system in relation to the picture naming task examined here, the left ventral visual stream emerges as important. This brain area, which consists of the fusiform, lingual, and parahippocampal gyri, has been implicated in the processing of semantic visual information (Chao, Haxby, & Martin, 1999; Feinberg, Schindler, Ochoa, Kwan, & Farah, 1994; Galton et al., 2001; Gold et al., 2006). Additional areas of importance include the left inferior and middle temporal gyri, which are noted here for their role in managing the connection between semantic concepts and their representations in the output lexicon (Foundas, Daniels, & Vasterling, 1998; Raymer, Moberg, Crosson, Nadeau, & Rothi, 1997). Of note, these semantic areas (i.e. left fusiform, lingual, parahippocampal, inferior temporal, and middle temporal gyri) additionally correspond to one of the semantic convergence zones

proposed by Binder, Desai, Graves, and Conant (2009). Together, then, they are implicated in the integration of semantic features across modalities as well as semantic concept retrieval.

Language in Alzheimer's Disease

The semantic contribution to language deficits in Alzheimer's patients is well-documented (e.g. Hodges, Salmon, & Butters, 1991; Salmon, Butters, & Chan, 1999; Salmon, Heindel, & Lange, 1999). These studies promoted the idea that naming deficits resulted from degraded semantic memory stores by remarking on loss of concept knowledge across task. Investigations of primed picture naming also suggested, however, that impaired lexical retrieval of intact semantic stores play a role in expressed anomia. Faust et al. (2004), for example, found that mild AD patients but not healthy older adults were susceptible to interference by phonologically similar words. Such phonological interference stresses the lexical nature of their deficit. Other studies have found additional evidence of phonological errors (i.e. substitution, addition, omission of phonemes) across task and suggest that difficulty activating lexical representations may be responsible for some semantic errors expressed downstream (Croot, Hodges, Xuereb, & Patterson, 2000; Galton, Patterson, Xuereb, & Hodges, 2000; Moreaud, David, Charnallet, & Pellat, 2001). Furthermore, case studies of atypical AD pathology reveal that these patients may present with aphasia as the prominent AD symptom or demonstrate phonological errors in word retrieval. In this way, it is likely that impaired semantic and lexical processing deficits contribute to poor naming performance in AD, though one may be more prominent than the other in any given patient (Croot et al., 2000; Galton et al., 2000).

Language, Alzheimer's Disease, and Functional Neuroimaging

Though the behavioral contributions of semantic and lexical processing to naming performance in AD are well-studied, fewer investigations have looked at the neurocorrelates of these processes. Broadly, a pattern has emerged with regards to the processing of verbal memory in these patients. Bookheimer et al. (2000), compared brain activation during a word pairing task in older adults at risk or not at risk for Alzheimer's disease. Those at risk had a greater magnitude and extent of activation in areas important for task performance, such as the left hippocampus, parietal lobe, and prefrontal cortex. Bookheimer et al. interpreted this activation as compensatory, which was supported by the fact that increased activation predicted cognitive decline two years after scanning. During a similar task, those with mild AD showed decreased activation in the left hippocampus and parietal lobe compared to healthy older adults (Backman et al., 1999). When considered together, these findings suggest that pre-symptomatic AD patients show increased activation in structures important for verbal memory. As deficits begin to emerge, however, deterioration of these structures is expressed in a reduction of activation.

Though the literature is somewhat inconsistent, this pattern is generally repeated in studies directly examining language and AD. Lexical and semantic processing have not been directly compared or distinguished, however, which may account for the discrepancies. Grossman, Koenig, Glosser, et al. (2003), for example, compared activation patterns during a semantic judgment task of nouns. They demonstrated decreased activation for AD patients compared to healthy older adults in left posterior perisylvian and superior temporal cortex, coupled with increased activation in adjacent left inferior temporal cortex. Similar activations patterns were shown during a semantic

judgment task of verbs. AD patients had weaker activation of left posterior perisylvian regions coupled with increased activation of smaller adjacent areas (Grossman, Koenig, DeVita, et al., 2003). In both cases the increased activation was cautiously interpreted as compensatory. Further analyses were not conducted, however, relating accuracy to activation increases, so the degree to which this activity is truly beneficial is unclear.

The frontal lobes additionally demonstrate increased activation in early AD patients. Some degree of frontal involvement in language tasks is expected, as these regions participate in selection and controlled semantic retrieval (Binder et al., 2009; Wagner, Pare-Blagoev, Clark, & Poldrack, 2001). However, several studies have shown the left dorsolateral prefrontal cortex to be more active in early AD patients than in healthy older adults during both verbal and semantic memory tasks (Becker et al., 1996; Saykin et al., 1999). Because this brain region is relatively less affected by neurofibrillary tangles early in the disease process (Braak & Braak, 1991; Foster et al., 1984; Wilcock & Esiri, 1982), the activation has been viewed as compensating for atrophy of more posterior lexical-semantic regions (i.e. the PPS and ITL). This viewpoint is supported by the positive association between activity of the left prefrontal cortex and semantic performance demonstrated by Saykin et al. (1999). In studies relating such activity and atrophy, a positive association was detected between the two in the left inferior frontal gyrus (Johnson et al., 2000). The same relationship was not detected between atrophy and activity in the superior temporal gyrus, raising the possibility that increased compensatory activity is an effect specific to this area. Wierenga and colleagues (2011) additionally found increased response in frontal regions in patients with AD, including the right inferior frontal gyrus. This brain pattern has also been

documented in healthy aging and may have been an example of the hemispheric asymmetry reduction in older adults (HAROLD) phenomenon. Of note, the functional implications of HAROLD are controversial: while some view the increased positive activity as compensatory (Park & Reuter-Lorenz, 2009), others have linked it to decreased semantic performance in older adults (Meinzer et al., 2012). Thus, the compensatory nature of increased activity in the right frontal lobes of Alzheimer's patients is uncertain. Though it may have the same relationship to behavioral performance as activity in the left hemisphere, it may instead interfere with successful language functioning.

Language, Alzheimer's Disease, and Structural Neuroimaging

Studies investigating the relationship between grey matter atrophy and language deficits are fairly consistent with the functional neuroimaging research. Galton and colleagues (2001), for example, were interested in common neurocorrelates of semantic deficits in semantic dementia and Alzheimer's disease. In a combined group of patients with these diagnoses, they were able to detect a positive correlation between semantic functioning and grey matter in the inferior and middle temporal gyri. Thus, atrophy of areas previously implicated in semantic processing was associated with lower scores on neuropsychological measures of semantic functioning. Later studies utilized voxel-based morphometry (VBM) to look at the relationship between atrophy and naming deficits in AD specifically (Gee et al., 2003; Grossman et al., 2004). They showed that AD patients had a pattern of atrophy that included key language areas underlying semantic and lexical processes, such as the left anterior and posterior lateral temporal lobes, left inferior temporal lobe, and left posterior perisylvian cortex. Of these areas, left anterior and lateral temporal atrophy were associated with poorer naming performance.

