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Functional Correlates Of Verbal Working Memory In Healthy Aging And Early Alzheimer's Disease

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FUNCTIONAL CORRELATES OF VERBAL WORKING MEMORY IN HEALTHY AGING AND EARLY ALZHEIMER'S DISEASE

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Introduction

Memory impairments and Alzheimer's disease

The hallmark symptoms of Alzheimer's disease (AD) include deficits in multiple memory systems. Specifically, episodic memory impairment is the earliest and most pronounced deficit in AD (Becker, 1988; Greene, Baddeley, & Hodges, 1996; Wilson, Bacon, Fox, & Kaszniak, 1983). Furthermore, poor performance on delayed recall measures in otherwise healthy older adults is a risk factor for developing AD (Aggarwal, Wilson, Beck, Bienias, & Bennett, 2005; Linn et al., 1995; Tierney et al., 1996). Procedural memory, on the other hand, appears to be relatively unaffected during the disease course, as AD patients typically perform comparably to controls on motor learning tasks (Deweer et al., 1994; Hirono et al., 1997).

Semantic memory impairment is also common in AD patients (Chertkow & Bub, 1990; Joubert et al., 2010; Mardh, Nagga, & Samuelsson, 2012; Verma & Howard, 2012). Loss of knowledge for more specific semantic information (e.g., facts, details) may be an early deficit in these patients, and as the disease progresses, knowledge for higher-order information (e.g., stimulus names or category labels) may also be susceptible to loss (Giffard et al., 2001; Seidenberg et al., 2009; Warrington, 1975). Semantic memory impairment may reflect a process unique to pathological aging. While gradual declines in episodic memory abilities are a normal part of healthy aging, semantic memory typically remains relatively intact with age (Nilsson, 2003). As such, functional neuroimaging of the semantic memory network has emerged as a promising line of research in the detection of risk for late-life cognitive decline and dementia (Sugarman et al., 2012).

Working memory impairment has also been associated with AD (A. D. Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991). However, the specific nature of these deficits has been

debated within the literature. The traditional cognitive model of working memory provides a context for discussing and interpreting these deficits, and the following section will include a brief overview of this model.

Working Memory Model

The most widely recognized model of working memory was originally conceived by Baddeley and Hitch (A. D. Baddeley, 1992; A. D. Baddeley & Hitch, 1974), who proposed that working memory involved the simultaneous processing and storage of auditory or visually presented information in three main components: 1) the "central executive system", which controls attentional processes and is responsible for manipulating information, 2) the "visuospatial sketch pad", a "slave system" which monitors available visual information, and 3) the "phonological loop", a second subordinate system responsible for the storage and rehearsal of auditory and speech information. A later revision to this model (A. Baddeley, 2000) included a fourth component, the "episodic buffer", a third slave system that integrates verbal, visual, and spatial stimuli into single pieces of information and also has connections to long-term memory and semantic information. Given the popularity of this model, many studies of working memory are designed to evaluate abilities in one or more of these components. Several such studies have been conducted with AD patients in an attempt to determine the specific working memory deficits in this population.

Working Memory Deficits in AD

Early studies (A. D. Baddeley, Logie, Bressi, Della Salla, & Spinnler, 1986; A. D. Baddeley et al., 1991) suggested that the core working memory deficit associated with AD was in the central executive system. One of the responsibilities of the central executive is to coordinate and manage information from multiple subordinate systems. Thus, the examination of

dual-task performance is a common way to study the central executive. One study (A. D. Baddeley et al., 1986) observed that when simultaneously performing a verbal digit span and visual tracking task, performance on both tasks compared to single-task conditions decreased considerably for AD patients. Age-matched controls were no more impaired than younger adults by the dual-task requirement. Furthermore, a longitudinal follow-up (A. D. Baddeley et al., 1991) indicated that as AD progressed, performance on each task remained stable, whereas dual-task performance was impaired considerably. These findings suggested that the central executive may be deficient in AD patients. A recent review of studies that required dual task completion substantiated these results (Huntley & Howard, 2010). Relative to cognitively intact controls, AD patients demonstrated greater decrements in performance between single and dual-task conditions in 19 of 21 samples.

Further research has indicated that the phonological loop, visuospatial sketchpad, and episodic buffer. may also be affected by AD pathology, although these findings are inconsistent (Huntley & Howard, 2010). The impairments in these domains may become more pronounced with disease severity. For example, forward digit span, a measure of verbal working memory that primarily stresses the phonological buffer, is intact in early AD but demonstrates progressive impairment consistent with disease course (Greene, Hodges, & Baddeley, 1995; Hodges & Patterson, 1995; Lines et al., 1991; Orsini, Trojano, Chiacchio, & Grossi, 1988). One study (Germano, Kinsella, Storey, Ong, & Ames, 2008) observed that mild AD patients may be impaired at meaningfully organizing new information, a responsibility of the episodic buffer Overall, studies suggest that the central executive is the earliest and most severely affected component in AD, whereas the other components of Baddeley's (1992) model display progressive deficits during the disease course.

Several studies have attempted to identify the potential neurobiological origins of these deficits using neuroimaging methods including positron emission tomography (PET). To fully understand the nature of these problems, it is first necessary to discuss the neural correlates of working memory in normally functioning individuals.

Neuroimaging studies of the functional correlates of working memory

Several PET studies of verbal working memory have attempted to identify the functional substrates of the components of Baddeley's (1992) model. One such study (Paulesu, Frith, & Frackowiak, 1993) required cognitively intact participants to learn and remember a string of visually presented English letters. Korean letters were used in a control task in which participants utilized the visuospatial sketch pad, but not the phonological loop in completing the task because the participants were not familiar with the Korean alphabet. The left supramarginal gyrus displayed greater rCBF recruitment for English compared to Korean letters, suggesting that this region was associated with the phonological store. In addition, participants completed a letter rhyming task, which engaged subvocal rehearsal of the letters but did not require storage of the phonological information (a letter similarity control task was used with the Korean letters). The authors determined that the main structural correlate of subvocal articulatory rehearsal is the left inferior frontal gyrus, more commonly known as Broca's area.

A subsequent study (E. Salmon et al., 1996) utilized this same task and replicated the findings that left supramarginal gyrus and Broca's area were implicated with phonological storage and articulatory rehearsal, respectively. In addition, they observed that lingual sensorimotor areas were recruited during the letter learning task even though no overt speech was required. The authors hypothesized that this activation may be due to motor planning during articulatory rehearsal. They also conducted a second verbal working memory task, in which

participants were instructed to learn a list of consonants and then were asked to indicate whether a subsequent probe was among the last six letters of the previous list. Thus, this task required that participants not only rehearsed the letter list, but also stored information concerning presentation order, a responsibility of the central executive. The authors found that in addition to the left supramarginal gyrus, they observed bilateral dorsolateral prefrontal cortex (DLPFC) recruitment during this task. This finding implied that DLPFC may be associated with the central executive.

A considerable body of subsequent research has substantiated this association between the central executive and DLPFC. Several groups have studied the central executive with PET (Collette et al., 1999) or event-related functional magnetic resonance imaging (fMRI) (D'Esposito, Postle, Ballard, & Lease, 1999; Postle, Berger, & D'Esposito, 1999) with a modified alphabet span task. In this task, participants were instructed to recall lists of words or letters either in alphabetical order or in the order of presentation. The alphabetical condition required manipulation by central executive processes, whereas the serial recall condition utilized the subordinate systems without manipulation of the information. The authors found greater recruitment in bilateral DLPFC for the alphabetical relative to the serial recall condition, suggesting that this region is involved with the manipulation and processing of the phonological loop. An earlier study (D'Esposito et al., 1995) found that DLPFC areas are activated during fMRI when two non-working memory tasks (semantic association and spatial rotation) are performed simultaneously, but not during either individually, suggesting that DLPFC regions assisted in managing the multiple demands. However, subsequent studies have not found additional regions of activation during dual task performance above and beyond the regions

associated with the individual tasks (Adcock, Constable, Gore, & Goldman-Rakic, 2000; Bunge, Klingberg, Jacobsen, & Gabrieli, 2000; Klingberg, 1998).

The cerebellum has also been identified as a functional correlate of verbal working memory tasks. Multiple groups have observed bilateral cerebellar activation during tasks of verbal working memory using PET (Schumacher et al., 1996; Smith, Jonides, & Koeppe, 1996) and fMRI (LaBar, Gitelman, Parrish, & Mesulam, 1999). Further evidence for this association comes from research with patients with cerebellar damage. A case study of a 18-year-old male who received a right cerebellectomy revealed a normal neuropsychological evaluation with the exception of selective deficits in digit span and the rapid forgetting of verbal information (Silveri, Di Betta, Filippini, Leggio, & Molinari, 1998). A more recent study (Ravizza et al., 2006) observed that a sample of 15 patients with selective cerebellar damage performed worse than controls on tasks of verbal working memory, but were relatively spared on spatial working memory tasks. Patients with cerebellar damage are also typically impaired during generative verbal fluency tasks, even when slowed naming speed due to motor deficits in language production is accounted for as a covariate (Stoodley & Schmahmann, 2009).

Task-related activation in these neurological correlates of word rehearsal has also been demonstrated to be associated with subsequent memory performance. Using fMRI, one study (Davachi, Maril, & Wagner, 2001) demonstrated that the magnitude of activation in left prefrontal, bilateral parietal, supplementary motor, and cerebellar regions during word rehearsal was significantly correlated with delayed episodic recognition performance of the same words. These findings suggest that regional recruitment during the encoding process may assist in creating a stronger representation for subsequent retrieval.

Neuroimaging studies of AD and working memory

Some of the earliest PET studies in AD patients (Chase et al., 1984; Foster et al., 1984) used [^{18}F] fluorodeoxyglucose (^{18}FDG) as the radioactive isotope tracker and observed that regional cerebral glucose metabolism was reduced about 30% compared to age-matched controls during resting state. However, these metabolism reductions were not uniform. Posterior parietal, posterior temporal, and anterior occipital lobes were the most hypometabolic relative to controls, whereas the frontal lobes were relatively intact. Another study (S. Minoshima et al., 1997) observed hypometabolism in the posterior cingulate cortex in a sample of non-demented participants who were complaining of memory impairment at the time of the scan and who later progressed to AD. This study suggested that ^{18}FDG PET may be sensitive to the cortical abnormalities associated with AD pathology. Consistent with previous studies, hypometabolism was not observed in frontal regions. One group (E Salmon et al., 1994) suggested that frontal hypometabolism is atypical for AD, and may be more representative of Pick's disease or frontal lobe dementia. A more recent study (Mosconi et al., 2008) found similar results, with the greatest hypometabolism in AD occurring in the hippocampus, posterior cingulate, inferior parietal lobule, and lateral temporal lobe. Alternatively, frontotemporal dementia (FTD) patients had the most pronounced hypometabolism in the prefrontal cortex and lateral temporal lobes. One group (S Minoshima, Frey, Koeppe, Foster, & Kuhl, 1995) noted that when frontal hypometabolism is present in AD patients, it is most frequently observed in more advanced cases.

In addition to these "resting state" PET studies of AD patients, there have also been limited task-activated rCBF studies of working memory. Resting state studies may not be the most optimal method for studying functional deficits in AD, as regions that are classified as hypometabolic at rest can still display task-activated recruitment (Duara et al., 1992). One study (Collette, Salmon, Van der Linden, Degueldre, & Franck, 1997) observed that the regions of

task-activated recruitment in a sample of AD patients during verbal and visual span tasks were similar to other studies of cognitively intact individuals (Paulesu et al., 1993; E. Salmon et al., 1996), specifically in the supplemental motor area and supramarginal gyrus. However, correlations between recruitment and performance on the visuospatial task were observed in occipital and temporal regions only. Prefrontal activity (associated with the central executive, as described above) was not correlated with task performance. The authors suggest that individuals with AD do not spontaneously recruit central executive resources in the frontal cortex when completing working memory tasks, consistent with the hypothesis of a central executive deficit in early AD (A. D. Baddeley, 1992).

Another study (J T Becker et al., 1996) observed patterns of compensatory recruitment in AD patients relative to controls during a word rehearsal task. Both groups displayed activation in regions including Broca's area, prefrontal cortex, and superior temporal gyrus. In these regions, the patients displayed a greater overall magnitude and extent of activation. However, the controls also recruited regions in the hippocampal formation and cerebellum, whereas the AD patients did not. The authors hypothesized that AD patients may utilize additional regions to compensate for declining functioning in other regions. However, methodological shortcomings limit the interpretation of this study. For example, only seven participants were in each group, rest was used as a comparison condition, and minimal memory demands were placed on the participants, as the rehearsal condition only required three-word rehearsal.

With regard to verbal word rehearsal in AD, the only other published PET study comes from a pilot study from the current data set containing six mild AD patients and six age, gender, and education matched controls (J.L. Woodard et al., 1998). Consistent with the previous study (J T Becker et al., 1996), AD patients displayed overall greater extent and magnitude of

recruitment than controls during word rehearsal compared to a reading control task. Interestingly, AD patients also had greater activation in bilateral cerebellum, which stands in contrast to the finding from the previous study (J T Becker et al., 1996). In the frontal lobes, AD patients displayed bilateral activation, whereas control participant recruitment was confined to the right hemisphere.

The finding of increased spatial extent and magnitudes of activation in older compared to younger adults has been documented in many studies (Cabeza, 2002; Park & Reuter-Lorenz, 2009). It has been hypothesized that a "scaffolding" process may occur, where older adults recruit additional areas that are not utilized in younger adults to support task performance (Park & Reuter-Lorenz, 2009). The functionality of neural resources declines precipitously with AD progression, and evidence suggests that AD patients may engage in scaffolding above and beyond their age-matched, cognitively intact counterparts. Indeed, findings of compensatory recruitment in AD patients compared to controls has been documented during both semantic and episodic memory tasks using PET (Backman et al., 1999; J T Becker et al., 1996; Grady et al., 2003) and fMRI (Grossman et al., 2003; Saykin et al., 1999). In one of these studies (Grady et al., 2003), greater recruitment in bilateral DLPFC and posterior regions was associated with superior task performance within the patient group. However, one study (Machulda et al., 2003) observed *decreased* activation in the medial temporal lobe in AD patients compared to controls during a picture encoding task. Another study (Grossman et al., 2003) also observed lesser activation in AD patients compared to controls in left parietal and frontal cortex and the caudate as well as *increased* activation in left temporal cortex during a semantic discrimination task. Overall, it appears that the neural mechanisms subserving performance for a wide range of cognitive tasks is altered in AD, and patterns of either hyper- or hypoactivation may occur,

depending on the task and region. Certain areas may possess deficiencies, such as the medial temporal lobes (Furst & Mormino, 2010; O'Brien et al., 2010) or left parietal lobe, and other regions may display greater activation to compensate for these deficits.

Study Summary and Hypotheses

The purpose of the current investigation is to determine the functional neurological correlates underlying verbal working memory in older adults and how they may be affected during the early phases of AD. Functional imaging affords an opportunity to study the mechanisms underlying the documented working memory impairments in AD patients. We will utilize a task that places variable demands on verbal working memory resources with high- and low-load word rehearsal conditions (Rundus, 1971; Rundus & Atkinson, 1970). The task primarily places demands on the phonological loop and central executive components of working memory (A. D. Baddeley, 1992). As a control task, we will include a repetitive reading task which requires overt word repetition but not rehearsal of multiple words. Therefore, it places minimal demands on working memory. These tasks will be performed by early AD patients and by cognitively intact, age-matched controls during PET. Through this design, we will accomplish three specific aims.

The first aim is to determine the functional neurobiological substrates of verbal word rehearsal and working memory in healthy older adults. To isolate the working memory component, our primary activation contrasts will investigate the two word rehearsal conditions relative to the reading condition. Within this aim, we have three specific hypotheses: 1) Consistent with previous studies of verbal working memory, we hypothesize task-activated recruitment for both rehearsal conditions compared to the reading condition in the DLPFC, supramarginal gyrus, supplementary motor area, hippocampus, and cerebellum in both groups.