This association supports the idea that these areas are associated with semantic deficits, as cognitive testing revealed the AD patients performed significantly worse than healthy controls on measures of animal fluency. Studies of atrophy patterns in atypical Alzheimer's cases additionally provide insight into the localization of lexical deficits. Croot et al. (2000) reported on 13 patients who presented with deficits in articulatory and phonological processing. Structural neuroimaging of these patients showed patterns of Alzheimer's pathology in areas of the brain typically associated with acquired speech and language disorders. That is, patients with lexical retrieval deficits appeared to have greater left posterior perisylvian pathology.

In light of these findings, the current study will explore the nature of naming deficits in Alzheimer's patients with regards to functional activity and atrophy. Given evidence of the relationship between the posterior perisylvian cortex and lexical deficits in these patients, we would expect a positive correlation between lexical functioning and functional activity during a language task in this region. We would expect a positive correlation between lexical functioning and grey matter density of this area, as well. In terms of semantic functioning, we would expect significantly positive correlations between functional activity and grey matter density of its associated neurocorrelate, the inferior temporal lobe. Finally, AD patients seem to demonstrate increased frontal activity during language tasks, but this activity does not appear to be specifically related to lexical or semantic functioning. Thus, we hypothesized the increased activity would be negatively related to lexical and semantic functioning. Because increased activity of the frontal lobes corresponds to increased atrophy of those regions, we hypothesized

that grey matter density would be positively related to both measures of language functioning.

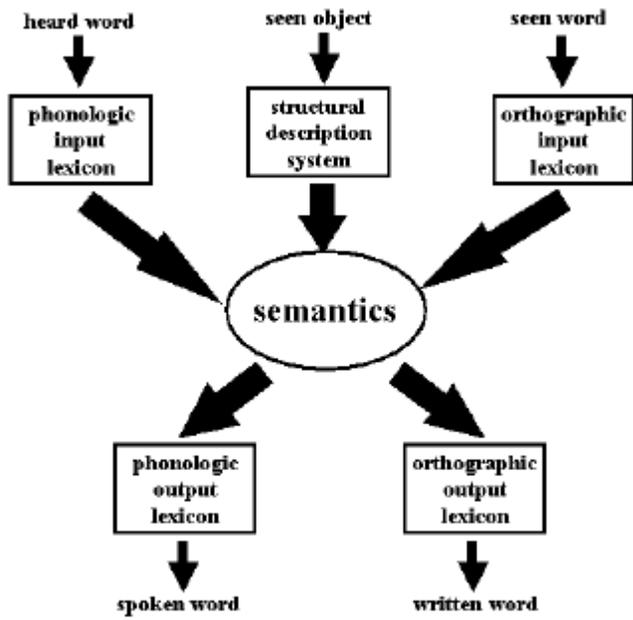


Figure 1-1. A depiction of the modular model of language.

CHAPTER 2 METHODS

Participants

Twelve older healthy adults at least 65 years of age (7 female) and ten participants (5 female) with early to moderate stage AD or multi-modality amnesic Mild Cognitive Impairment (MCI) participated in the current study. Amnesic MCI patients were recruited because this condition has been referred to as prodromal Alzheimer's disease (Dubois et al., 2010) and those with impairments across multiple domains have increased conversion rates to AD (Tabert et al., 2006). In the impaired group, six participants had a diagnosis of AD and four had a diagnosis of MCI with impairments in memory and at least one other domain. Of note, all participants with multi-modality amnesic MCI met NINCDS criteria for probable degenerative dementia of the Alzheimer's type (AD), as functional impairment is not required for this classification. As shown in Table 2-1, the AD/MCI group and healthy control group did not differ significantly in age or level of education. Healthy older adults were recruited from the Gainesville community at large. AD/MCI participants were recruited either through the University of Florida Memory and Cognitive Disorders neurology clinic (UF MCD) or the community. Given that the study involved participating in functional magnetic resonance imaging (fMRI), individuals with pacemakers, metal implants, claustrophobia, or other conditions contraindicated for MRI were excluded. All participants were right-handed as determined by the Edinburgh Handedness Inventory (Oldfield, 1971) and spoke English as their first language. General medical exclusionary criteria for participants consisted of history of head trauma, neurological disorder (e.g., stroke), learning disability (e.g., dyslexia), psychiatric disorder (e.g., schizophrenia), drug or alcohol abuse, and any

chronic medical condition likely to impair cognition (e.g., renal or hepatic failure).

Medical records reviews were conducted on all AD/MCI participants prior to enrollment in the study. To rule out other causes for cognitive deficits, imaging results (e.g., clinical MRI, thyroid function tests, B12 levels and syphilis test results (e.g., HATTS) were reviewed to rule out other causes of cognitive deficits. Patients recruited from the UF MCD had a consensus diagnosis of AD or multiple domain amnesic MCI. Additionally, for those participants recruited outside of the UF MCD, case consensus diagnosis of AD or multi-modality amnesic MCI was established through the UF MCD team, with other forms of dementia or medical comorbidities likely to affect a clear-cut diagnosis of AD (e.g., mixed dementia with significant vascular impact) used as exclusionary criteria for the current study. Pre-existing neuroradiological imaging results were reviewed by the UF MCD team. Participants with leukoaraisis compromising 50% or more of white matter (Junque scale; Junque et al., 1990) were excluded, and structural neuroimaging results collected during the current study were reviewed by the senior neuropsychologist and/or neurologist on the study to verify that participants did not currently meet exclusionary criteria with regards to major hemorrhagic or ischemic stroke, lacunar infarct, or leukoaraisis affecting greater than 50% of white matter.

Pharmacological exclusionary criteria for healthy control participants included benzodiazapines, antiepileptic, antipsychotic, dopaminergic, and anticholinergic classes of medications, due to their potential effects on cognition. Participants with AD or MCI who were on antiepileptic medication were excluded. Participants with AD or MCI were not excluded if currently medically stable on pharmacological agents used to manage behavioral sequelae of AD or MCI (e.g., antidepressants, antipsychotics). Participants

with AD or MCI were also not excluded if currently taking medications to manage the cognitive sequelae of dementia (e.g., Aricept, Namenda), given the current medical standard of care for individuals with AD and such drugs' prevalence in the treatment of cognitive sequelae in AD. All but two participants in the AD/MCI group were taking a fixed dosage of such medication. All participants remained on their regular medication regimen at both study appointments. Informed consent was obtained from participants according to guidelines established by the Health Science Center Institutional Review Board at the University of Florida. Participants were paid US \$200 for participation. Of note, an additional nine AD/MCI patients were consented but were not used for analyses due to inability to complete neuropsychological testing or the naming task.

Procedures

Neuropsychological Testing

All participants underwent neuropsychological assessment at a separate appointment within 1 to 2 months prior to the fMRI session. The neuropsychological assessment included the following measures:

- The Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) was administered to screen for possible dementia and Mild Cognitive Impairment (MCI) in the healthy control group and to document current level of general cognitive functioning in the AD group. Healthy older adults who scored below a 27 were excluded.
- In order to assess dementia severity, the Clinical Dementia Rating (Morris, 1993) semi-structured interview was completed.
- The California Verbal Learning Test, Second Edition (CVLT-II; Delis, Kramer, & Kaplan, 2000) was used to assess verbal learning and memory. Potential healthy controls scoring at 2 SD or below on the long-delay free recall portion of the test were excluded. Conversely, all AD participants were expected to score at least 2 SD below the mean on the long-delay free recall and thus were excluded if a verbal memory deficit was not present.

- Constructional praxis and visuospatial immediate and delayed recall were evaluated using the Rey Osterrieth Complex Figure Test (Lezak, 1995). The test was scored using the Meyers and Meyers (1995) criteria.
- The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 2001) is a 60-item confrontation naming test that was used to assess participants' abilities to name objects.
- The Verbal Fluency subtest of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) was administered in order to assess phonological and semantic fluency and semantic fluency switching. During the phonological fluency portion of Verbal Fluency, participants were given 3 letters (i.e., F, A, S) and asked to generate items beginning with each letter. The semantic fluency portion of Verbal Fluency consists of generating items belonging to a semantic class (i.e., animals, boys' names). The Verbal Fluency category switching subtest consists of alternating between providing items across 2 categories (e.g., fruits, furniture).
- Phonological Blocking task (PB) used by Faust et al. (2004) that has demonstrated significant phonological blocking during picture naming in mild AD patients was administered to quantify lexical impairments in the current study. One hundred pictures were paired with neutral, unrelated, semantic, or phonological primes, all of which were real words. Phonological blocking consists of the difference between errors on picturing naming for the phonological prime and errors for the unrelated prime.
- The picture version of the Pyramids and Palm Trees Test (P&PT; Howard & Patterson, 1992) was administered as a test of semantic functions. Participants were presented with a probe picture and 2 pictures from which to choose the one that is more appropriately related to the probe.
- All participants were additionally assessed for visual agnosia and apraxia of speech. Participants who showed evidence of either condition were excluded.

To further investigate the nature of lexical and semantic functioning in our AD/MCI participants, composite scores were created. The lexical composite score was based on performance on the letter fluency subportion of D-KEFS and Phonological Blocking. The semantic composite score was based on performance on the animal fluency subportion of D-KEFS and Pyramids and Palm Trees. In both cases, composite scores were created by standardizing raw scores across both groups. The z-scores of each

lexical measure and each semantic measure were then summed to create the composite scores.

fMRI Naming Task

Within 48 hours prior to fMRI, patients and controls underwent a mock scanning session during which no data was collected. Ten picture naming stimuli not used in the fMRI picture naming task were presented in the mock scanner with simulated scanning noise. The mock scanning session was designed to acclimate subjects to the scanning environment in order to reduce the effects of novelty on the scanning session. At the MRI scanner, participants completed an overt picture naming task during five functional imaging runs (Figure 2-1). The picture naming task stimuli were the same as those used by Wierenga et al. (2008) and consisted of grayscale photographs of 20 animals, 20 vehicles, and 20 tools equated for size and resolution. Stimuli for each of the three categories were balanced for English frequency (Francis and Kucera, 1982) and familiarity (Coltheart, 1981). Each photograph was presented once for a total of 60 naming trials during the scanning session. Pictures were presented one at a time for eight seconds (four images) each, and participants named the picture aloud. An event-related design was implemented to allow for overt responses, in order to assess performance accuracy and response latency. Between overt picture naming trials, participants were instructed to rest and not think of any words while passively viewing abstract patterns. The abstract patterns presented during rest were created by pixelating photographs from the naming task using Adobe PhotoShop 7.0. Intertrial intervals were pseudorandomly varied between 14, 16 and 18 seconds (7, 8, and 9 images, respectively) in order to minimize effects of physiological noise and to prevent subsequent overt responses contaminating the hemodynamic response (HDR) by

allowing the hemodynamic response to return to baseline before the patient spoke again. Experimental runs began and ended with a rest interval, and there were 12 naming trials in each experimental run. Each naming fMRI run was 316 seconds in length and 158 functional images were acquired for each slice. Visual stimuli were projected onto a translucent screen above the subject's head via the Eloquence Functional Imaging System (Philips) using E-Prime Version 1 software. Overt verbal responses were monitored and recorded using a bidirectional dual microphone system (Commander XG, Resonance Technology, Inc.), noise-canceling fiber optic microphone (Phon-Or), laptop computer (Dell), and Audacity software (Adobe). Overt responses were scored for accuracy and reaction time off-line.

fMRI Motor Task

A motor task was used during separate experimental runs from the picture-naming task to ensure that subjects were capable of generating blood-oxygen-level-dependent (BOLD) HDRs. The motor task was not a control task for picture naming. Lack of detectable BOLD HDRs was an exclusionary factor due to some evidence suggesting that BOLD-contrast HDRs can be diminished or absent in some older adults. Subjects failing to show a significant ($R^2 > .16$) volume of activity (volume $> 50 \mu\text{l}$) in the left hand sensorimotor region during the motor task would have been assumed to have subnormal HDRs and been excluded from the study, though none failed to show the response. The motor task involved pressing the right index finger on a Button Response Unit in synchronization with a visually presented flashing green star. During the baseline task, participants viewed a static red star. Three runs were administered to all participants for a total of 30 activation events. Movement was performed for 2 seconds (1 image) following by variable intervals of rest consisting of 14, 16, or 18 seconds (7, 8,

or 9 images, respectively). The total length of each imaging run was 206 seconds (103 images).