We do not anticipate activity in Broca's area, which has been associated with subvocal articulatory rehearsal (Paulesu et al., 1993), because both word rehearsal and reading task conditions require articulation; 2) Given the association between the DLPFC and demands on the central executive, we expect to observe greater recruitment in this region during high- compared to low-load rehearsal conditions; 3) We anticipate that activity in DLPFC, hippocampus, and cerebellum will be correlated with rehearsal performance and delayed free recall of the word lists because this regional activity may be critical to the formation of memory traces.

The second specific aim is to determine the effectiveness of task-activated PET during the word rehearsal task in discriminating between early AD patients and cognitively intact controls. We hypothesize that regional recruitment will differ between the groups in the following ways: 1) For the rehearsal versus reading contrasts, we expect to observe bilateral frontal recruitment in AD patients, compared to predominantly right hemisphere rCBF in control participants, consistent with previous research (J.L. Woodard et al., 1998); 2) We hypothesize that AD patients will demonstrate overall greater (compensatory) activity in cortical and cerebellar regions (Backman et al., 1999; Grady et al., 2003; J.L. Woodard et al., 1998) for rehearsal compared to reading conditions and hypoactivity compared to controls in the hippocampus (Furst & Mormino, 2010; O'Brien et al., 2010); 3) We hypothesize that AD patients will not display activation in DLPFC for the high-load minus low-load subtraction because AD patients are impaired in recruiting central executive resources to support task performance (Collette et al., 1997).

The third specific aim is to determine the extent to which task-activated rCBF is related to neuropsychological abilities. We have access to a wealth of neuropsychological data from our participants, including several measures of working and episodic memory. For convergent

validity, we hypothesize that regional recruitment during the word rehearsal task will be significantly correlated with the neuropsychological tests, potentially providing further support that our variables are indeed neurobiological correlates of memory. Significant findings from these analyses would indicate that PET activation may effectively serve as an index of neuropsychological functioning.

Methods

Participants

Fifteen patients diagnosed with probable AD (eight males, M_{age} = 68.5 years) and 16 age, gender, and education-matched controls (eight males, M_{age} = 71.5 years) served as the participants in this study. AD diagnoses were determined by the National Institute of Neurological and Communications Disorders and Stroke and Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) research criteria (McKhann et al., 1984). Participant demographics are displayed in Table 1. All participants denied taking any psychoactive medications other than acetylcholinesterase inhibitors and denied current or past history of psychiatric disorder. No participants scored ≥ 11 on the Geriatric Depression Scale (GDS) (Yesavage et al., 1983), although patients scored significantly higher than controls. All participants completed neuropsychological testing and $H_2{}^{15}O$-injected PET.

	AD Patients (n = 15)				Controls (n = 16)					
Variable	Mean	SD	Min	Max	Mean	SD	Min	Max	p	d'
Age (years)	68.53	7.14	56	81	71.50	6.20	61	82	.228	0.44
Education (years)	15.80	2.62	12	20	16.31	2.06	12	20	.552	0.22
Race	93% Caucasian, 7% Other				100% Caucasian				.484	-
Gender	8 male, 7 female				8 male, 8 female				1.00	-
GDS*	5.50	2.21	2	9	3.13	2.50	0	10	.010	1.00

Table 1. Participant demographics. GDS = Geriatric Depression Scale. *p < .05

Neuropsychological measures

All participants received a thorough neuropsychological evaluation spanning several domains, with an emphasis on tests of memory. Global intellectual abilities were assessed using the Ward Short Form (Ward, 1990) of the Wechsler Adult Intelligence Test – Revised (WAIS-R) (Wechsler, 1981), which includes the Information, Digit Span, Arithmetic, Similarities, Picture Completion, Block Design, and Digit Symbol subtests. These subtests yield an estimate of the Full Scale (FSIQ), Verbal (VIQ), and Performance (PIQ) Intelligence Quotients, all of which have been demonstrated to correlate with the values generated by the full test at r = .95 or better (Ward, 1990). One-year test-retest reliabilities in healthy older adults for the full WAIS-R administration are r = .90, .86, and .85 for FSIQ, VIQ, and PIQ scores, respectively (Snow, Tierney, Zorzitto, Fisher, & Reid, 1989).

We measured memory functioning with a variety of tests. Six subtests from the Wechsler Memory Scale – Revised (WMS-R) (D Wechsler, 1987) were administered to all participants, including both immediate and delayed (25-35 minutes) recall measures for auditory presentations of stories (Logical Memory), graphomotor reproductions of visually presented designs (Visual Reproduction), and the recall of word pairs (Verbal Paired Associates). This short form generates estimates of the General Memory and Delayed Recall index scores, which both correlate with the values generated by a complete test administration (Adjusted R^2 = .97) (John L. Woodard & Axelrod, 1995). Four- to six-week test-retest reliability coefficients for immediate memory subtest scores range from r = .56 to .83 and from r = .58 to .82 for delayed memory scores (D. Wechsler, 1987).

Additionally, the California Verbal Learning Test (CVLT) (Delis, Kramer, Kaplan, & Ober, 1987) was administered to all participants as a neuropsychological measure of verbal

learning and memory. This test yields measures of free recall of a list of 16 words across five study-test trials, as well as indices of learning rate. Additionally, there are both free and cued recall trials after short and long (~20 minutes) delays. One-year test-retest reliability coefficients for scores in healthy older adults for Trials 1-5 and free and cued recall trials at both delay intervals range from r = .66 to .76 (Paolo, Troster, & Ryan, 1997).

The Boston Naming Test (BNT) (Kaplan, Goodglass, & Weintraub, 1983) was also administered to all participants. Participants are asked to name 60 individually-presented line drawings of objects that decrease in their frequency of occurrence. The test is intended to identify difficulties with object naming (anomia) and semantic memory retrieval. One study (Dikmen, Heaton, Grant, & Temkin, 1999) observed a test-retest reliability of r = .92 for total BNT scores, with a median test-retest interval of 11 months in healthy adults. The Category Fluency test and Controlled Oral Word Association Test (COWAT) (Benton & des Hamsher, 1976) were administered as further measures of semantic memory retrieval, as well as verbal fluency. Participants are asked to list as many items from a category as they can during a one-minute span, including animals, fruits, vegetables, and words beginning with the letter(s) C, F, and L. Scores from the COWAT have been reported to demonstrate a 11-month test-retest reliability of r = .72 (Dikmen et al., 1999).

The Dodrill version of the Stroop Test (Dodrill, 1978; Stroop, 1935) was administered as a measure of oral reading fluency, selective attention, and resistance to interference. Participants were required to read two lists of color names – one written in black ink and one written in ink colors that differed from the color names. For the latter list, participants are asked to name the color of the ink while trying to ignore the color name. Measures of total reading time and errors were recorded for each list, as well as two interference scores that are calculated by 1)

subtracting the reading time for the first list from the second list or 2) dividing the second list reading time by the first list. The latter interference score is designed to demonstrate interference while controlling for baseline differences in reading fluency and/or processing speed. Test-retest reliability coefficients in healthy adults at 11 months for reading time on both lists are r = .84 (Dikmen et al., 1999).

The Wisconsin Card Sorting Test (WCST) (Heaton, Chelune, Talley, Kay, & Curtiss, 1993) was administered as a measure of learning and cognitive flexibility ("set-shifting"). This test yielded a measure of total number of categories completed as well as perseverative responses. Test-retest reliability coefficients in healthy older adults at 1.1 years are r = .65 and .66 for categories completed and perseverative responses, respectively (Paolo, Axelrod, & Troster, 1996). Finally, the short-form alternative of the Judgment of Line Orientation Test (JLO) (Benton, Hamsher, Varney, & Spreen, 1983; J. L. Woodard et al., 1996) was administered as a motor-free measure of visuospatial perception. Scores from the JLO have split-half reliability of .91 (Benton et al., 1983), and the two short forms correlate with each other at r = .76 (J. L. Woodard et al., 1996).

Experimental Procedure

Three 5-word, three 10-word, and three 30-word lists of bisyllabic nouns matched on imagery and recallability (Christian, Bickley, Tarka, & Clayton, 1978) were constructed for a total of nine lists. The 5- and 10-word lists were used for the low-load and high-load rehearsal conditions, respectively. The 30-word lists were used during the reading control condition, which was designed to control for basic cognitive processes common to the rehearsal tasks (visual input, verbal output, linguistic processing of words, etc.) without placing any demands on working memory.

In each condition, words were presented individually on a computer cathode-ray tube screen positioned one meter above the participants in the PET scanner. The words were written in 2.5-in. tall capital letters using a sans serif font in white letters against a black background. Words were presented at a fixed rate of four seconds per word for a total of 120 seconds. Thus, a total of 30 words were presented for each of nine sessions. For the 5- and 10-word lists, participants were instructed to verbally rehearse each word presented, as well as all other words that had been presented for the current list, thereby requiring continuous rehearsal of as many list words as possible throughout the session. For the 30-word reading condition, participants were instructed to read only the presented word aloud repeatedly until the next word was presented.

Ten seconds after starting the task, participants received an intravenous injection of a 45 mCi bolus of $H_2{}^{15}O$, and scanner acquisition commenced ten seconds later. The scan acquisition lasted 90 seconds, and the task continued for ten seconds after the conclusion of scanner acquisition. We collected a total of nine PET scans for each participant. The nine lists were presented in three blocks, with each block consisting of a 5-word list, 10-word list, and a reading list. The same sequence was followed for all participants. We made audio recordings of the verbal output for each participant to facilitate an in-depth analysis of rehearsal rate and the number of unique words rehearsed during each four-second interval.

Immediately following each rehearsal or reading trial, participants were verbally presented with four arithmetic distractor problems designed to clear the short-term memory store and prevent further rehearsal. Most participants took 20-30 seconds to complete these problems. Participants were then asked to spontaneously recall as many words from the just-performed list as possible. After the participants recalled as many words as they could remember, they were administered a verbal recognition task during rehearsal conditions only. Each word from the just-

performed list was presented, randomly interspersed with an equivalent number of bisyllabic foils. Participants were instructed to indicate whether each word was on the previous list. The delayed recognition task was not presented for 30-word lists, due to our difficulty in finding a sufficient number of foils that were matched to the list items in terms of word frequency and recallability.

PET scan

After participants were positioned in the PET scanner, a custom face mask (Tru Scan, Annapolis, MD) was used to limit head movement. A modified autoradiographic method (Herscovitch, Markham, & Raichle, 1983; Raichle, Martin, Herscovitch, Mintun, & Markham, 1983) was used to acquire images of regional cerebral blood flow (rCBF). As described above, a bolus of 45 mCi $H_2{}^{15}O$ was injected intravenously during the behavioral task, and scanning began 10 seconds later. Each of the nine scans for every participant was reconstructed using calculated attenuation correction, with the boundaries derived from each emission scan sonogram. A separate transmission scan was acquired for the head holder to correct for attenuation of the rCBF signal. The final attenuation corrections for each image were derived by multiplying the brain and head-holder maps together. Calculated attenuation correction prevented an extra transmission scan for each participant and minimized head movement artifacts. rCBF was estimated through images of radioactive counts (Fox, Mintun, Raichle, & Herscovitch, 1984; Mazziotta et al., 1985).

PET scans were acquired with a Siemens 951 (14 controls, 14 patients) or 921 (two controls, one patient) tomograph in two-dimensional mode. Thirty-one (Siemens 951) or 47 (Siemens 921) contiguous 3.375-mm plane slices were collected for each participant. Following acquisition, image-smoothing was conducted with a multi-step process. Images were

reconstructed with a ramp filter cutoff at the Nyquist frequency, then filtered in three dimensions with a Hanning filter with a cutoff at 1 cycle/cm. The final resolution of the images was isotropic and 11.8 mm at full width half maximum (FWHM).

PET Analysis

Image processing and analysis was performed using the Statistical Parametric Mapping (SPM8; Wellcome Department of Cognitive Neurology, London, UK) package for MATLAB version R2009a (The MathWorks, Natick, MA). We preprocessed images with a three-step approach: 1) realignment of all images for each participant to reduce artifacts due to head movement between scans, 2) spatial normalisation into standard stereotaxic space, and 3) smoothing to suppress noise and effects due to residual differences in functional and gyral anatomy during group analysis.

For each participant, a mean resliced image of all nine scans was created. All scans were realigned to the mean image with a 2nd Degree B-Spline interpolation. Prior to the estimation of realignment parameters, each scan was smoothed with a Gaussian smoothing kernel with FWHM 7 mm. Following realignment, each scan was subjected to an affine and non-linear spatial normalisation to match the SPM8 PET brain template in Montreal Neurological Institute (MNI) standard space (Collins, Neelin, Peters, & Evans, 1994). Finally, all images were smoothed with a 10 mm by 10 mm by 12 mm Gaussian smoothing kernel in the X, Y, and Z directions, respectively. To account for differences between participants in total rCBF, all images were scaled proportionally to have the same global rCBF value of 50 ml/dl/min.

Available Variables

Behavioral data. Several indices of working and long-term episodic memory were available with our task. During both rehearsal and reading conditions, we calculated the rehearsal

rate as the average number of words spoken across each 4 sec intertrial interval. We also recorded the mean number of *unique* words rehearsed during each four-second interval for the rehearsal conditions only (for the reading condition, this value was constant at one). The mean number of unique words rehearsed is a more direct measure of working memory than rehearsal rate. For example, a lack of variation in the words rehearsed could reflect a difficulty maintaining multiple words in a rehearsal set, yet it may not be accurately reflected in the overall rehearsal rate if a participant chose to perseverate on a single word.

Free recall data were available for all three conditions. We also had recognition data for rehearsal conditions only. However, performance was at near-ceiling levels both rehearsal conditions in both the control and patient groups. Thus, the recognition variables may not provide any utility in data analyses.

Neuropsychological test data. The vast amount of neuropsychological testing afforded us variables in several domains for inclusion in our analyses. We compared structural and functional working memory correlates to neuropsychological measures of working memory, long-term episodic memory, learning, attention, visuospatial judgments, verbal fluency, and composites of intellectual abilities.

For working memory, available variables included the raw scores from the Arithmetic and Digit Span subtests of the WAIS-R. Episodic memory measures included several variables from the CVLT, including Trial 1, Trial 5, Trials 1-5, delayed recall (both free and cued), and recognition scores. Additional measures of episodic memory included the immediate and delayed recall from the Logical Memory, Visual Reproduction, and Verbal Paired Associates subtests of the WMS-R. For long-term semantic memory retrieval, measures included the BNT, COWAT, Category Fluency, and the Information and Picture Completion subtests of the WAIS-R.

Executive functioning measures included the number of categories completed and perseverative responses on the WCST. Attention measures included the interference scores from the Dodrill-Stroop Test. The JLO was available as a motor-free measure of visuospatial perception. Lastly, verbal fluency measures included the COWAT, Category Fluency, and the first part of the Stroop test, in which all color words are written in black ink. Lastly, we had estimates of global intellectual abilities from the Ward Short Form of the WAIS-R, including FSIQ, VIQ, and PIQ.

Unfortunately, we did not have measures of dementia severity available for every participant – the Mattis Dementia Rating Scale (DRS) (Mattis, 1988) was only administered to eight control participants and five patients, and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (Welsh, Butters, Hughes, Mohs, & Heyman, 1992), which contains the Mini-Mental State Examination (MMSE) (Folstein, Folstein, & McHugh, 1975) was administered to 10 controls and 6 patients.

PET estimation models. For within-group analyses, the effects were based on a multivariate model of condition, repetition, and participant. Condition referred to the 5-, 10-, or 30-word lists, each of which was repeated three times during the experiment. Repetition was included as a variable to account for differential practice effects on rCBF between participants and groups. Five planned comparisons for the effects of task condition were conducted for each group. The first comparison was intended to identify recruitment specific to low-load rehearsal, and included regions displaying greater rCBF during 5-word rehearsal compared to reading conditions. The second comparison was high-load (10-word rehearsal) compared to reading. The third comparison was a combination of the first two, creating a composite of the rehearsal conditions by combining 5- and 10- word conditions and comparing to the reading condition.

The final two comparisons were designed to determine whether low- and high-load rehearsal conditions differed with respect to rCBF, including both 5- compared to 10-word and 10-compared to 5-word conditions.