Image Acquisition

Images were acquired on a Philip 3 Tesla Achieva instrument with a SENSE multiple arrayed head coil. Head motion was minimized using foam padding. Functional images were obtained with a 1-shot gradient echo EPI scan (TR=2000ms; TE=30ms; FOV=240mm; matrix size=80 x 80; 3mm x 3mm in-plane resolution, flip angle=80°). Thirty-eight 3mm thick axial slices covering the whole brain were acquired and the total number of images differed depending on which of the two fMRI paradigms was being implemented. A high-resolution T1-weighted anatomic scan (TR=8.1ms; TE=3.7ms; FOV=240mm; FA=8°; matrix size=240 x 240; 180 X 1.0mm slices) was obtained prior to functional imaging to provide anatomic reference. FLAIR imaging was collected in order to verify that subjects did not meet leukoaraisis exclusionary criteria for leukoaraisis affecting greater than 50% of white matter (TR=8000ms; TE=337ms; FOV=256mm; matrix size=256 x 256; 180 1.0mm slices). These images were occasionally inspected when participants recruited from the community did not have adequate scans of white matter abnormalities prior to enrollment in the study.

Neuroimaging Data Analyses

fMRI data were analyzed and overlaid onto structural images with the Analyses of Functional Neuroimaging (AFNI) program from the National Institutes of Health (Cox, 1996). The first seven images of each functional run were discarded to ensure that the spin lattice attained a steady state. To minimize the effects of head motion, time series images were spatially registered in three-dimensional space to the first image of the first functional image run, since its acquisition immediately followed the acquisition of the

anatomic reference scan. Quality control procedures were applied to the data to detect residual motion or susceptibility artifact, and distribution of voxelwise coefficient of variation as well as maximum displacement statistics were inspected. Images were additionally visually inspected for gross artifacts. One subject was asked to be rescanned as a result of these quality control measures. All subjects in the current study demonstrated an adequate HDR in the left sensory-motor cortex during the finger tapping task. The five naming and three motor imaging runs were detrended for low frequency signal drifts and concatenated into a single time series for each task. To minimize the negative effects of overt speech on the functional neuroimaging results, the two images (four seconds) occurring at the time of stimulus presentation for each naming stimulus were removed from each of the naming runs prior to concatenation. Voxels in which the SD of acquired time series exceeded 8% of mean signal ($SD/mean \text{ signal intensity} > .08$) were set to zero, to minimize large vessel effects downstream from activity changes or other artifacts. Functional images were co-registered with structural images. To compensate for individual differences in structural and functional anatomy, functional images were spatially smoothed (Gaussian filter, 6 mm full width at half maximum) prior to analysis. HDRs for picture-naming trials were derived with AFNI's deconvolution program. Area under the curve (AUC) of the deconvolved HDR was the dependent variable in the functional analyses. To calculate the AUC statistic, we summed signal intensities at each of the eight TRs comprising the HDR. Anatomic and functional AUC images were non-linearly warped to 2 x 2 x 2 mm MNI space and co-registered using the FMRIB Software Library (FSL) package (Smith et al., 2004; Woolrich et al., 2009).

Region-of-Interest (ROI) Analyses

Three regions of interest (ROIs: inferior temporal lobe [ITL], posterior perisylvian cortex [PPS], and frontal lobes [FL]) were constructed for each hemisphere by combining regions from the Harvard-Oxford atlas distributed with FSL (the anterior most portion of frontal polar cortex was eliminated from frontal ROIs, but medial frontal and lateral frontal cortex were included). The blurred and standard-space transformed AUC images for each participant were masked with these ROIs. Clusters within the ROIs were retained if each voxel was significant at $p < .001$ and the cluster had a volume of at least 116 μl . This threshold/volume combination was determined by Monte Carlo simulation in order to protect ROI-wise probability of false positives of at least $p < .05$. The HDRs of each cluster within an ROI were then examined to ensure that conflicting directionality of the functions would not affect an average value for the entire ROI (e.g. a positive BOLD response would not be cancelled out by an equally large negative BOLD response in an adjacent cluster). The HDRs of all clusters within an ROI were next averaged to create one HDR per ROI. We then calculated the Spearman's correlation between the AUC of this average HDR and lexical and semantic composite scores.

Voxel Based Morphometry (VBM) Analyses

T1-weighted images DICOM files were converted to .nii.gz format. Structural data was analysed with FSL-VBM (Douaud et al., 2007), an optimised VBM protocol (Good et al., 2001) carried out with FSL tools (Smith et al., 2004). First, structural images were skull-stripped and grey matter-segmented before being registered to the MNI 152 standard space using non-linear registration (Andersson, Jenkinson, & Smith, 2007). A visual inspection of all images was completed to control the quality of brain extraction and registration of each image. These images were then averaged and flipped along the

x-axis to create a left-right symmetric, study-specific grey matter template. Second, all native grey matter images were non-linearly registered to this study-specific template and "modulated" to correct for local expansion (or contraction) due to the non-linear component of the spatial transformation. The modulated grey matter images were then smoothed with an isotropic Gaussian kernel with a sigma of 3 mm (FWHM = 7.05 mm). Finally, voxelwise GLM was applied using permutation-based non-parametric testing for comparison of grey matter density between HC and AD/MCI groups (5000 permutations). FWE was used to correct for multiple comparisons across space, and threshold-free cluster enhancement was used to assess cluster significance. To determine if areas of group difference within our a priori language-related ROIs were associated with task performance, we carried out additional ROI analyses. Average grey matter density for the areas of group difference that fell within our a priori ROIs was calculated for each participant. Thus, we created average grey matter density scores for each ROI using the intersection between the significant group differences mask and the ROI masks. We then calculated the Spearman's correlation between these average grey matter density scores and lexical and semantic composite scores.

Table 2-1. Demographics of the healthy control (HC) and Alzheimer's disease/mild cognitive impairment (AD/MCI) groups

	Diagnosis				<i>t</i> value	<i>p</i> -value (two-tailed)
	HC, <i>n</i> = 12		AD/MCI, <i>n</i> = 10			
	Mean	SD	Mean	SD		
Age, year	70.92	4.54	72.60	3.27	-1.01	0.33
Education, year	15.54	3.17	16.10	3.25	-0.41	0.69

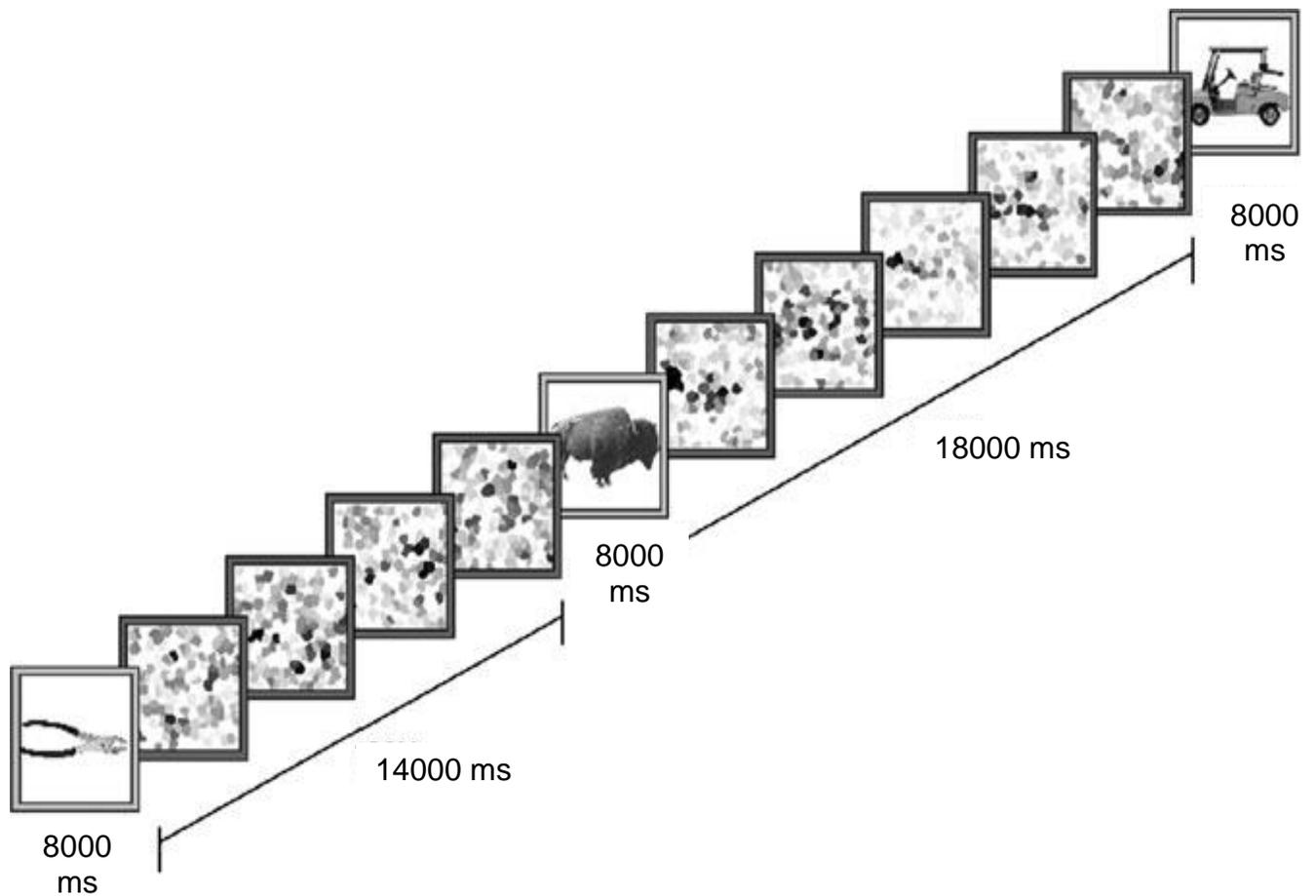


Figure 2-1. Schematic of picture naming task. Participants were presented with greyscale photographs of 20 tools, 20 animals, and 20 vehicles, which they were asked to name out loud. In between naming stimuli, participants were presented with pixelated versions of these same photographs. While these pixelated images were on the screen, patients were instructed to just relax.

CHAPTER 3 RESULTS

Behavioral Results

Neuropsychological assessment performance is presented in Table 3-1. Independent samples t-tests were conducted to investigate significant differences in cognitive functioning between groups. As expected, the AD/MCI patients performed significantly worse than healthy older adults on measures of global cognition, MMSE, $t(11.037) = -3.55, p < .001$; CDR, $t(9) = 8.68, p < .001$. They also performed significantly worse on measures of verbal learning and memory, CVLT total recall, $t(20) = -8.49, p < .001$; CVLT long delay free recall, $t(14.38) = 11.81, p < .001$, visuospatial memory (ROFT, $t(20) = 5.35, p < .001$), and general naming ability, BNT, $t(11.8) = 2.85, p = .02$. Contrary to our hypotheses, the AD/MCI patients and healthy older adults were not significantly different on letter fluency, $t(20) = 1.31, p = .21$, or phonological blocking, $t(19) = -1.29, p = .21$. It follows, then, that they were also not significantly different in their lexical composite scores, $t(19) = 1.50, p = .15$. Finally, differences between the groups were not consistently found on measures of semantic functioning. While the AD/MCI patients performed significantly worse than healthy older adults on category fluency, $t(20) = 3.96, p = .001$, there were no significant differences in performance on Pyramids and Palm Trees, $t(20) = 1.41, p = .17$. However, AD/MCI patients did have significantly lower semantic composite scores overall, $t(20) = 2.96, p = .008$.

fMRI ROI Analysis Results

Average AUC of suprathreshold clusters within a priori ROIs was calculated for each participant, and Spearman correlations were conducted between this measure and lexical and semantic composite scores (Table 3-2). Bonferroni corrections were applied

to account for multiple comparisons. Contrary to our hypotheses, neither the lexical nor semantic scores were significantly related to functional activity of their associated language cortices, left PPS $r_s(19) = -.014, p = ns$; left ITL $r_s(20) = -.251, p = ns$, respectively. Lexical and semantic functioning were similarly not significantly correlated with activity in the left or right frontal lobes, left FL $r_s(19) = -.105, p = ns$; right FL $r_s(19) = -.002, p = ns$, left FL $r_s(20) = -.47, p = .168$; right FL $r_s(20) = -.32, p = .906$, for lexical and semantic scores respectively. There was, however, a significant negative correlation between both the lexical and semantic measures and AUC of the right posterior perisylvian cortex, $r_s(19) = -.56, p = .048$, $r_s(20) = -.63, p = .012$, respectively. Specifically, less functional activity in the right PPS moderately predicted better lexical performance and semantic performance (Figure 3-1).

VBM Results

VBM: Whole-Brain Results

To investigate whole-brain differences between the AD/MCI patients and healthy older adults, voxelwise GLM analyses were conducted (Figure 3-2). The analyses revealed the expected density reductions in medial temporal cortex for AD/MCI patients. Additional bilateral reductions were detected in regions of the frontal, temporal, parietal, occipital, and insular cortices.