For each comparison, a t-test was conducted for every voxel and a t-map image was generated with a familywise error correction and a threshold of $p < .05$, resulting in a minimum contrast of $t(242) = 4.76$ to be included on the map. The minimum cluster size was set to 50 voxels. The t-map was superimposed on a reference MNI atlas, and regional clusters of rCBF were identified. Peak sites on the t-map for each cluster were localized. The coordinates for these peak sites were converted into Talairach space (Talairach & Tournoux, 1988) using the MATLAB command "icbm_other2tal.m" (Lancaster et al., 2007). These coordinates were then entered into Talairach Client v2.4.2 (Research Imaging Center, University of Texas Health Science Center San Antonio) to determine the specific structural location and Brodmann area (Brodmann, 1906).

Between-group comparisons. Each of the four planned comparisons described above were compared across groups to determine whether patients or control participants selectively recruited distinct regions to a significantly greater extent than the other group. SPM models were set up to test for the group by condition interactions, and the resulting t-maps displayed voxels demonstrating significant interaction effects. For each comparison, the model was run twice to show regions preferentially utilized in controls and patients, respectively, for each contrast. Due to the weaker power associated with between-group effects, a more liberal statistical threshold was applied to these tests ($t(153) = 3.14$, $p < .001$ uncorrected) with a minimum cluster size of 50 voxels. The same procedures described above for regional identification and localization was repeated.

Single-participant PET data. Individual region of interest (ROI) data was extracted for each participant using the Marseille Boîte À Région d'Intérêt (MarsBaR) toolbox for SPM (Brett, Anton, Valabregue, & Poline, 2002). This program is capable of defining structural ROIs and conducting analyses for predefined contrasts to determine the average t-statistic and contrast value, a measure of effect size. The purpose of these analyses was to determine if blood flow in any specific region was associated with working memory performance. Thus, bivariate correlation analyses were run between the contrast values for each ROI and both the rehearsal rate and the average number of unique words rehearsed per four-second interval. ROIs were taken directly from the clusters derived from the within-group SPM analyses. Specifically, we analyzed the 5-word compared to reading and 10-word compared to reading contrasts and determined whether blood flow in any region was associated with superior behavioral performance, and whether these patterns differed between groups.

Analyses

The goal of the current study is to investigate the functional correlates of working memory deficits associated with healthy older adults and AD patients. We have access to a unique database that allows for access to a wide range of variables to address these issues, and we conducted several analyses to address the three specific aims detailed in the hypothesis section.

Specific Aim 1 (neural correlates of verbal working memory in older adults) was investigated using clusters derived from the within-group SPMs for the control group. For the rehearsal versus reading contrasts, we hypothesized significant clusters will be present in DLPFC, supramarginal gyrus, supplementary motor area, hippocampus, and cerebellum, consistent with previous research. Furthermore, we anticipated significant clusters in DLPFC for

the 10-word condition relative to the 5-word condition, due to the additional demand on central executive resources.

Next, we correlated contrast values for each significant cluster (as determined through the ROI analyses with MarsBaR) with task performance (mean number of unique words rehearsed and delayed free recall) to determine whether recruitment in any specific region was associated with working memory or subsequent episodic memory performance. We hypothesized that activity in DLPFC, cerebellum, and hippocampus would be significantly correlated with both behavioral measures in both 5-word and 10-word conditions.

To investigate Specific Aim 2 (the effectiveness of task-activated PET in discriminating between groups), we analyzed both the within-group SPMs for the patient group and the between-groups SPMs. We expected that AD patients demonstrated activation in similar regions to controls but expressed a greater extent and magnitude of recruitment (J T Becker et al., 1996; J.L. Woodard et al., 1998). Specifically, bilateral recruitment was expected in AD patients in frontal regions compared to right-lateralized frontal activation in controls (J.L. Woodard et al., 1998). Greater recruitment was also expected in the cerebellum in the patient group. This additional (compensatory) recruitment was expected because persons with fewer cognitive resources typically have less efficient recruitment of neural resources and display greater demand-related recruitment (Stern, 2009). Furthermore, in the patient group we anticipated that DLPFC recruitment for the 10-word compared to 5-word comparison would be absent, due to the lack of spontaneous recruitment of central executive resources in AD patients (Collette et al., 1997).

Specific Aim 3 was designed to determine the effectiveness of task-activated rCBF as an index of neuropsychological abilities. Using the ROI values derived with MarsBaR, we

determined if the working memory variables from neuropsychological testing, including the Digit Span and Arithmetic scores from the WAIS-R, were significantly correlated with recruitment during rehearsal compared to reading subtractions. Given that regional recruitment during working memory tasks may assist in establishing a stronger trace for subsequent episodic recall (Davachi et al., 2001), we also hypothesized that ROI values would be significantly correlated with measures of episodic recall. These measures include CVLT Trials 1-5 and Delayed Recall and the Logical Memory I and II subtests from the WMS-R.

Results

Neuropsychological Performance

Performance for both groups on all neuropsychological measures is shown in Table 2. As expected, patients exhibited poorer average performance than control participants on all administered measures. Given the high level of education in our sample, the average FSIQ in the control group was well above the population average at 127.9. Thus, while the patient group's mean FSIQ (101.5) was in the Average range, it was still significantly lower than the control group. Given that the groups had equivalent levels of education, it is highly likely that the patient group experienced cognitive decline from a presumed previous level of functioning. In addition to general intellectual abilities, the patient groups also demonstrated impairment on several measures of episodic recall, visual-spatial processing, naming, and verbal fluency.

	Patients (n = 15)				Controls (n = 16)					
Measure	Mean	SD	Min	Max	Mean	SD	Min	Max	p	d'
WAIS-R										
FSIQ***	101.5	13.8	78	120	127.9	8.3	113	147	<.001	2.31
VIQ***	101.7	13.9	76	120	123.1	5.4	113	132	<.001	2.03
PIQ***	100.7	15.7	70	122	126.9	10.8	110	145	<.001	1.95
WMS-R										
Logical Memory I***	16.3	9.5	4	37	30.4	6.5	17	39	<.001	1.74
Logical Memory II***	9.1	10.3	0	34	25.8	7.3	13	35	<.001	1.86
Visual Reproductions I**	25.1	9.3	9	39	35.2	5.4	23	41	.001	1.32
Visual Reproductions II**	15.3	12.6	0	38	29.2	8.0	7	41	.001	1.32
Verbal Paired Associates I**	11.9	5.4	2	21	17.1	3.7	11	22	.005	1.11
Verbal Paired Associates II**	4.3	2.4	0	8	6.8	1.7	2	8	.004	1.16
CVLT										
Trials 1-5**	38.5	13.4	20	56	55.0	13.3	32	74	.002	1.23
Long Delay***	5.1	4.3	0	11	11.8	3.7	4	16	<.001	1.67
Recognition Hits*	13.9	1.8	11	16	15.3	1.0	12	16	.014	0.96
False Positives**	7.3	6.2	0	21	2.1	2.4	0	7	.008	1.09
Stroop										
Congruent Reading Time (s)**	47.7	6.4	39	59	39.9	8.1	27	57	.006	1.06
Incongruent Reading Time (s)**	198.0	71.9	113	325	127.9	38.7	80	239	.005	1.21
Interference (s)*	150.7	71.3	73	277	87.9	36.6	50	196	.010	1.11
WCST										
Categories Completed***	2.9	2.0	0	6	5.6	1.5	0	6	<.001	1.51
Perseverative Responses**	36.7	19.4	11	73	13.9	16.2	4	68	.001	1.27
*JOLO***	25.6	4.0	17	31	29.9	3.5	20	34	.003	1.16
*Boston Naming**	47.5	12.7	17	60	57.1	2.2	53	60	.011	1.05
*COWAT***	32.3	8.9	13	47	42.7	7.5	31	58	.002	1.27
*Category Fluency****	11.8	3.2	6.0	17.7	16.9	4.0	9.0	22.3	<.001	1.40

Table 2. Neuropsychological test performance of both groups. WAIS-R = Wechsler Adult Intelligence Scales, Revised, FSIQ = Full Scale Intelligence Quotient, VIQ = Verbal Intelligence Quotient, PIQ = Performance Intelligence Quotient, WMS-R = Wechsler Memory Scales, Revised, CVLT = California Verbal Learning Test, WCST = Wisconsin Card Sorting Test, JOLO = Judgment of Line Orientation, COWAT = Controlled Oral Word Association Test. *Note:* COWAT performance is summed across the letters C, F, and L and Category Fluency is averaged across the categories of animals, fruits, and vegetables. *p < .05, **p < .01, ***p < .001

Behavioral Performance

Rehearsal Performance. The two main working memory variables of task performance were the total number of words rehearsed and the average number of unique words rehearsed during each four-second rehearsal interval. Data for both groups are presented in Table 3 and were compared with independent-samples t-tests (separate variances assumed). The total number of words rehearsed did not significantly differ between groups for all three rehearsal conditions, suggesting that articulatory loop mechanisms in this patient sample were intact compared to the control group. However, the mean number of unique words rehearsed was significantly lower in the patient group for both 5-word and 10-word conditions. This finding suggests that while articulatory rehearsal may have been intact in the patient group, the ability to simultaneously track and remember multiple items was deficient. The patient group may have included more repeated words during each four-second interval. Thus, verbal working memory abilities appeared to be impaired in the patient sample.

Recall and Recognition Performance. Following each scan, participants completed a series of four simple arithmetic problems and were then asked to recall as many words as they could from the previous list. AD patients recalled significantly fewer words than control participants for both 5-word and 10-word conditions (see Table 3), suggesting that the AD group rapidly forgot the information at a greater rate. An alternative but not mutually exclusive explanation is that the encoding of the word lists was weaker in the patient group (as demonstrated by the lower unique words rehearsed), resulting in the impaired performance. Further support for this latter explanation is demonstrated by the lack of a significant difference between groups on free recall of words from the reading condition, which did not include a working memory component.

A recognition task was also presented after the 5-word and 10-word rehearsal trials, where each word was presented with an equivalent number of foils and participants were instructed to indicate whether each word was on the previous list. Non-significant trends ($p < .10$) towards worse recognition in the patient group were observed in both conditions. This finding may imply that recognition performance was relatively spared in the patient group, compared to their free recall abilities. However, patients did display a significantly higher number of false positive recognitions of foils in the 10-word condition, and a non-significant trend ($p = .07$) towards more false positives in the 5-word condition. Thus, the patients appeared to have more difficulty than the control group in accurately identifying words from the previous list. Overall, the behavioral results indicate impairments in verbal working memory and both free and cued episodic recall abilities in the patient group.

	Patients (n = 15)				Controls (n = 16)					
Task Performance	Mean	SD	Min	Max	Mean	SD	Min	Max	p	d'
Average Words Rehearsed										
5 Word	4.94	1.34	2.90	7.14	5.52	1.38	3.28	7.30	.247	0.42
10 Word	4.60	1.38	2.92	7.86	4.62	1.10	3.02	6.46	.977	0.01
Reading	5.57	1.63	2.86	8.68	4.75	1.52	3.34	9.57	.159	0.52
Average Unique Words Rehearsed										
5 Word*	3.23	0.63	2.32	4.18	3.84	0.63	2.83	4.64	.012	0.97
10 Word*	2.98	0.69	2.04	4.19	3.57	0.71	2.40	5.21	.027	0.84
Delayed Recall										
5 Word*	4.13	1.04	1.67	5.00	4.79	0.38	3.67	5.00	.034	0.84
10 Word*	4.93	1.59	2.33	8.00	6.54	1.28	3.33	8.33	.005	1.11
Reading	2.49	2.04	0.00	6.67	3.21	1.46	1.00	5.67	.272	0.41
Recognition: Correct Hits										
5 Word	4.80	0.33	4.00	5.00	4.96	0.11	4.67	5.00	.094	0.65
10 Word	8.49	1.83	4.33	10.00	9.46	0.75	7.67	10.00	.073	0.69
Recognition: False Positives										
5 Word	0.62	1.13	0.00	3.33	0.04	0.17	0.00	0.67	.067	0.72
10 Word*	1.40	1.69	0.00	5.33	0.35	0.82	0.00	3.33	.042	0.79

Table 3. Behavioral performance of the word rehearsal task during $H_2{}^{15}O$ PET. Average number of Words and Unique Words rehearsed refers to the average number rehearsed per word presentation (four-second interval). *$p < .05$

PET Results

Within-groups analyses: Rehearsal compared to reading. In the two rehearsal conditions, participants were required to actively hold a list of words in their working memory store while actively articulating. In the reading condition, participants actively articulated but with no demands on working memory. Thus, subtractions of regional cerebral blood flow between the rehearsal and reading conditions were conducted to identify regions which may correspond to verbal working memory abilities while controlling for visual input and active vocalization. These analyses were conducted separately for each group, and regional foci of significant clusters ($p <$

.05 with family-wise error correction and minimum cluster size of 50 voxels) are displayed for 5-word relative to reading and 10-word relative to reading in Tables 4 and 5, respectively.

Overall, the control group displayed a greater number of significant activation foci for both rehearsal conditions. For the 5-word compared to reading, the strongest activation focus in the control group was in the right superior parietal lobe. Significant activation foci were also observed in right middle temporal gyrus and bilaterally in the cerebellum and supramarginal gyrus. Importantly, several foci were observed bilaterally in the frontal lobes, including in Frontopolar cortex (FPC), supplementary motor area (SMA), and other regions in the middle frontal gyrus. DLPFC activation was observed in the left hemisphere.

In contrast, during 5-word compared to reading the patient group displayed right lateralized activation in the frontal lobes, with the strongest focus in the right middle frontal gyrus. Bilateral activation was observed in SMA. Other activation foci included left cerebellum and precuneus. No significant clusters were observed in other regions detected in the control group, including supramarginal gyri or FPC.

Region	Talairach Coordinates X	Y	Z	k	t_{max}	z-score
Regions of Activation for Controls						
Right Superior Parietal Lobule (Area 7)	40	-71	44	1262	7.75	7.32
Right Supramarginal Gyrus (Area 40)	53	-52	44	*	5.39	5.23
Left Medial Cerebellum	-1	-72	-36	4903	7.47	7.08
Left Lateral Cerebellum	-40	-51	-35	*	7.17	6.82
Right Lateral Cerebellum	38	-59	-35	*	6.83	6.53
Right FPC (Area 10)	31	51	10	840	7.35	6.98
Right SMA (Area 6)	36	11	52	1337	7.24	6.88
Right Middle Frontal Gyrus (Area 8)	38	26	37	*	6.25	6.01
Left Medial Precuneus (Area 7)	-2	-71	43	417	6.63	6.35
Left DLPFC (Area 9)	-42	21	30	338	6.57	6.3
Left FPC (Area 10)	-42	47	11	240	6.2	5.97
Right Middle Temporal Gyrus (Area 21)	72	-26	-6	117	5.85	5.66
Left SMA (Area 6)	-31	-3	52	222	5.8	5.61
Left Supramarginal Gyrus (Area 40)	-35	-55	37	87	5.63	5.45
Left Medial SMA (Area 6)	-3	8	51	98	5.33	5.18
Right Pars Triangularis (Area 45)	42	19	8	52	5.19	5.05
Regions of Activation for AD Patients						
Right Middle Frontal Gyrus (Area 8)	38	28	39	785	7.18	6.83
Left SMA (Area 6)	-33	-1	48	221	6.16	5.93
Left Lateral Cerebellum	-46	-54	-39	334	6	5.79
Left Lateral Cerebellum	-50	-68	-40	*	5.11	4.97
Left Precuneus (Area 7)	-11	-67	47	85	5.65	5.47
Right Medial Cerebellum	1	-76	-38	60	5.52	5.35
Right SMA (Area 6)	25	0	56	83	5.38	5.22

Table 4. Significant ($p < .05$ with familywise error correction) foci of regional cerebral blood flow increases resulting from 5-word rehearsal minus reading subtraction. DLPFC = dorsolateral prefrontal cortex, FPC = frontopolar cortex, SMA = supplementary motor area. k = number of voxels in the cluster. *regional maxima is adjoined to above cluster.