VBM: ROI Analyses

Further analyses were limited to areas of group difference located within a priori ROIs. Average grey matter density for these regions was calculated for each participant, and Spearman's correlations were conducted between this measure and lexical and semantic composite scores (Table 3-3). Bonferroni corrections were applied to account for multiple comparisons. Contrary to our hypotheses, neither the lexical nor semantic

scores were significantly related to grey matter density of their associated language cortices, left PPS $r_s(19) = .078$, $p = \text{ns}$; left ITL $r_s(20) = .097$, $p = \text{ns}$, respectively. Lexical and semantic functioning were similarly not significantly correlated with grey matter density in the left or right frontal lobes, left FL $r_s(19) = .378$, $p = .55$; right FL $r_s(19) = .17$, $p = \text{ns}$, left FL $r_s(20) = .48$, $p = .15$; right FL $r_s(20) = .45$, $p = .204$, for lexical and semantic scores respectively. There was, however, a significant positive correlation between the grey matter density in the right posterior perisylvian cortex and semantic composite score, $r_s(20) = .577$, $p = .03$. Specifically, higher grey matter density in the right PPS moderately predicted better semantic performance.

Table 3-1. Neuropsychological raw/composite scores of the healthy control (HC) and Alzheimer's disease/mild cognitive impairment (AD/MCI) groups

Variables	Diagnosis				t value	p-value (two-tailed)
	HC, n = 12		AD, n = 10			
	Mean	SD	Mean	SD		
Global Cognition						
MMSE	29.00	1.21	25.40	3.27	3.30	0.01 ^a
CDR	0.00	0.00	0.75	0.49	-4.88	0.00 ^b
Memory						
CVLT list 1-5 total recall	52.00	8.01	25.40	6.36	8.49	0.00 ^a
CVLT list 1-5 long delay free recall	11.92	3.00	0.90	1.10	11.81	0.00 ^a
RCFT long delay free recall	13.33	4.31	4.15	3.60	5.35	0.00 ^a
General Language						
Boston Naming Test	55.91	2.91	49.40	6.72	2.85	0.02 ^a
Lexical Functioning						
Letter fluency (FAS total)	39.75	9.75	34.20	10.06	1.31	0.21
Phonological blocking	0.34	1.82	1.38	1.84	-1.29	0.21 ^c
Lexical composite	0.49	1.35	-0.53	1.76	1.45	0.15 ^c
Semantic Functioning						
Category fluency (animals)	21.33	5.14	13.90	3.21	4.13	0.00 ^a
Pyramids and Palm Trees	50.50	1.88	49.40	1.71	1.43	0.17
Semantic composite	0.86	1.76	-1.03	1.09	3.09	0.01 ^a

MMSE = Mini Mental State Exam; CDR = Clinical Dementia Rating; CVLT = California Verbal Learning Test; RCFT = Rey Complex Figure Test.

^a Statistically significant pairwise comparison AD/MCI < HC

^b Statistically significant pairwise comparison AD/MCI > HC

^c AD/MCI n = 9

Table 3-2. Spearman correlations between functional activity and behavioral language performance

Measure	PPS		ITL		FL	
	Left	Right	Left	Right	Left	Right
Lexical composite	-.01	-.56*	-.52	-.24	-.11	-.002
Semantic composite	-.12	-.63*	-.25	-.14	-.47	-.32

PPS = Posterior Perisylvian Cortex; ITL = Inferior Temporal Lobe; FL = Frontal Lobe

* $p < .05$, FWE corrected

Table 3-3. Spearman correlations between grey matter density and behavioral language performance

Measure	PPS		ITL		FL	
	Left	Right	Left	Right	Left	Right
Lexical composite	.08	.35	.09	.38	.38	.17
Semantic composite	.18	.58*	.10	.36	.48	.45

PPS = Posterior Perisylvian Cortex; ITL = Inferior Temporal Lobe;
 FL = Frontal Lobe

* $p < .05$, FWE corrected

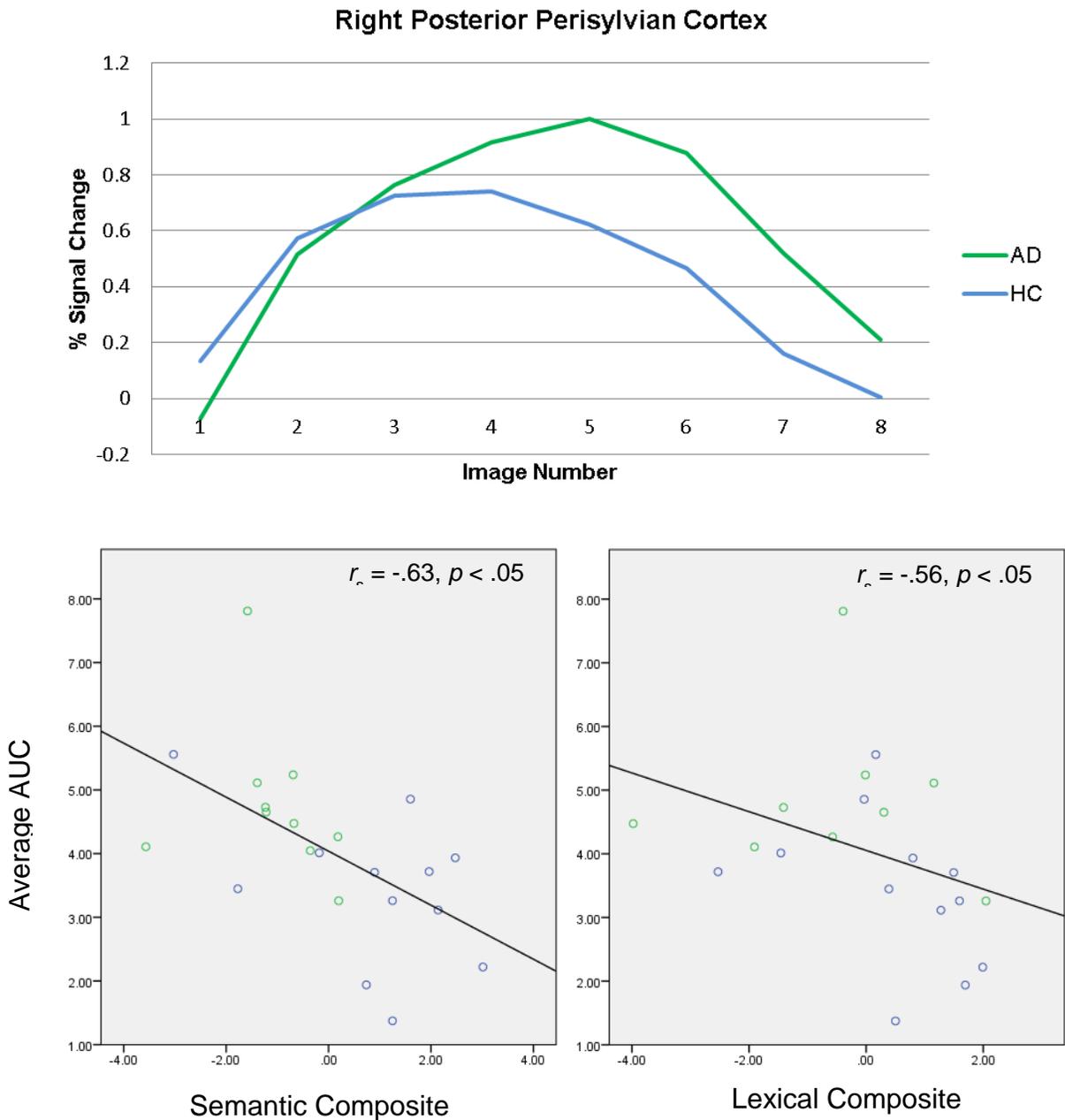


Figure 3-1. Hemodynamic response function in the right PPS during the picture naming task is presented for each group. Scatter plots for the relationship between activity and semantic and lexical composite scores are shown for each group with the fitted least-squares regression line. AD/MCI is represented in green; HC is represented in blue.

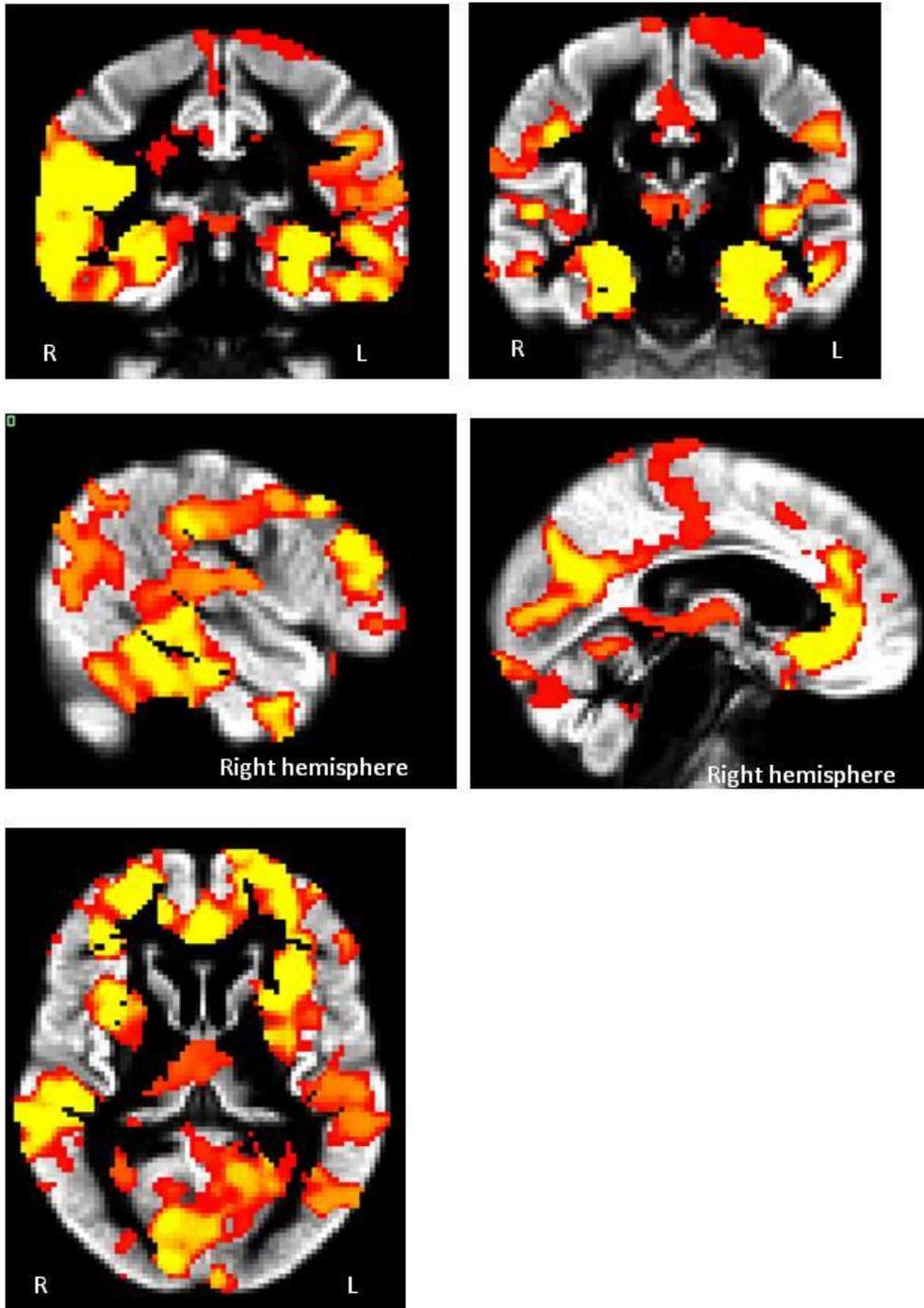


Figure 3-2. Whole brain comparison of grey matter density between HC and AD/MCI groups. Thresholded and clustered results (protecting a whole brain $p < .05$) are presented. Warm colors represent areas where AD/MCI patients had significantly lower grey matter density than HCs. Results are overlaid on to a study-specific average brain that has been non-linearly transformed into MNI space and smoothed at 7.05mm FWHM.

CHAPTER 4 DISCUSSION

This study aimed to investigate the neural correlates of naming impairment in Alzheimer's disease. Based on case studies of atypical AD presentation, it was hypothesized that not only semantic but also lexical deficits occur during language processing in these patients. Thus, functional brain activity during a naming task and average grey matter density in language-related brain regions were correlated with offline measures of lexical and semantic functioning. Contrary to our hypotheses, lexical performance was not significantly related to functional activity or grey matter density in the left posterior perisylvian cortex. Similarly, semantic performance was not significantly related to functional activity or grey matter density in the left inferior temporal lobe.

Several significant associations were detected, however, with the right posterior perisylvian cortex. This area was included in analyses as the right hemisphere homologue to the chosen lexical region-of-interest. Our results indicate that functional activity in this region is negatively related to performance on lexical measures; thus, the greater the activation in the lexical right hemisphere homologue, the poorer the performance on lexical tasks. This finding is notable given the nature of the participants' lexical functioning: the AD/MCI patients did not have significantly lower scores in this domain than the healthy older adults. In this sense, the negative association may not reflect deficits that arise from the disease process; instead, it may be related to changes in language processing that are associated with the aging process in general. Activity in the right posterior perisylvian cortex was also significantly negatively related to semantic functioning, while grey matter density in this area was significantly positively related to

semantic functioning. Together these results suggest that both increased activity and increased atrophy of this region are associated with poor semantic performance.