During 10-word compared to reading, the most prominent foci in the control group were located bilaterally in both the cerebellum and DLPFC. Bilateral recruitment was also observed in the anterior frontal lobes, in FPC and orbital gyri. Left SMA activation was also observed. In the parietal lobes, activation was observed in left precuneus and right supramarginal gyrus and right superior parietal lobule. Bilateral activation was also observed in insular cortex.

Similar to 5-word relative to reading, the patient group displayed fewer activation foci and right lateralized activation in the frontal lobes during 10-word relative to reading. The strongest recruitment was observed in right middle frontal gyrus and FPC. Further foci were observed in right supramarginal gyrus, bilateral SMA, and left cerebellum.

Region	Talairach Coordinates X	Y	Z	k	t_{max}	z-score
Regions of Activation for Controls						
Right Medial Cerebellum	1	-72	-36	2000	7.85	7.4
Left Cerebellum	-36	-51	-35	1490	7.08	6.74
Left Cerebellum	-25	-65	-32	*	6.32	6.07
Left DLPFC (Area 9)	-40	23	29	412	6.71	6.42
Right DLPFC (Area 9)	40	28	35	1101	6.67	6.38
Right FPC (Area 10)	31	49	8	*	6.35	6.1
Right FPC (Area 10)	40	40	24	*	5.13	4.99
Left SMA (Area 6)	-29	-3	52	834	6.52	6.25
Left SMA (Area 6)	-46	-1	50	*	5.44	5.28
Right Cerebellum	38	-61	-33	551	6.52	6.25
Right Cerebellum	35	-60	-46	*	5.99	5.78
Left Precuneus (Area 7)	-7	-71	47	607	6.35	6.1
Left Medial SMA (Area 6)	-5	12	48	702	6.31	6.07
Left Medial SMA (Area 6)	-7	2	60	*	6.29	6.05
Left Insula (Area 13)	-38	16	3	134	6.04	5.83
Right Orbital Gyrus (Area 11)	20	35	-24	145	6.03	5.81
Right SMA (Area 6)	25	2	57	688	5.87	5.67
Right SMA (Area 6)	38	8	52	*	5.64	5.46
Right SMA (Area 6)	21	9	64	*	5.54	5.37
Left Orbital Gyrus (Area 11)	-29	38	-31	98	5.59	5.41
Right Sup. Parietal Lobule (Area 7)	38	-69	44	232	5.58	5.41
Right Supramarginal Gyrus (Area 40)	42	-60	41	*	5.12	4.98
Left FPC (Area 10)	-44	54	4	169	5.58	5.41
Right Insula (Area 13)	35	19	4	143	5.35	5.2
Regions of Activation for AD Patients						
Right Middle Frontal Gyrus (Area 8)	38	30	39	1576	8.36	7.81
Right FPC (Area 10)	35	48	22	*	6.48	6.21
Right FPC (Area 10)	38	50	-1	*	6.07	5.85
Left SMA (Area 6)	-31	-3	52	262	5.78	5.59
Left Lateral Cerebellum	-44	-56	-39	118	5.66	5.48
Right Supramarginal Gyrus (Area 40)	53	-51	54	95	5.59	5.42
Right SMA (Area 6)	25	4	53	105	5.42	5.26
Left Medial SMA (Area 6)	-5	6	49	70	5.32	5.16

Table 5. Significant ($p < .05$ with familywise error correction) foci of regional cerebral blood flow increases resulting from 10-word rehearsal minus reading subtraction. DLPFC = dorsolateral prefrontal cortex, FPC = frontopolar cortex, SMA = supplementary motor area. k = number of voxels in the cluster. *regional maxima is adjoined to above cluster.

One further analysis was conducted combining both rehearsal conditions and comparing to reading. This analysis was intended to further elucidate which regions may be implicated in working memory processes. The combination of the two rehearsal conditions afforded more statistical power than the previous analyses. Regional foci of significant clusters are displayed in Table 6. In the control group, clusters were observed bilaterally in cerebellum, FPC, DLPFC, SMA, and insula and also in left precuneus and right middle temporal gyrus and superior parietal lobule. The patient group displayed a right-lateralized pattern of recruitment in the frontal lobes, with foci in BA 8 and 10. Interestingly, a cluster emerged in left DLPFC, suggesting that the patient group did utilize both hemispheres despite the strong lateralization. Further clusters were observed in bilateral SMA, right supramarginal gyrus, left precuneus, and in left cerebellum.

Region	Talairach Coordinates X	Y	Z	k	t_{max}	Z-score
Regions of Activation for Controls						
Left Medial Cerebellum	-1	-72	-36	6330	8.43	Inf
Left Lateral Cerebellum	-38	-51	-35	*	7.92	7.46
Right Lateral Cerebellum	38	-59	-35	*	7.48	7.08
Right FPC (Area 10)	31	51	10	3184	7.62	7.21
Right Middle Frontal Gyrus (Area 8)	40	26	37	*	7.10	6.76
Right SMA (Area 6)	36	10	52	*	7.05	6.72
Right Superior Parietal Lobule (Area 7)	40	-71	44	1207	7.47	7.08
Left DLPFC (Area 9)	-40	23	29	587	7.37	6.99
Left Precuneus (Area 7)	-5	-71	45	621	7.04	6.71
Left SMA (Area 6)	-31	-3	52	867	6.89	6.58
Left SMA (Area 6)	-44	-1	47	*	5.50	5.34
Left SMA (Area 6)	-24	-1	72	*	5.10	4.97
Left Medial SMA (Area 6)	-5	10	48	693	6.41	6.16
Right Middle Frontal Gyrus (Area 8)	2	18	45	*	5.78	5.59
Left FPC (Area 10)	-44	49	11	410	6.38	6.13
Right Middle Temporal Gyrus (Area 21)	72	-26	-6	81	5.83	5.63
Right Insula	36	19	2	153	5.67	5.49
Left Insula (Area 13)	-37	18	5	58	5.43	5.27
Regions of Activation for AD Patients						
Right Middle Frontal Gyrus (Area 8)	38	30	39	1777	8.62	Inf
Right FPC (Area 10)	35	48	21	*	6.24	6.00
Right FPC (Area 10)	38	50	-1	*	6.24	6.00
Left SMA (Area 6)	-33	-3	50	454	6.53	6.26
Left Lateral Cerebellum	-46	-56	-39	415	6.44	6.18
Right SMA (Area 6)	25	2	55	227	5.93	5.73
Left Medial SMA (Area 6)	-5	6	51	136	5.67	5.49
Left DLPFC (Area 9)	-39	23	29	99	5.42	5.26
Right Supramarginal Gyrus (Area 40)	53	-53	52	78	5.42	5.26
Left Precuneus (Area 7)	-11	-67	49	56	5.33	5.17
Right Medial Cerebellum	10	-49	-20	66	5.32	5.17

Table 6. Significant ($p < .05$ with familywise error correction) foci of regional cerebral blood flow increases resulting from 10-word rehearsal minus reading subtraction. DLPFC = dorsolateral prefrontal cortex, FPC = frontopolar cortex, SMA = supplementary motor area. k = number of voxels in the cluster. *regional maxima is adjoined to above cluster.

Overall, the results of these analyses indicate distinct patterns of regional recruitment in each group. In the frontal lobes, the control group utilized both hemispheres, including DLPFC. In contrast, AD patients primarily utilized the right frontal lobe and the primary focus was anterior to DLPFC, in middle frontal gyrus (BA 8). The control group displayed prominent activation in bilateral cerebellum, whereas the patient group had weaker cerebellar activation that

was left lateralized. The control group also demonstrated recruitment in several additional regions, including precuneus, supramarginal gyrus, middle temporal lobe, and insular cortex. These regions were recruited to a weaker extent or not observed in the patient group. Figure 1 displays recruitment for both groups during both rehearsal versus reading contrasts. Figure 2 displays recruitment for the combination of the two rehearsal conditions relative to reading.

Within-groups analyses: Load demands. Two additional comparisons were conducted within each group to determine if regional recruitment systematically varied as a function of working memory demand. These analyses included subtractions of 10-word relative to 5-word and 5-word relative to 10-word conditions. The statistical threshold of a family-wise error correction at an alpha level of $p < .05$ proved to be too stringent for these analyses (no significant clusters were detected), so a more liberal threshold was utilized ($p < .001$, uncorrected, minimum cluster size 50 voxels). Thus, the following analyses should be interpreted with caution due to the elevated probability of Type 1 errors.

The 10-word compared to 5-word contrast (Table 7) was designed to identify regions which may assist in managing higher demands on working memory abilities. In the control group, six significant clusters were identified, in regions in bilateral frontal cortex, right hippocampus, and left caudate and insula. In the patient group, a cluster in left SMA was the only significant frontal focus. Interestingly, three clusters in the occipital lobe were also detected, in left posterior cingulate and bilateral lingual gyrus. These differing patterns suggest that individuals with early AD may recruit alternative regions in an attempt to manage high task demands.

Region	Talairach Coordinates X	Y	Z	k	t_{max}	z-score
Regions of Activation for Controls						
Left Caudate	-20	22	14	95	4.03	3.96
Left FPC (Area 11)	-36	48	-20	193	3.98	3.92
Right SMA (Area 6)	13	12	66	175	3.73	3.67
Right Hippocampus	27	-13	-13	71	3.69	3.63
Left Insula (Area 13)	-31	-3	23	86	3.56	3.51
Right Postcentral Gyrus (Area 3)	23	-34	57	60	3.46	3.42
Regions of Activation for AD Patients						
Left Medial SMA (Area 6)	-3	28	60	225	4.08	4.01
Right Medial Lingual Gyrus (Area 18)	2	-79	25	190	3.81	3.75
Left Posterior Cingulate (Area 23)	-3	-70	11	*	3.36	3.32
Left Lingual Gyrus (Area 18)	-24	-76	-8	51	3.61	3.56

Table 7. Significant ($p < .001$, uncorrected) foci of regional cerebral blood flow increases resulting from 10-word rehearsal minus 5-word rehearsal subtraction. FPC = frontopolar cortex, SMA = supplementary motor area. k = number of voxels in the cluster. *regional maxima is adjoined to above cluster.

The 5-word compared to 10-word contrast (Table 8) was designed to identify regions that may be utilized in low-demand situations and deactivated during high demands. Regions in bilateral temporal lobes were observed in both groups. Additional clusters were observed in middle frontal gyri in right (control) and left (patients) hemispheres. Lastly, a cluster was observed in left thalamus in the patient group.

Region	Talairach Coordinates X	Y	Z	k	t_{max}	z-score
Regions of Activation for Controls						
Right Superior Frontal Gyrus (Area 8)	-20	22	14	123	4.03	3.96
Left Middle Temporal Gyrus (Area 39)	-36	48	-20	146	3.98	3.92
Right Middle Temporal Gyrus (Area 39)	13	12	66	113	3.73	3.67
Right Middle Temporal Gyrus (Area 21)	23	-34	57	85	3.46	3.42
Regions of Activation for AD Patients						
Left Thalamus	-14	-11	3	170	4.64	4.54
Left Middle Frontal Gyrus (Area 8)	-48	19	39	140	4.51	4.41
Left Middle Temporal Gyrus (Area 37)	-59	-46	-6	208	4.44	4.35
Right Superior Temporal Gyrus (Area 22)	62	-56	14	177	4.03	3.96
Left Fusiform Gyrus (Area 20)	-57	-18	-22	151	3.88	3.81

Table 8. Significant ($p < .001$, uncorrected) foci of regional cerebral blood flow increases resulting from 5-word rehearsal minus 10-word rehearsal subtraction. k = number of voxels in the cluster.

Between-groups analyses. The within-groups analyses indicated that the two groups displayed differing patterns of task-related activation. However, these analyses are unable to determine in which regions specifically each group displayed significantly greater amounts of activation for each contrast. Thus, two task-by-group interaction analyses were conducted for each contrast. The resulting activation maps displayed clusters with significant interaction effects in one group compared to the other between two task conditions. For example, a 10-word rehearsal versus reading comparison for the control compared to the patient group included two types of clusters: 1) regions with greater recruitment for 10-word relative to reading in the control group and 2) regions with greater recruitment for *reading relative to 10-word subtraction in the patient group*. These analyses were intended to interpret contrast type 1 only. To address this concern, an inclusive mask for the clusters identified in the within-groups analyses above (with familywise error correction at $p < .05$ and minimum cluster size 50) was applied to each SPM in order to isolate cluster type 1 (greater activation for rehearsal relative to reading) and eliminate clusters for the opposing interaction effect (reading relative to rehearsal). These analyses have reduced power compared to the within-groups analyses. Thus, a liberal statistical threshold of $p < .001$ uncorrected and minimum cluster size 50 was utilized, and findings should be interpreted with caution due to the elevated probability of Type I error.

The within-groups analyses implied that the control group utilized a greater extent and magnitude of activation for reading relative rehearsal conditions than the patient group. Furthermore, the patient group demonstrated right lateralized recruitment in frontal cortex while the control group showed bilateral frontal recruitment. Between-groups analyses of the control group compared to the patient group (Table 9) substantiated these findings. For rehearsal relative to reading subtractions, the control group demonstrated greater recruitment in bilateral

cerebellum, right SMA, left FPC, and left insula. For 10-word compared to 5-word subtraction, the control group demonstrated greater recruitment in the left caudate.

	Talairach Coordinates					
Region	X	Y	Z	K	t_{max}	z-score
10-word rehearsal vs. reading						
Left Medial Cerebellum	-3	-53	-31	413	5.52	5.26
Left FPC (Area 10)	-44	52	4	156	5.18	4.97
Left Insula (Area 13)	-40	18	3	66	4.17	4.05
Right Cerebellum	14	-68	-39	143	4.06	3.95
Left Medial Cerebellum	-5	-75	-47	85	3.52	3.45
Right Medial Cerebellum	1	-72	-34	*	3.46	3.39
5-word rehearsal vs. reading						
Left Frontopolar Cortex (Area 10)	-42	47	12	207	4.53	4.38
Left Medial Cerebellum	-3	-52	-31	81	4.00	3.90
Right Cerebellum	16	-64	-37	76	3.77	3.68
Left Cerebellum	-22	-74	-35	65	3.56	3.48
Rehearsal conditions vs. reading						
Left Medial Cerebellum	-3	-52	-31	389	5.38	5.23
Left FPC (Area 10)	-42	50	5	358	4.91	4.79
Right Cerebellum	14	-66	-37	254	4.45	4.36
Right SMA (Area 6)	40	8	46	78	3.70	3.64
10-word vs. 5-word rehearsal						
Left Caudate	-20	24	13	53	3.91	3.81
5-word vs. 10-word rehearsal						
No Significant Clusters						

Table 9. Significant ($p < .001$, uncorrected) foci of regional cerebral blood flow demonstrating greater recruitment in the control group compared to the patient group. FPC = frontopolar cortex, SMA = supplementary motor area. k = number of voxels in the cluster. *regional maxima is adjoined to above cluster.

Analyses for the patient compared to the control group (Table 10) failed to identify any clusters with significantly greater recruitment in the patient group in the three rehearsal relative to reading contrasts. However, the patient group demonstrated some interesting recruitment effects related to load demands. For 10-word compared to 5-word conditions, two foci in left cuneus were identified. Clusters in left thalamus and middle frontal gyrus were observed for 5-word compared to 10-word rehearsal.

Region	Talairach Coordinates X	Y	Z	k	t_{max}	z-score
10-word rehearsal vs. reading						
No Significant Clusters						
5-word rehearsal vs. reading						
No Significant Clusters						
Rehearsal conditions vs. reading						
No Significant Clusters						
10-word vs. 5-word rehearsal						
Left Cuneus (Area 18)	-1	-73	23	148	3.82	3.73
Left Cuneus (Area 18)	-5	-70	13	*	3.72	3.63
5-word vs. 10-word rehearsal						
Left Thalamus	-14	-9	3	71	3.97	3.87
Left Middle Frontal Gyrus (Area 8)	-50	21	39	55	3.84	3.74

Table 10. Significant ($p < .001$, uncorrected) foci of regional cerebral blood flow demonstrating greater recruitment in the patient group compared to the control group. k = number of voxels in the cluster. *regional maxima is adjoined to above cluster.

Correction for behavioral performance. The comparison of regional recruitment within and between groups is confounded by the differences in behavioral performance across participants. Thus, the within- and between-groups analyses were repeated with the addition of the number of unique words rehearsed as a covariate. For each participant, the average number of unique words rehearsed across the three scans for both 5-word and 10-word conditions were entered in the SPM models as a covariate value. This procedure allowed for a re-interpretation of the reading versus rehearsal contrasts. Note that this design does not allow for a direct comparison of 5-word and 10-word conditions or a combination of rehearsal conditions.

The SPM maps were largely unchanged from the previous analyses following the addition of these covariates. Significant ($p < .05$ with familywise error correction, minimum cluster size 50 voxels) clusters of activation for the 5-word relative to reading comparison are displayed in Table 11. In the control group, two additional cerebellar foci were observed when compared to the previous analysis without the covariate. Additionally, the clusters in left supramarginal gyrus and right pars triangularis were not significant in this analysis. In the patient

group, activation foci were also highly similar to the previous analysis, with the exception that one focus in the right cerebellum was no longer significant with the addition of the covariate.

Between-groups analysis indicated four clusters in which significantly ($p < .001$, uncorrected) greater activation was observed in the control group for the 5-word versus reading contrast, and these foci were in approximately the same locations as the four clusters identified in the previous between-groups analysis. The locations of these foci are indicated on Table 11 with marks next to the corresponding cluster in the control group.

Region	Talairach Coordinates X	Y	Z	k	t_{max}	z-score
Regions of Activation for Controls						
Right Superior Parietal Lobule (Area 19)	40	-73	45	1075	7.90	7.22
Right Supramarginal Gyrus (Area 40)	53	-52	44	*	5.29	5.06
Left Medial Cerebellum[+]	-1	-72	-36	3548	7.58	6.97
Left Lateral Cerebellum	-40	-49	-37	*	6.72	6.28
Left Cerebellum	-22	-72	-38	*	6.64	6.21
Right FPC (Area 10)	29	51	12	664	6.89	6.42
Right SMA (Area 6)	36	11	52	1073	6.70	6.26
Right Middle Frontal Gyrus (Area 8)	38	26	37	*	6.03	5.7
Left DLPFC (Area 9)	-40	23	30	289	6.50	6.1
Right Lateral Cerebellum[+]	42	-51	-38	960	6.46	6.06
Right Lateral Cerebellum	36	-61	-35	*	6.42	6.03
Right Cerebellum	18	-63	-32	*	5.61	5.34
Left Precuneus (Area 7)	-3	-71	43	292	6.40	6.01
Left FPC (Area 10) [+]	-42	47	11	199	6.35	5.97
Right Middle Temporal Gyrus (Area 21)	72	-24	-8	115	5.98	5.65
Left SMA (Area 6)	-33	-3	-50	160	5.84	5.54
Left Medial SMA (Area 6)	-3	8	51	56	5.29	5.06
Regions of Activation for AD Patients						
Left SMA (Area 6)	-33	-1	48	266	6.89	6.42
Right Middle Frontal Gyrus (Area 8)	38	28	41	513	6.79	6.33
Left Lateral Cerebellum	-44	-54	-39	235	5.96	5.64
Left Lateral Cerebellum	-50	-66	-40	*	5.12	4.91
Right SMA (Area 6)	25	0	56	75	5.53	5.26
Left Precuneus (Area 7)	-11	-67	47	50	5.40	5.15

Table 11. Significant ($p < .05$ with familywise error correction) foci of regional cerebral blood flow increases resulting from 5-word rehearsal minus reading subtraction, with the inclusion of the average number of unique words rehearsed as a covariate in the model. DLPFC = dorsolateral prefrontal cortex, FPC = frontopolar cortex, SMA = supplementary motor area. k = number of voxels in the cluster. *regional maxima is adjoined to above cluster. [+]Between-groups comparison indicated a significant ($p < .001$, uncorrected) interaction effect between group and task in which greater recruitment for 5-word vs. reading was observed in the control group.

For 10-word compared to reading, significant clusters were observed in nearly identical regions to the previous analysis within the control group. In the patient group, regions were also unchanged with the exception of a lack of a cluster in medial SMA that was identified without the covariate. The strongest focus in the patient group was detected in right frontal cortex in a similar location to the previous analysis (4.1 mm away), but the exact location was in DLPFC (BA 9) rather than in middle frontal gyrus (BA 8), as was the case in the previous analysis.

Between-groups analyses revealed seven clusters in which the control group demonstrated greater recruitment than the patient group, in regions including the cerebellum, left insula, left FPC, and right SMA. Six of these regions were identical to the previous analysis, and the right SMA cluster was unique to this analysis.

Region	Talairach Coordinates X	Y	Z	k	t_{max}	z-score
Regions of Activation for Controls						
Right Medial Cerebellum[+]	1	-72	-34	3342	8.00	7.29
Left Lateral Cerebellum	-36	-51	-35	*	6.87	6.40
Left Lateral Cerebellum	-23	-64	-34	*	6.37	5.99
Left SMA (Area 6)	-30	-5	54	1805	6.93	6.44
Left Medial SMA (Area 6)	-7	4	60	*	6.72	6.28
Left Medial SMA (Area 6)	-7	10	48	*	6.64	6.21
Left DLPFC (Area 9)	-42	25	29	386	6.86	6.39
Right Lateral Cerebellum[+]	40	-59	-33	547	6.70	6.26
Right Lateral Cerebellum	37	-58	-46	*	6.16	5.81
Right DLPFC (Area 9)	40	28	35	1183	6.62	6.20
Right FPC (Area 10)	31	51	8	*	6.45	6.05
Right SMA (Area 6)[+]	25	2	57	851	6.26	5.89
Right SMA (Area 6)	32	6	50	*	6.25	5.89
Right SMA (Area 6)	21	9	64	*	5.79	5.50
Left Precuneus (Area 7)	-9	-73	48	416	6.24	5.88
Left Insula (Area 13)[+]	-38	16	5	123	6.15	5.80
Left FPC (Area 10)[+]	-44	52	4	198	6.00	5.67
Right Orbital Gyrus (Area 11)	20	35	-22	79	5.65	5.37
Right Insula (Area 13)	35	19	6	177	5.61	5.34
Right Superior Parietal Lobule (Area 7)	40	-71	44	110	5.39	5.14
Right Supramarginal Gyrus (Area 40)	42	-60	41	*	4.96	4.77
Regions of Activation for AD Patients						
Right DLPFC (Area 9)	36	32	36	1494	8.01	7.30
Right FPC (Area 10)	35	48	22	*	6.31	5.93
Right FPC (Area 10)	38	50	-1	*	6.01	5.68
Left SMA (Area 6)	-30	-5	54	275	6.02	5.69
Right SMA (Area 6)	25	4	53	137	5.79	5.49
Right Supramarinal Gyrus (Area 40)	53	-51	54	95	5.46	5.22
Left Lateral Cerebellum	-46	-58	-39	74	5.34	5.10

Table 12. Significant ($p < .05$ with familywise error correction) foci of regional cerebral blood flow increases resulting from 10-word rehearsal minus reading subtraction, with the inclusion of the average number of unique words rehearsed as a covariate in the model. DLPFC = dorsolateral prefrontal cortex, FPC = frontopolar cortex, SMA = supplementary motor area. k = number of voxels in the cluster. *regional maxima is adjoined to above cluster. [+]Between-groups comparison indicated a significant ($p < .001$, uncorrected) interaction effect between group and task in which greater recruitment for 10-word vs. reading was observed in the control group.

ROI Analyses

Correlations with task performance. Several ROI analyses were conducted to determine whether blood flow increases in any particular region were correlated with task behavioral performance. Specifically, these analyses were designed to correlate rehearsal versus reading clusters with the number of unique words rehearsed and delayed free recall. Furthermore, these analyses attempted to determine whether behavior-related recruitment may differ between control participants and early AD patients. ROIs were identified via significant clusters in an analysis including all participants SPMs for 5-word compared to reading and 10-word compared to reading contrasts. For each region, the statistical threshold was adjusted (between $t = 3.8$ and $t = 7.6$) in order to specify ROIs which were contained to a single region. Clusters ranged in size from 61 to 2176 voxels.

The MarsBaR toolbox was utilized to determine a contrast value (a measure of the average effect size across all voxels, in arbitrary units) for each ROI in every participant. ROI contrast values were unable to be obtained for one control participant and three patients. Thus, the following analyses may be underpowered, and results should be interpreted with caution due to the elevated probability of Type II error. Statistical significance was determined at $p < .05$ with 2-tailed significance testing for each correlation, with no corrections for multiple comparisons.

Data for 5-word compared to reading are displayed in Table 13. Thirteen ROIs were identified in regions in bilateral frontal, parietal, and cerebellar regions. Within each group, no significant correlations with the number of unique words rehearsed were observed. A non-significant ($p = .08$) inverse relationship was observed in the control group in left SMA. Interestingly, a non-significant positive relationship ($p = .06$) was observed in the patient group.

However, this latter relationship appears to have been primarily driven by a single extreme value (with that value removed, the relationship was non-significant at $p = .27$). In the analysis containing all participants, significant correlations with unique words rehearsed were observed in two cerebellar ROIs (Figure 4). Within each group in these regions, the relationships were positive and of similar magnitudes and may have lacked the statistical power to detect significance.

Region	Left DLPFC	Right Middle Frontal Gyrus	Left SMA	Medial SMA	Right SMA	Left FPC	Right FPC	Left Precuneus	Right Precuneus	Left Angular Gyrus	Left Cerebellum	Medial Cerebellum	Right Cerebellum
Controls	-.297	.032	-.467^{+}	-.226	.007	-.186	-.032	-.331	-.203	-.355	.308	.389	.077
Patients	-.162	.217	.560^{+}	-.374	.082	-.135	.269	.058	-.033	.442	.489	.246	-.131
All Subjects	-.173	.003	-.032	-.198	.114	-.207	.187	-.103	.010	.025	.439*	.435*	.173

Table 13. Correlations between regional recruitment for the 5-word minus reading subtraction and the average number of unique words rehearsed. DLPFC = dorsolateral prefrontal cortex, FPC = frontopolar cortex, SMA = supplementary motor area. $^{+}p < .10$, $*p < .05$.

Thirteen ROIs were also identified for 10-word compared to reading (Table 14). Within the control group, rCBF in ROIs in left and right SMA and left precuneus were all significantly inversely correlated with the number of unique words rehearsed. However, the right SMA finding was mainly the result of two extreme values (see Figure 5; after removing the two values the correlation was non-significant at $p = .13$). Left precuneus recruitment was also significantly correlated with delayed free recall in the control group. Significant relationships were not detected in these regions within the patient group. A non-significant relationship ($p = .07$) with unique words rehearsed was observed within the patient group in left cerebellum. No significant correlations with delayed recall were observed in the patient group. Across all participants, the correlation between unique words rehearsed and regional recruitment was significant in left cerebellum. Non-significant ($p < .08$) relationships were observed with delayed recall in ROIs in

left and medial cerebellum. Scatterplots demonstrating the relationships with behavioral performance between and within groups are shown in Figure 5.

Region	Left DLPFC	Right DLPFC	Left SMA	Medial SMA	Right SMA	Left FPC	Right FPC	Left Precuneus	Right SPL	Right Insula	Left Cerebellum	Medial Cerebellum	Right Cerebellum
Controls													
Unique Words	-.268	.059	-.565*	-.105	-.640*	.334	-.410	-.694**	-.323	.366	.418	.243	.169
Delayed Recall	-.424	.144	-.288	.258	-.227	.220	-.127	-.529*	-.131	.433	.159	.138	-.120
Patients													
Unique Words	-.055	-.093	-.004	.137	.199	-.325	.487	-.086	-.022	-.094	$.533^{+}$	-.139	.283
Delayed Recall	.100	.354	-.213	-.188	.178	-.036	$.569^{+}$	-.372	-.036	-.060	.435	.256	.146
All Subjects													
Unique Words	-.052	-.035	-.233	-.076	-.318	-.015	.053	-.313	-.181	.179	.502**	.258	.283
Delayed Recall	-.024	.125	-.123	.131	-.038	.119	.260	-.256	-.104	.195	$.348^{+}$	$.363^{+}$	.121

Table 14. Correlations between regional recruitment for the 10-word minus reading subtraction and behavioral performance across all participants. DLPFC = dorsolateral prefrontal cortex, FPC = frontopolar cortex, SMA = supplementary motor area, SPL = superior parietal lobule. $^{+}p < .10$, $*p < .05$, $**p < .01$.

Correlations with neuropsychological abilities. The following analyses are designed to validate the experimental task and regional blood flow as indices of neuropsychological abilities. The number of unique words rehearsed has been our primary index of working memory ability for the current study. Participants also completed two psychological measures of working abilities: the Digit Span and Arithmetic subtests of the WAIS-R. Across all participants, raw scores from these two subtests were strongly correlated with the number of unique words rehearsed, which supports this measure as an index of working memory abilities. Likewise, delayed recall of the 10-word lists was significantly correlated with several measures of episodic memory, including raw scores from the immediate and delayed WMS-R subtests and several indices from the CVLT, including Trial 1, Trials 1-5, and Delayed Recall. However, unique words rehearsed was also significantly correlated with several measures of episodic memory, and free recall was also correlated with measures of working memory (Table 15).

Given that there may be substantial shared variance between memory processes, these correlations between working and episodic memory were not unexpected. Thus, we also correlated unique words rehearsed and free recall with neuropsychological indices that have minimal memory requirements: the JLO and the WAIS-R Block Design and Picture Completion Subtests (Table 15). All correlations were $r \leq .50$ and appeared to be appreciably lower than the correlations between most of the memory variables (note that given the relatively small sample size we are underpowered to detect statistically significant differences between these correlations). Thus, the behavioral indices of unique words rehearsed and free recall appear to be validated as legitimate measures of working and episodic memory measures, respectively.

	Unique words rehearsed		**Free recall**
Neuropsychological Measure	5-word	10-word	10-word
Working Memory			
WAIS-R Digit Span	*.465*	*.542*	*.536*
WAIS-R Arithmetic	*.639*	*.673*	*.648*
Episodic Memory			
CVLT Trial 1	*.507*	.406	*.569*
CVLT Trials 1-5	*.575*	.434	*.641*
CVLT Short Delay	*.570*	.420	*.677*
CVLT Long Delay	*.608*	*.467*	*.703*
WMS-R Logical Memory I	*.682*	*.621*	*.839*
WMS-R Logical Memory II	*.610*	*.545*	*.740*
WMS-R Visual Reproductions I	*.595*	*.480*	*.801*
WMS-R Visual Reproductions II	*.569*	*.456*	*.773*
WMS-R Verbal Paired Associates I	*.529*	*.458*	*.587*
WMS-R Verbal Paired Associates II	*.574*	*.514*	*.576*
Other Abilities			
JLO	.346	.279	.354
WAIS-R Block Design	*.498*	.329	*-.467*
WAIS-R Picture Completion	.248	,162	,286

Table 15. Correlations between task performance measures and neuropsychological testing. WAIS-R = Wechsler Adult Intelligence Scale, Revised, CVLT = California Verbal Learning Test, WMS-R = Wechsler Memory Scales, Revised. Values in italics represent significant correlations at $p < .01$.

Further analyses were conducted to determine if rCBF during the verbal rehearsal task was related to cognitive abilities, using the ROIs created for the analyses in the previous section.

Given that the regions were active during a working memory task, the primary neuropsychological indices utilized in these analyses were Digit Span and Arithmetic. Given the relatively poor reliability of individual subtests, correlations with WAIS-R composite measures (namely FIQ, VIQ, and PIQ) were also analyzed. ROIs from 10-word compared to reading were utilized in this analysis (Table 16). The most striking finding from this analysis was the large correlations between recruitment in left DLPFC and FIQ, VIQ, and PIQ. Right FPC recruitment was correlated with FIQ and PIQ in the control group only (Figure 6).

Additionally, two regions that were significantly inversely correlated with the number of unique words rehearsed in the control group (left SMA and left precuneus) were also inversely correlated with Digit Span and/or Arithmetic in the control group only. Likewise, left cerebellum, which was positively correlated with unique words rehearsed across all participants, was also correlated with Arithmetic across all participants (Figure 7).