While unexpected, this association between the right posterior perisylvian cortex and several different measures of language functioning may be due to participant characteristics. As noted earlier, no lexical deficits were detected among our AD/MCI patients, which may be due in part to our inclusion criteria. We chose to include multi-modality *amnestic* MCI patients, as these cases show higher conversion rates to Alzheimer's disease. In doing so, however, we may have failed to include patients with Alzheimer's pathology who presented with atypical complaints (i.e. phonological impairments), as such patients may be diagnosed with primary progressive aphasia. Croot et al. (2000), for example, reported that 3 of the 10 case studies included in their description of atypical AD presentations were classified as progressive aphasia until postmortem analyses were performed.

To interpret our results, then, we look outside the AD literature and into the realm of aging and language research in general. Our chosen correlational analyses lend themselves well to this type of interpretation in that our participants span the continuum of healthy to pathological aging. This assertion is especially apt in light of recent research regarding increased amyloid burden among a subset of cognitively normal older adults (Codispoti et al., 2012; Kikuchi et al., 2011; Sperling et al., 2009). These studies suggest that while up to 30% of healthy older adults may have amyloid deposition patterns similar to those of Alzheimer's patients, on behavioral measures of cognition they do not show impaired functioning. Amyloid deposition may, however, impact functional brain activity, such that high amyloid burden in cognitively normal older adults

is associated with aberrant neural activity in networks that support memory functions (Sperling et al., 2009). In this sense, it is likely that some cognitively normal older adults in our healthy control group demonstrated aberrant neural activity while successfully completing neuropsychological measures. Our analyses, then, allow us to ask if we are detecting a phenomenon of healthy aging that is aggravated by the effects of neuropathology rather than an effect of the pathology itself.

Recent studies of the hemispheric asymmetry reduction in older adults (HAROLD) phenomenon lend support to this idea. Meinzer and colleagues (2012) examined functional brain activity during semantic and phonemic fluency in healthy younger and older adults. They specifically looked at increased task-positive activity as well as decreased task negative activity in older adults to investigate their relationship to language performance. Of note, they looked at both frontal and more posterior brain regions, including regions of interest of the current study. Overall, Meinzer and colleagues found that older adults performed better when their brain activity more closely resembled that of younger adults. In other words, increased task-positive activity was associated with poorer semantic performance and decreased task-negative activity was associated with poorer semantic performance. Relevant to the findings of this study, they found a cluster of decreased negative BOLD in the right inferior parietal lobule, and this cluster fell within the right posterior perisylvian ROI we investigated. Adjacent to this cluster, Meinzer and colleagues found an area of increased positive BOLD in the right superior parietal lobule amongst older adults. These results resemble our findings in that increased positive BOLD in the right posterior perisylvian cortex

during a language task was associated with poorer semantic performance amongst healthy older adults.

Zlatař and colleagues (in press) examined possible neural mechanisms underlying these differences in brain activity between healthy younger and older adults during a semantic fluency task. They looked at activation in young adults, sedentary older adults, and active older adults and found brain patterns very similar to those reported by Meinzer et al. (2012) for sedentary older adults. Older adults performed better when their activation more closely resembled that of younger adults. Like Meinzer et al. (2012), they found BOLD response patterns in the right posterior perisylvian cortex that corresponded to those detected in the current study. While younger adults showed negative BOLD responses, both groups of older adults had task-positive activity in this area. Furthermore, the increased positive activity was associated with decreased semantic functioning. Zlatař and colleagues related this increased BOLD response to decreased inhibition by examining the ipsilateral silent period (iSP, a measure of interhemispheric inhibition obtained during transcranial magnetic stimulation). They found that increased activity in the right PPS was negatively associated with the iSP, suggesting that the positive BOLD detected is the result of decreased suppression of the region. In this sense, the right posterior perisylvian cortex was active during a task in which it is usually suppressed, and this activation interfered with efficient semantic functioning in sedentary older adults.

It is important to note that in both of the studies described the task that elicited increased activation of the right posterior perisylvian cortex was semantic fluency. We utilized a different task of language functioning, picture naming, to investigate the neural

correlates of anomia. However, our correlational analyses did not rely on naming accuracy; rather, they used a measure of functioning that included semantic fluency. Thus, while our investigation does not align completely with those previously mentioned, the overlap in processes examined allows us to cautiously extend their findings. Indeed, these studies have interesting implications for the interpretation of our results. They suggest that the increased task-positive activity we found in right PPS may be a part of the aging process. Similar activity in previous studies has been linked to decreased interhemispheric inhibition, which begs the question: is this activity related to the loss of one brain area's ability to suppress another in aging? Such an assertion is supported by the fact that this activity is associated with poorer semantic and lexical functioning, which makes it unlikely that activation of the right posterior perisylvian cortex is compensatory. Rather, the increased activation of this region may be interfering with efficient language functioning, or it may be an indication of decreased efficiency in processing throughout the brain. Thus, we may have detected a process of healthy aging that is aggravated by Alzheimer's pathology, as opposed to an effect of the disease process itself. Research involving the default mode network (DMN) functioning and beta amyloid deposition have shown similar phenomena occur in the attention network. While younger adults typically show strong task-negative activity within the DMN, healthy older adults show weaker task-negative activity and those with a high amyloid burden show task-*positive* activity (Sperling et al., 2009). Moreover, while default mode connectivity is disrupted in normal aging, high amyloid burden is associated with further decreased connectivity that can be detected before clinical signs of AD are evident (Hedden et al., 2009).

In summary, the expected relationship between semantic and lexical deficits in AD patients and their associated neurocorrelates was not detected in the current study. Rather, we found that increased activation of the right posterior perisylvian cortex was associated with poorer semantic and lexical functioning. Increased atrophy of the same region was also associated with semantic deficits. In this sense, the right PPS may be sensitive to functional changes of the aging process, such as a loss of suppression, which are aggravated by the neuropathology of Alzheimer's disease. To better elucidate this phenomenon, future studies should address the relationship between the right PPS, cognition, and amyloid burden. A healthy younger adult group should additionally be included. Further investigation of this trend opens the door for new discussion of language treatment in Alzheimer's disease, allowing us to ask if we should look first to treatment of language deficits due to the healthy aging processes.

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BIOGRAPHICAL SKETCH

Amanda Garcia graduated in 2011 from the University of Florida with a Bachelor of Science in psychology and a Bachelor of Arts in linguistics and Spanish. In 2011, she began a Doctor of Philosophy program in the Department of Clinical and Health Psychology. Her research interests include semantic memory and dementia.