	Left DLPFC	Right DLPFC	Left SMA	Medial SMA	Right SMA	Left FPC	Right FPC	Left Precuneus	Right SPL	Right Insula	Left Cerebellum	Medial Cerebellum	Right Cerebellum
WAIS-R FIQ													
Controls	.519*	-.111	.142	.186	.243	-.267	.570*	.378	.491^{+}	.084	-.120	-.497^{+}	-.062
Patients	.533^{+}	-.003	-.097	.258	.347	-.242	.318	.084	-.248	.210	.054	.056	-.373
All	.537$^{\#}$	-.132	.174	.299	.211	-.016	.351^{+}	.346^{+}	-.071	.127	.228	.268	.185
WAIS-R VIQ													
Controls	.377	.025	.180	.033	.299	-.302	.208	.161	.275	-.237	.241	-.154	.164
Patients	.525^{+}	.129	-.325	.053	.194	-.050	.337	.017	-.156	.131	.000	.054	-.406
All	.488$^{\#}$	-.048	.073	.181	.178	.070	.273	.248	-.094	.043	.292	.339^{+}	.212
WAIS-R PIQ													
Controls	.400	-.251	.082	.284	.045	-.104	.567*	.456^{+}	.375	.291	-.344	-.476^{+}	-.166
Patients	.403	-.174	.285	.514^{+}	.534^{+}	-.459	.236	.187	-.324	.292	.126	.071	-.227
All	.479*	-.228	.280	.423*	.201	-.119	.347^{+}	.412*	-.111	.221	.142	.228	.150
Digit Span													
Controls	-.196	-.001	-.442	-.020	-.402	.238	-.275	-.569*	.144	.379	.212	.040	.001
Patients	.316	-.020	-.122	-.029	.230	-.475	.193	.109	-.223	.268	.027	.076	-.336
All	.145	-.069	-.167	.085	-.150	-.074	-.014	-.130	-.078	.315	.290	.283	.117
Arithmetic													
Controls	-.252	-.074	-.664$^{\#}$	-.133	-.372	-.140	-.310	-.542*	-.400	.007	.007	.209	.101
Patients	.495	-.138	-.135	.204	.189	-.391	.066	.034	-.267	.229	.229	-.055	-.362
All	.252	-.148	-.168	.159	-.072	-.137	-.026	-.036	-.306	.125	.389*	.349^{+}	.181

Table 16. Correlations between regional recruitment during 10-word minus reading subtraction and measures of general cognitive functioning and working memory. DLPFC = Dorsolateral prefrontal cortex, FPC = frontopolar cortex, SMA = supplementary motor area, SPL = superior parietal lobule, WAIS-R = Wechsler Adult Intelligence Scale, Revised, FIQ = Full Scale Intelligence Quotient, VIQ = Verbal Intelligence Quotient, PIQ = Performance Intelligence Quotient. $^{+}p < .10$, $*p < .05$, $^{\#}p < .01$.

Discussion

This study identified functional correlates of the verbal working memory system in cognitively intact older adults and demonstrated that this system is disrupted in mild AD. Further, we identified specific regions where recruitment was correlated with behavioral performance and neuropsychological indices of intellectual abilities.

Cognitively intact older adults exhibited an extensive bilateral network of recruitment during the contrast of rehearsal relative to reading conditions. Specifically, significant activation foci were observed in regions including bilateral frontal regions (DLPFC, FPC, and SMA), bilateral parietal regions (supramarginal gyrus and precuneus), and bilateral cerebellum. These regions are consistent with the predictions based on previous PET studies of verbal working memory. Interestingly, bilateral insular activation was also observed during 10-word rehearsal only.

The mild AD patient group recruited a similar network of regions, but to a lesser extent than the cognitively intact control group. Specifically, frontal activation appeared to be right-lateralized (with the exception of SMA, which was bilateral), cerebellar activity was left-lateralized, and recruitment in parietal regions appeared to be less prominent than in the control group. The strongest activation was in right middle frontal gyrus for both rehearsal conditions. No activation was observed in insular regions. This lesser activation in the patient group stands in contrast to several studies which suggest that Alzheimer's patients may display increased, or compensatory, recruitment compared to cognitively intact older adults (Backman et al., 1999; J.T. Becker et al., 1996; Grossman et al., 2003; J.L. Woodard et al., 1998). There are multiple interpretations of the differential patterns of recruitment between the two groups.

One possibility is that the patient group may have possessed functional deficits in several regions, including left frontal cortex and right cerebellum, resulting in the inability to recruit

these regions during task completion. However, when functional deficits are present in certain regions, it is typically observed that a *greater* number of regions are utilized to complete the task (Park & Reuter-Lorenz, 2009). Some insight regarding this situation may be gained from the compensation-related utilization of neural circuits hypothesis (CRUNCH) (Reuter-Lorenz & Cappell, 2008). Although this hypothesis was developed for the comparison of older and younger adults, it may have relevance regarding the current findings. According to CRUNCH, older adults typically display increased activation when task demands are manageable and behavioral performance is comparable to younger adults. However, when task demands are more difficult and lower behavioral performance is observed in the older group, brain recruitment becomes *hypo*-activated compared to younger adults. Put another way, brain activity typically increases to support task performance in all adults. However, older adults have a lower task demand threshold where they are adequately able to complete the task. At task difficulty levels beyond this threshold, no additional recruitment will be observed. In contrast, younger adults are able to perform at a higher level than the older adults and will continue to show increased brain recruitment (and superior behavioral performance) at higher task demands. Thus, for easier tasks where behavioral performance is equivalent between groups *hyper*-activation is observed, and for more difficult tasks where performance is lower in older adults *hypo*-activation occurs.

Because compensatory recruitment has been observed in Alzheimer's patients (Backman et al., 1999; J T Becker et al., 1996; J.L. Woodard et al., 1998), the CRUNCH theory can be applied to the current study. The patient group demonstrated significantly poorer behavioral performance, as indicated by the lower number of unique words rehearsed across both conditions. Thus, it is possible that the reduced activation in the patient group could be a product of the difficulty of the task. The word rehearsal task places demands on visual, phonological, and

articulatory fluency mechanisms, and these demands were sufficient to detect impaired performance in the patient group. Because the task was too difficult for the patient group to perform at a comparable level to controls, it could logically follow that decreased activation would be observed in this group.

Although this interpretation appears to be logical, other task-activated studies of AD patients are difficult to interpret within the CRUNCH model. One PET study (J T Becker et al., 1996) observed increased activation in AD patients compared to controls during both three-word repetition and eight-word free recall. The two groups had comparable behavioral performance during three-word repetition, but the patients performed significantly worse during eight-word free recall. If the CRUNCH hypothesis were to be applied to this population, reduced activity would be expected for the eight-word condition. However, in this study there were also several regions where lesser activation was observed in the AD group, including hippocampus and cerebellum.

In another PET study (Backman et al., 1999) where participants performed a task involving the cued retrieval of word stems, AD participants performed significantly poorer than controls at the experimental task. Increased recruitment in the AD group compared to controls (interpreted as compensatory by the authors) was observed in several regions including cerebellum and prefrontal cortex. This finding is inconsistent with CRUNCH because reduced activity would be expected with impaired behavioral performance. However, greater activation was also observed in the *control* group in left hippocampal and parietal regions. Overall, it appears that in AD, selective functional impairments are present, particularly in hippocampal and parietal areas. Other regions, particularly in the prefrontal cortex, may display increased recruitment to compensate for these functional deficiencies, resulting in patterns of hyper- and

hypoactivation relative to their cognitively intact peers. Thus, the CRUNCH model may not adequately encapsulate the results from all functional imaging studies of AD patients, although in the current study it appears to be relevant.

Perhaps most striking about the findings from the current work is the contrast with the pilot study which utilized an almost identical experimental design (J.L. Woodard et al., 1998). In the pilot study, increased activity was observed in AD patients, particularly in the frontal lobes. Further, bilateral prefrontal activity was observed in the AD group while right-lateralized prefrontal activity was observed in the control group. While no definitive explanation regarding the discrepancies between the two studies is available, there are a number of differences between the Woodard et al. (1998) pilot and the current analysis that may be related to the discrepant findings. First, the major methodological difference between the two studies is that task order (5-word, 10-word, and reading) was pseudo-randomized for each participant in the pilot study, and presented in a fixed order in the current study. Rehearsal rate and unique words rehearsed also did not differ significantly between groups in the pilot study. According to CRUNCH, compensatory recruitment in the patient group might be expected in this situation.

Additionally, the findings from this analysis are more statistically robust. The total sample size is 31 participants, compared to 12 in the pilot study. The statistical threshold for significant voxels of activation in the current study is $p < .05$ with family-wise error correction for multiple comparisons, corresponding to roughly $p < 1*10^{-5}$ uncorrected. In contrast, the pilot study utilized a threshold of $p < .005$ uncorrected. Thus, the pilot study allowed for a greater probability of Type I errors and the results from the current analysis are more reliable. Additional differences between the two studies may be partially attributable to the usage of different software for image analysis.

Prefrontal regions including DLPFC (BA 9), middle frontal gyrus (BA 8), and FPC (BA 10) were recruited in both groups to assist with working memory demands. Utilization of prefrontal resources is a common finding in working memory studies and appears to assist in managing task demands (Collette et al., 1999; D'Esposito et al., 1995; Grady et al., 2003), a responsibility of the central executive system. Moreover, in the control group, it appears that prefrontal resources may have been utilized to a greater extent for the 10-word compared to 5-word condition. As shown in Table 7, significantly greater recruitment was observed in Left FPC during 10-word rehearsal. Additionally, for 5-word rehearsal the strongest activation focus was in right superior parietal lobule, and for 10-word the strongest foci were located in cerebellar and prefrontal regions (see Tables 4 and 5). This shift from parietal to frontal regions is consistent with the working memory model which suggests that frontal regions may assist in managing high load demands (Collette et al., 1999; D'Esposito et al., 1995). Although prefrontal activity is associated with working memory, at the individual level specific patterns of recruitment do not appear to be related to working memory *abilities*. DLPFC and FPC recruitment were not correlated with unique words rehearsed for either group or task condition.

Additionally, the patterns of frontal recruitment indicated that both groups may have been primarily *retrieving* rather than encoding the word lists. It has been well-documented that the left prefrontal cortex is preferentially biased towards the encoding of new information into episodic memory, whereas right prefrontal cortex is more active during the retrieval of previously-encoded information (Habib, Nyberg, & Tulving, 2003; Nyberg, Cabeza, & Tulving, 1996; Tulving, Kapur, Craik, Moscovitch, & Houle, 1994). For both rehearsal compared to reading contrasts, exclusively right prefrontal activation was observed in the patient group. Further, while the control group did exhibit left prefrontal activity, the more prominent foci were

consistently in right prefrontal cortex (see Tables 4-6 and Figures 2 and 3). Given the nature of the task, the right lateralization is somewhat unexpected because the participants were learning (encoding) new lists of words for active storage and repetitive rehearsal. However, given that the PET scan did not commence until 20 seconds into the task (after five words had been displayed), it could logically follow that participants had already completed much of the encoding prior to scanner acquisition. As such, the active repetitive rehearsal performed during PET may have been primarily a retrieval process, although it appears that the control group was still actively encoding as well. Episodic encoding deficits are a hallmark feature of AD (Becker, 1988; Greene et al., 1996; Wilson et al., 1983), and this impairment may be reflected by the absence of left prefrontal activity and also by the inferior delayed recall performance of the word lists.

For all analyses, no recruitment was observed in Broca's area, which has been previously identified as a functional correlate of articulatory rehearsal. The lack of recruitment in this region may be due to the articulatory demands of the repetitive reading control task. It is logical that a comparison between two conditions that both require this demand should not display recruitment in Broca's area. If recruitment was observed it might have indicated that this region also assists in phonological loop demands above and beyond articulatory rehearsal.

SMA (BA 6) recruitment was also observed bilaterally across both groups and rehearsal conditions. The SMA has been implicated with motor control, planning, and the execution of complex movements (Penfield & Welch, 1951; Roland, Larsen, Lassen, & Skinhoj, 1980). In relation to the current study, superior task performance could be associated with enhanced articulatory fluency. Specifically, rehearsing the list of words requires rapidly learning and articulating a set of bisyllabic words. In contrast, the reading condition requires repetition of only one word, and complex fluency and motor planning are not required.

Interestingly, in the control group *inverse* correlations were observed between regional recruitment in ROIs in left and right SMA and the number of unique words rehearsed (Figure 5). A similar inverse correlation was observed with Arithmetic, a WAIS-R working memory subtest (Figure 7). Given the role of motor fluency in the performance of this word rehearsal task, the inverse nature of the correlations may appear to be paradoxical. However, reduced activity may represent *more efficient* fluency, thus resulting in the higher number of unique words rehearsed. In the patient group, the relationship between SMA and rehearsal performance was absent, suggesting that perhaps the relationship between SMA and motor coordination may be disrupted in mild AD.

Likewise, the cerebellum has also been associated with motor planning, procedural memory, and the learning of complex movements (Albus, 1971; Marr, 1969). Thus, the cerebellar activation observed in both groups could reflect a process similar to the motor fluency contributions of the SMA. Neuroimaging studies have also implicated various regions of the cerebellum with higher-order cognitive processes such as word generation and explicit and implicit learning and memory (Desmond & Fiez, 1998). Furthermore, the cerebellum also appears to be a functional correlate of working memory and specifically the phonological loop, as demonstrated by selective cerebellar lesion studies (Ravizza et al., 2006; Stoodley & Schmahmann, 2009) and neuroimaging studies of verbal working memory (Schumacher et al., 1996). Phonological loop resources are involved with active rehearsal processes, either internally or out loud. Even though internal rehearsal does not require the use of motor mechanisms, it is possible that similar resources could account for the cerebellum's role in motor fluency and phonological rehearsal. Further, some cerebellar efferents project directly to prefrontal regions

including DLPFC (Thach, 1996), substantiating the cerebellum's role in the working memory system.

Significant correlations were observed between recruitment in left cerebellar ROIs and unique words rehearsed across all participants in the sample during both 5-word and 10-word conditions (Figures 4 and 5). Although these correlations were not significant within each group, similar relationships were present for both groups and the lack of statistical significance may be primarily a power issue. These findings suggest that not only is the cerebellum associated with working memory, but utilization of this region may reflect superior task performance. Furthermore, this relationship between the cerebellum and working memory appears to be intact in individuals with mild AD. Additionally, some efferents from the dentate nucleus of the cerebellum project to contralateral DLPFC (Middleton & Strick, 1994). Thus, the left-lateralized cerebellar activity may be related to the right-lateralized frontal activity observed in our sample.

The precuneus (BA 7) is a region that is somewhat "hidden" in the medial parietal lobe, and as such has historically garnered relatively little research attention due to the scarcity of selective lesion studies. However, functional neuroimaging has indicated that this region may play a role in several higher-order cognitive functions, including visuo-spatial imagery, episodic memory retrieval, and taking first-person perspectives (Cavanna & Trimble, 2006). Additionally, several neuroimaging studies have observed precuneus activation during working memory tasks (Collette et al., 1999; E. Salmon et al., 1996; Schumacher et al., 1996; J.L. Woodard et al., 1998). The precuneus also has afferent and efferent connections to SMA (Cavanna & Trimble, 2006). These connections may be partially responsible for the inverse correlation between the number of unique words rehearsed (10-word) and precuneus recruitment in the control group (see Table 14 and Figure 5). A similar finding was observed when correlating recruitment with

neuropsychological indices of working memory (Table 16 and Figure 7). This inverse relationship could indicate that less recruitment indicates more efficiency and enhanced task performance, analogous to the relationships observed in SMA. Interestingly, this functional association in the precuneus was only observed in the control group. The precuneus has been identified as a site of prominent atrophy in Alzheimer's patients (Buckner et al., 2005; Karas et al., 2007; Scahill, Schott, Stevens, Rossor, & Fox, 2002). It is possible that the functional abilities of this region were disrupted in the AD group due to atrophy, resulting in the lack of significant correlations with behavior performance. Further, impaired parietal functioning could account for the relative prominence of frontal (rather than parietal) recruitment in the AD group.

An unexpected finding from the current study was activation in the insula, observed bilaterally for the control group during the 10-word condition only. Although not typically associated with the working memory system, evidence does support the insula's role in working memory processes. One fMRI study (Soros et al., 2007) implicated the insula as a functional correlate of vibrotactile working memory. Further, a recent model of insular functioning (Menon & Uddin, 2010) suggested that a key role of this region is for the detection and processing of salient events, including deploying attentional resources and assisting with some central executive aspects of working memory. Thus, it could logically follow that the insula would be associated with verbal working memory, especially with high load demands.

The recruitment of DLPFC during working memory tasks has been identified as a neural strategy for monitoring increased task demands. The results of the current study also indicate that DLPFC recruitment may also be correlated with general intellectual abilities in late life. The control group utilized bilateral DLPFC resources, whereas the patient group displayed significant activation in right DLPFC only. Furthermore, across all participants and in the control group

alone, a significant correlation was observed between estimated WAIS-R FIQ and recruitment in Left DLPFC during the verbal working memory task. As such, activity in this region may potentially serve as a tool for the interpretation of late-life cognitive abilities.

There are several limitations to this study that should be carefully considered. First, while the sample size is relatively large for a neuroimaging study, the analyses may be underpowered. Although a conservative statistical threshold of a familywise error correction at $p < .05$ was sufficient to detect several clusters of significant rCBF, additional regions were likely implicated that did not meet this stringent threshold. In contrast, a liberal threshold of $p < .001$ uncorrected was applied to the analyses comparing the two word rehearsal conditions and the between-group interactions. While this lower threshold was necessary to detect significant clusters in either analysis, there is an elevated probability these foci were Type I Errors. However, the 50-voxel minimum cluster threshold was applied to counteract the probability of false positives. Although there was an elevated probability that individual voxels would display spurious activation, it would be unlikely for 50 voxels in the same region to display this type of recruitment.

The limitation of sample size is especially relevant for the ROI analyses. The analyses between regional recruitment and task performance were novel and exploratory. With limited sample sizes in each group, it is difficult to detect significant correlations. As shown in Tables 12-14 and Table 16, several correlation coefficients of greater than $|r| = .40$ failed to reach statistical significance. If correlations of these magnitudes were detected in a larger sample, they would most likely be statistically significant. However, correlational analyses in small groups are also susceptible to disproportionate influences by extreme individual values. Additionally, the high number of ROIs analyzed increased the probability of Type I errors.

The limited inference due to the small within-group sample sizes was the motivation behind conducting the ROI analyses with all participants. However, when combining two groups that systematically differ on two dimensions (in this situation, working memory performance and regional recruitment), an important issue must be considered. It can occur that within each group, no correlation may be present but across all participants a spurious correlation can exist due to the between-group differences (Shweder, 1973). Thus, in these analyses, correlations within each group were still displayed, and each group was separately marked on each scatterplot. In some regions (e.g., the cerebellum), similar relationships were observed in both groups, and in others (e.g., SMA and precuneus) the relationships appeared to differ between the groups.

In conclusion, this study demonstrated that the verbal working memory system in older adults includes a distributed neural network of frontal, parietal, cerebellar, and insular regions. As working memory load (task demand) increases, there may be a shift from parietal to frontal recruitment, demonstrating the involvement of the central executive component of the working memory system. Mild AD patients were not able to perform this task at a comparable level to cognitively intact age-matched peers. While the mild AD group recruited a similar neural network of regions while completing the task, they did so to a lesser extent to the control group. The CRUNCH model (Reuter-Lorenz & Cappell, 2008) posits that this lesser activity could be due to the patient's inability to tolerate the high demand load. Additionally, the relative prominence of frontal rather than parietal activation in the patient group suggests early parietal deficits in AD and may reflect a compensatory process. Activity in SMA and precuneus may be inversely related to working memory task performance, indicating that lesser activity in these regions may represent more efficient recruitment. However, these relationships appeared to be disrupted in the mild AD group, potentially due to atrophy and functional deficits in frontal and

parietal regions. Across all participants, left cerebellar activity was positively correlated with working memory performance. This finding further implicated the cerebellum with working memory abilities and indicated that cerebellar functioning may be relatively intact in early AD. Lastly, although DLPFC was not directly related to working memory task performance, recruitment in this region was related to general intellectual abilities.

APPENDIX

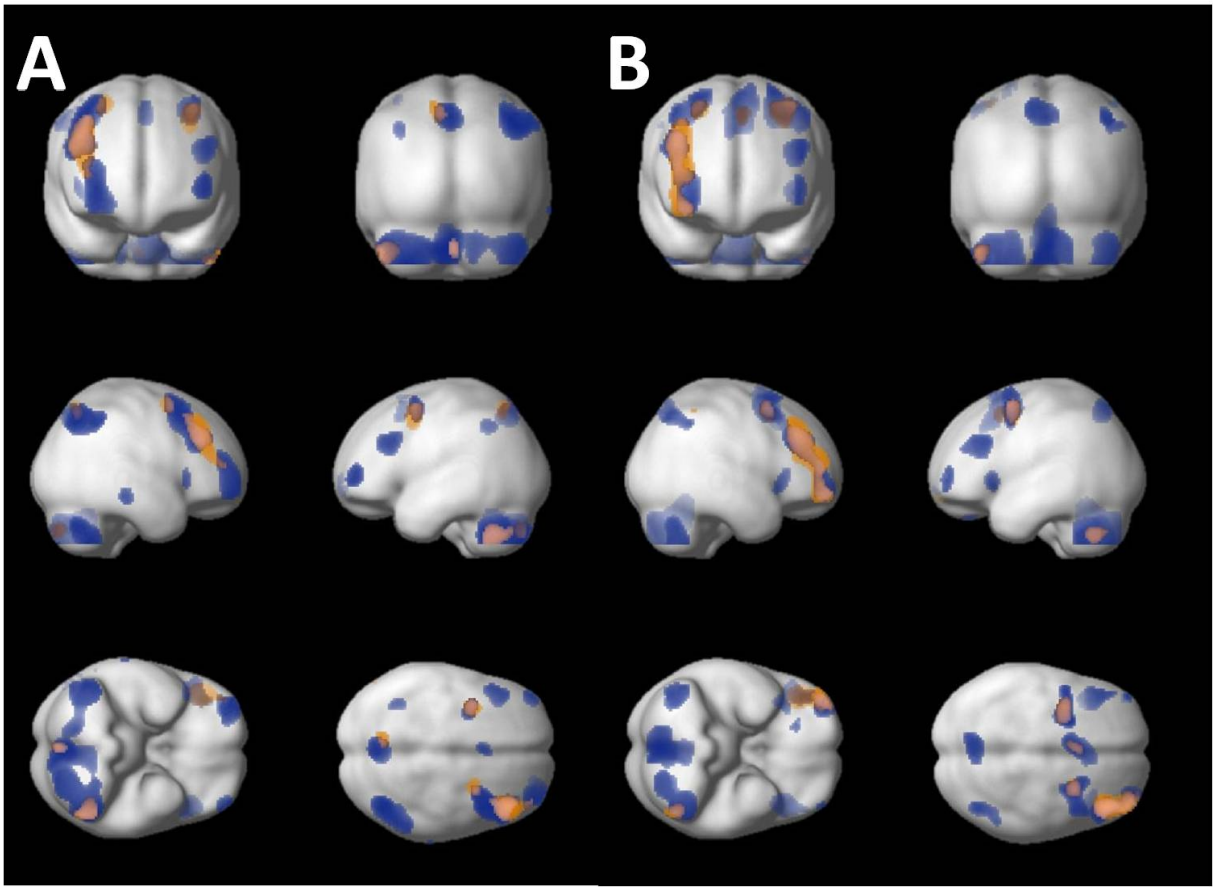

Figure 1. Significant clusters of regional recruitment for A) 5-word compared to reading subtraction and B) 10-word compared to reading. Regions in blue are for the control group, orange for the patient group.

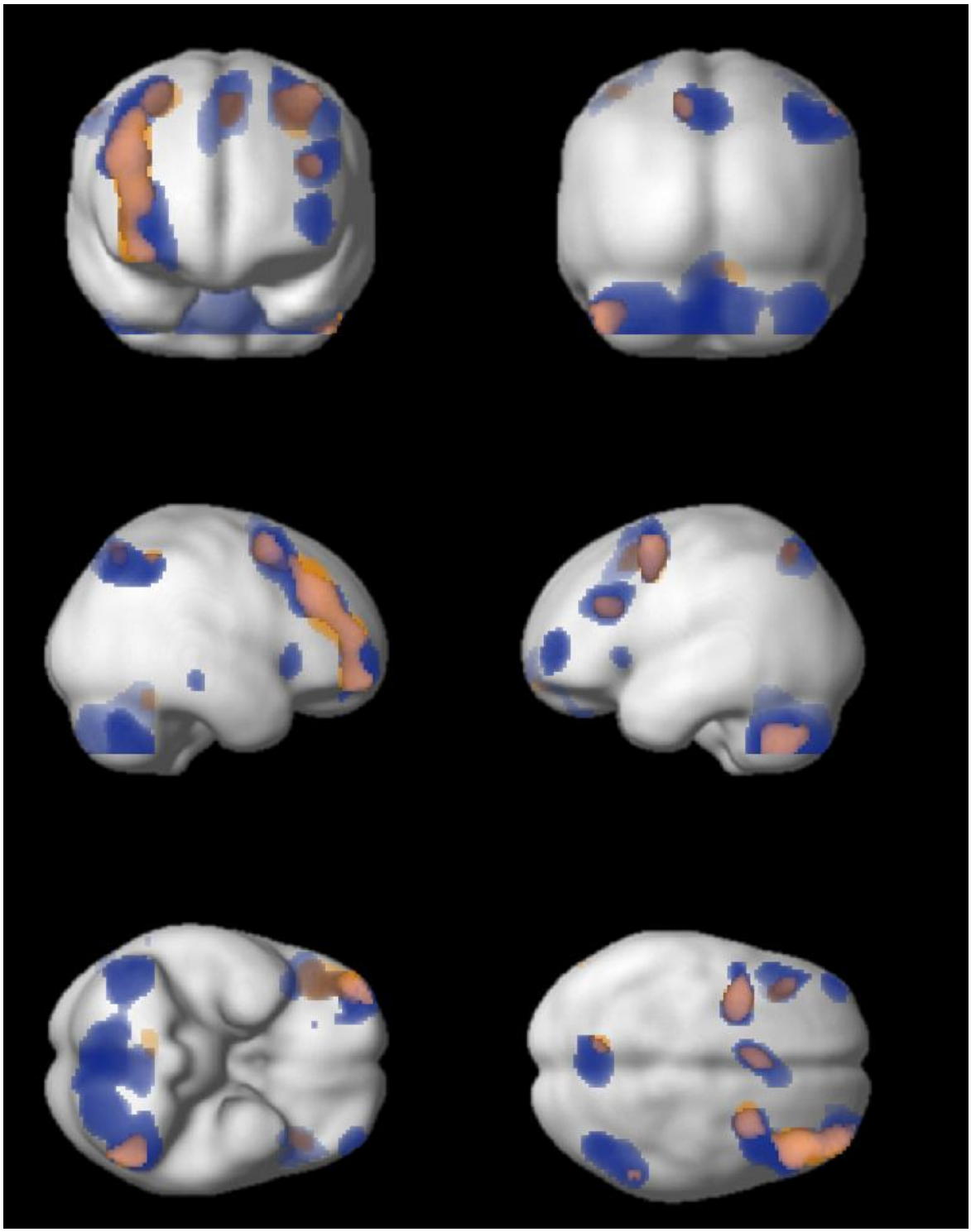

Figure 2. Significant clusters of regional recruitment for the combination of 5-word and 10-word rehearsal compared to reading. Regions in blue are for the control group, orange for the patient group.

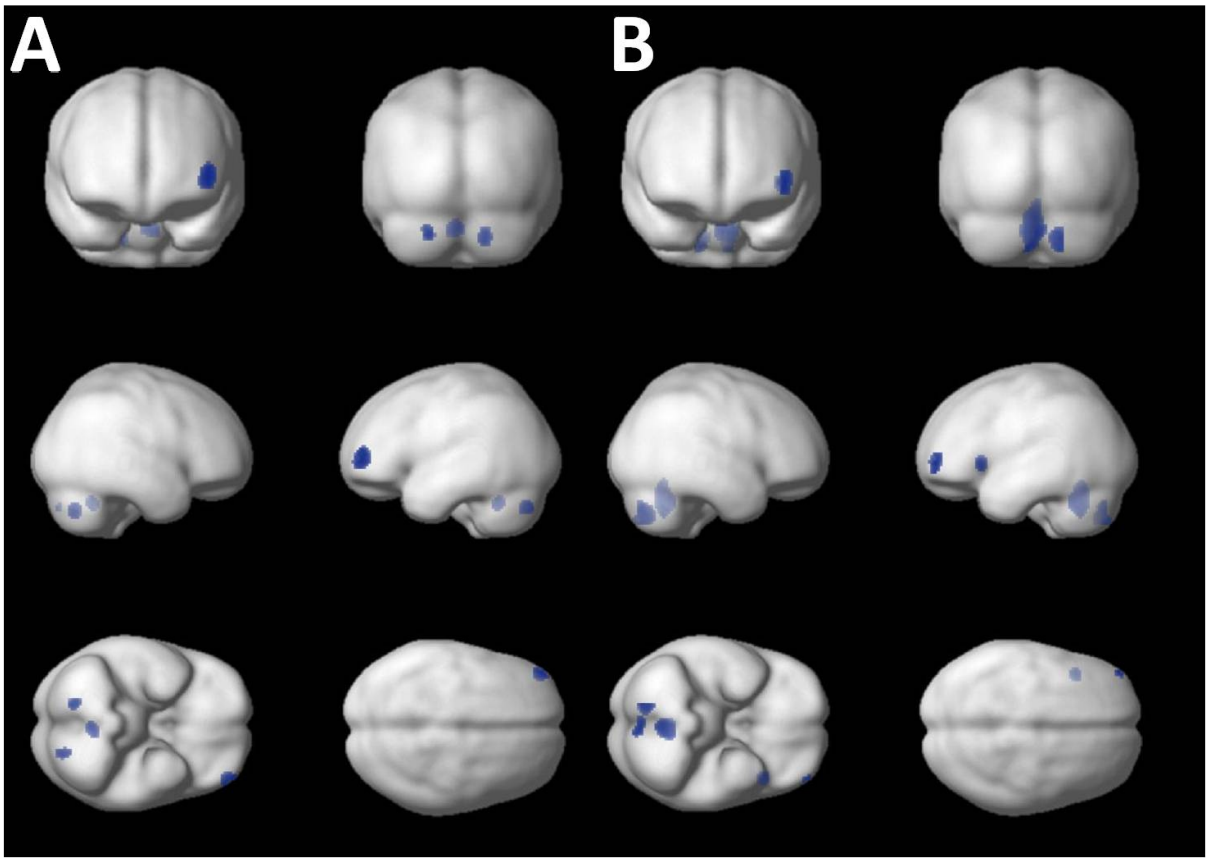

Figure 3. Regions demonstrating significantly ($p < .001$) greater recruitment in the control group compared to the patient group for A) 5-word versus reading and B) 10-word versus reading subtractions. Of note is the greater utilization of cerebellum and left FPC.

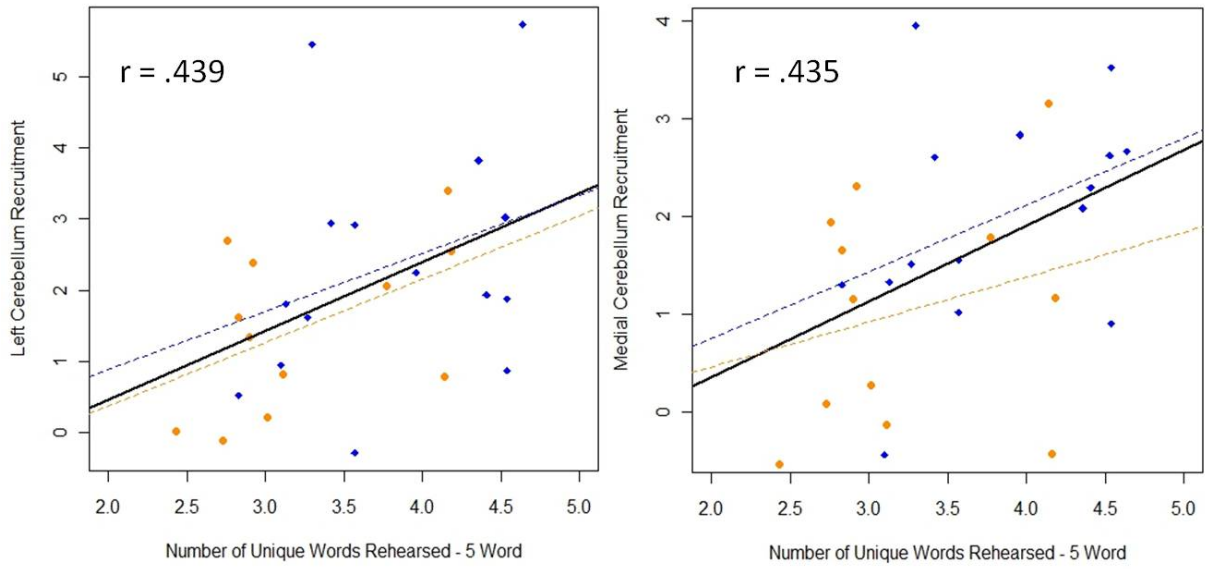

Figure 4. Correlations between regional recruitment for 5-word minus reading subtraction and behavioral performance in two cerebellar ROIs. Blue values and trend lines represent the control group, orange represents the patient group. The black trend line represents all participants combined. In both ROIs, the correlation was not statistically significant ($p < .05$) within each group but was for the combined sample. Coefficient values are for the combined sample. Recruitment values are in arbitrary units.

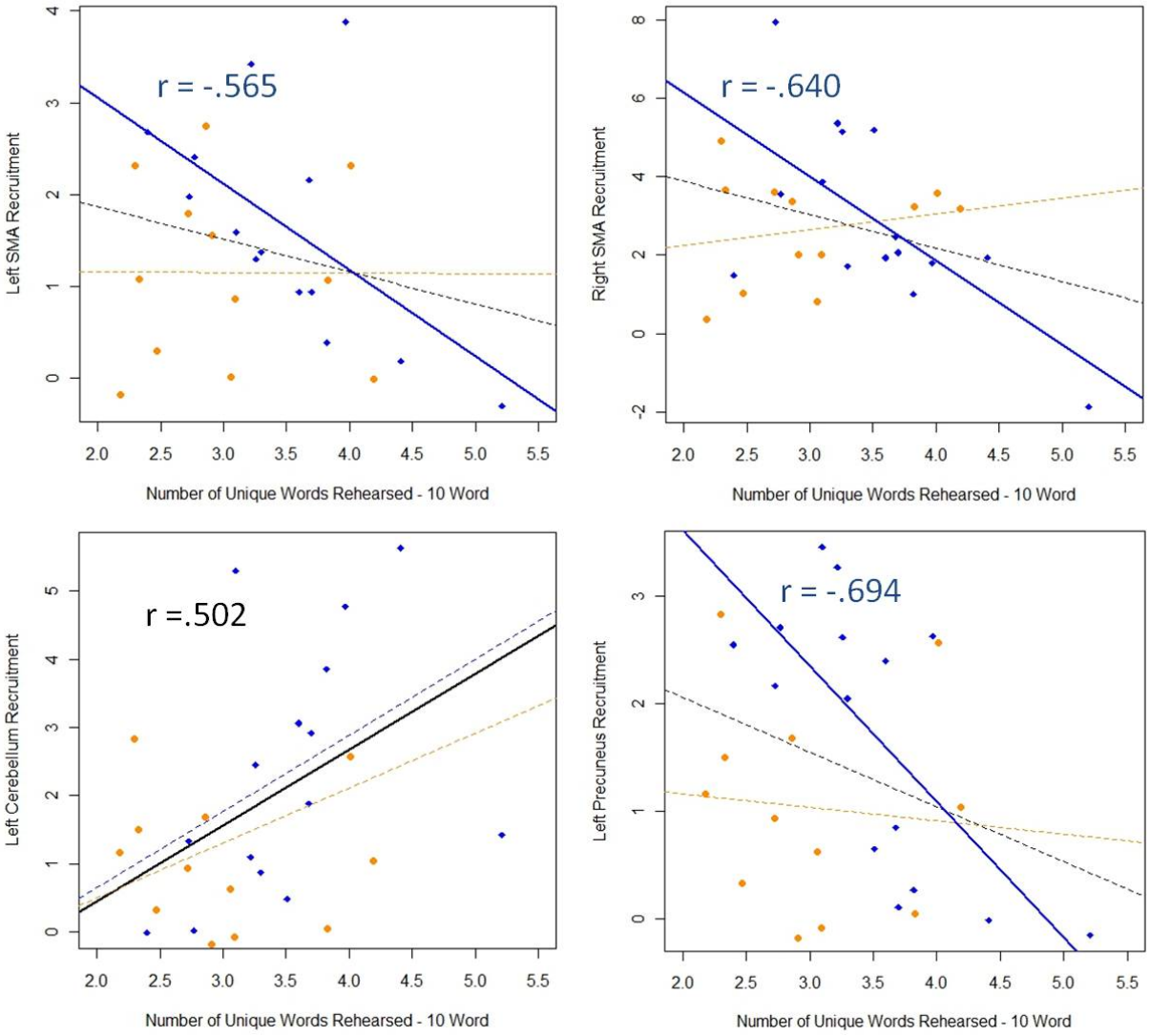

Figure 5. Correlations between regional recruitment for 10-word versus reading and behavioral performance in four ROIs. Blue values and trend lines represent the control group, orange represents the patient group. The black trend line represents all participants combined. Bold trend lines represent statistically significant correlations ($p < .05$), dotted lines are non-significant relationships. Coefficients are displayed for statistically significant correlations only. Recruitment values are in arbitrary units. SMA = supplementary motor area.

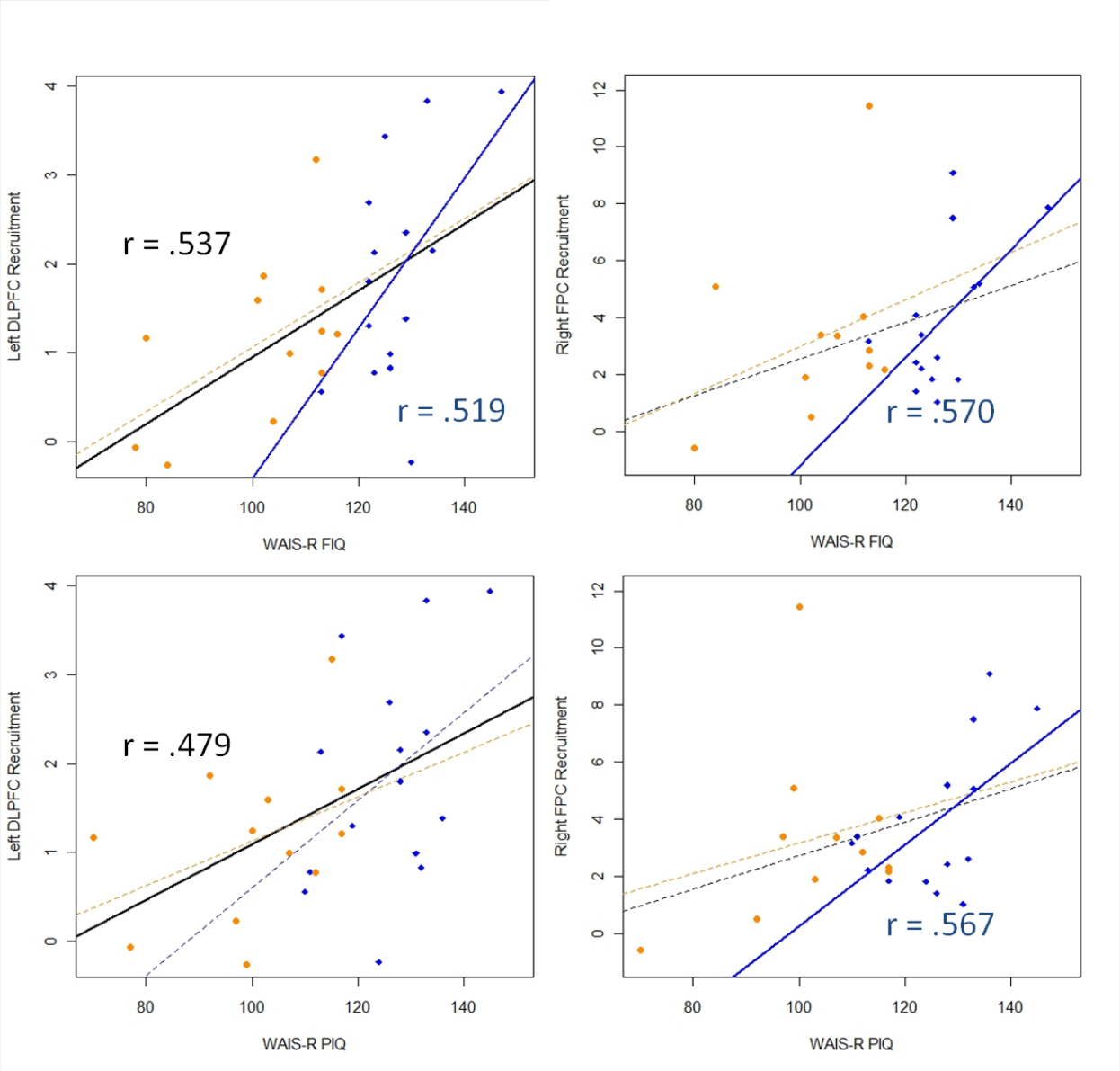

Figure 6. Correlations between regional recruitment for 10-word minus reading subtraction and measures of general intellectual abilities. Blue values and trend lines represent the control group, orange represents the patient group. The black trend line represents all participants combined. Bold trend lines represent statistically significant correlations, dotted lines are non-significant relationships. Coefficients are displayed for statistically significant correlations only. Recruitment values are in arbitrary units. DLPFC = dorsolateral prefrontal cortex. FPC = frontopolar cortex. WAIS-R = Wechsler Adult Intelligence Scales, Revised, FIQ = Full Scale Intelligence Quotient, PIQ = Performance Intelligence Quotient.

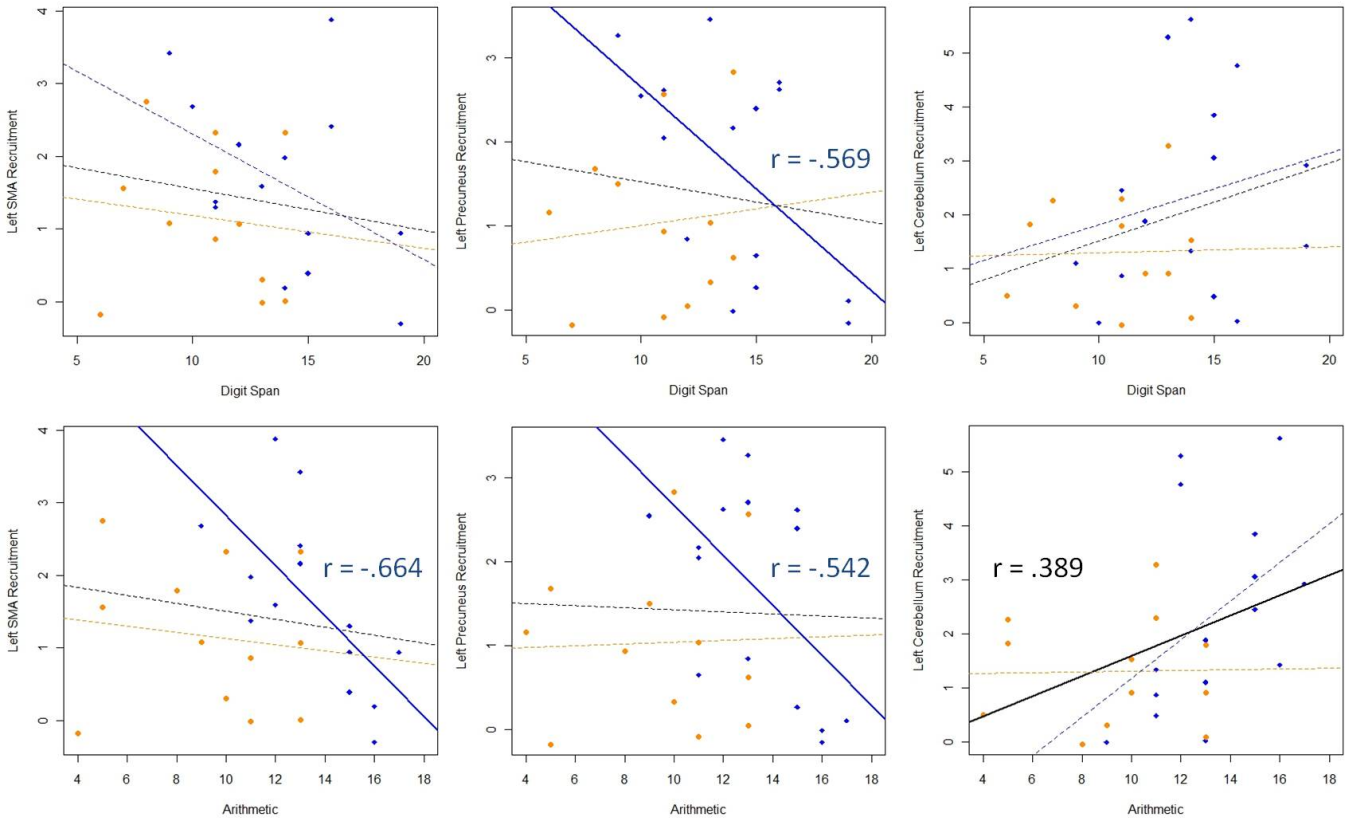

Figure 7. Correlations between regional recruitment for 10-word minus reading subtraction and measures of working memory. Blue values and trend lines represent the control group, orange represents the patient group. The black trend line represents all participants combined. Bold trend lines represent statistically significant correlations, dotted lines are non-significant relationships. Coefficients are displayed for statistically significant correlations only. Recruitment values are in arbitrary units. SMA = supplementary motor area.

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ABSTRACT

FUNCTIONAL CORRELATES OF VERBAL WORKING MEMORY IN HEALTHY AGING AND EARLY ALZHEIMER'S DISEASE

by

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Deficits in the working memory system are common in patients diagnosed with Alzheimer's disease (AD). However, little is known regarding the neurobiological basis of this impairment. The current study examined the neurobiological functional correlates of the working memory system in early AD patients and cognitively intact control participants using a word list repetition task performed during positron emission tomography (PET). Compared to a reading control task, both the AD and control groups utilized a network of parietal, frontal, and cerebellar regions while completing the word rehearsal task. However, control participants displayed greater activation in all regions, especially in the parietal lobes. In the frontal lobes, AD patients displayed right-lateralized recruitment compared to bilateral frontal recruitment in the control group. Comparison of 10-word list rehearsal to 5-word indicated a shift from parietal activity to more prominent frontal and cerebellar activity in the control group with increased load demands. This type of shift in activity was not observed in the patient group. Additionally, parietal activity was inversely correlated with working memory performance in the control group only. Left cerebellar activity was correlated with behavioral performance in both groups. Overall, it appears that the working memory deficits observed in AD patients may be related to dysfunction in

parietal contributions to the working memory network, and compensatory activity may occur in the frontal lobes.

AUTOBIOGRAPHICAL STATEMENT

Michael A. Sugarman graduated from the University of Rochester in May 2009 with a Bachelor's of Science in Brain and Cognitive Sciences with Highest Honors and Highest Distinction. His undergraduate research advisor was Daphne Bavelier, PhD. Mr. Sugarman entered the Doctorate Program in Psychology (Major: Clinical; Minor: Neuropsychology) at Wayne State University in August 2010 under the academic supervision of John L. Woodard, PhD.

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