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Depressive Symptoms, Brain Volumes and Subclinical Cerebrovascular Disease in Postmenopausal Women: The Women's Health Initiative MRI Study

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Abstract

Objective—Late-life depressive symptoms (DS) increase the risk of incident mild cognitive impairment and probable dementia in the elderly. Our objectives were to examine the relationship between elevated DS and regional brain volumes including frontal lobe subregions, hippocampus and amygdala, and to determine whether elevated DS were associated with increased subclinical cerebrovascular disease in postmenopausal women.

Methods—DS were assessed an average of 8 years prior to structural brain MRI in 1372 women. The 8-item Burnam regression algorithm was used to define DS with a cut-point of 0.009.

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Adjusting for potential confounders, mean differences in total brain, frontal lobe subregions, hippocampus and amygdala volumes and total ischemic lesion volumes in the basal ganglia and the cerebral white and gray matter outside the basal ganglia were compared between women with and without DS.

Results—Depressed women had lower baseline global cognition and were more likely to have prior hormone therapy history. After full adjustment, DS at baseline were associated with smaller superior and middle frontal gyral volumes. Hippocampal and amygdala volumes, and ischemic lesion volumes were similar in depressed and non-depressed women.

Limitations—Depression was not assessed based on semi-structured interview, and we were unable to determine the temporal relationships between DS and frontal lobe volume differences due to the availability of only one MRI scan.

Conclusions—Elevated DS were associated with lower volumes in certain frontal lobe subregions but not in the medial temporal lobe structures. Our findings support the role of frontal lobe structures in late-life DS among women.

Keywords

Late-life Depression; regional brain volumes; subclinical cerebrovascular disease; structural magnetic resonance imaging

INTRODUCTION

The societal impact of clinically significant depressive symptoms among the geriatric population is enormous. Syndromal and subthreshold depression is associated with poorer outcomes of co-morbid medical disorders and accelerated cognitive and functional decline (Alexopoulos, 2005; Steffens et al., 2006; Dotson et al., 2008; Lyness et al., 2009). Further, late-life depressive symptoms (DS) are also associated with subsequent cognitive impairment, including increased incidence of mild cognitive impairment (MCI) and probable dementia (Devanand et al., 1996; Chen et al., 1999; Barnes et al., 2006). However, the neurobiological mechanisms of these relationships are not well understood despite evidence that as many as 43% of individuals with late-life depression and mild cognitive deficits at baseline will ultimately be diagnosed with dementia (Alexopoulos et al., 1993). Neurodegeneration and cerebrovascular disease are two plausible mechanisms that may explain the relationship between DS, cognitive decline, and incident cognitive impairment (Alexopoulos, 2005; Steffens et al., 2006).

Cross-sectional and longitudinal studies have shown volumetric declines in the frontal and temporal lobes in individuals with geriatric depression (Sheline et al., 1996; Kumar et al., 1998; Sheline et al., 1999; Steffens et al., 2000; Bell-McGinty et al., 2002; Steffens et al., 2002; Ballmaier et al., 2004; O'Brien et al., 2004; Taylor et al., 2007; Andreescu et al., 2008; Smith et al., 2009; Dotson et al., 2009, a). Specifically, volume reductions in the frontal lobe subregions including the orbitofrontal cortex (Ballmaier et al., 2004; Taylor et al., 2007; Andreescu et al., 2008), anterior cingulate cortex (Ballmaier et al., 2004), superior, middle and inferior frontal gyri (Ballmaier et al., 2004; Andreescu et al., 2008; Smith et al., 2009), are reported in late-life subsyndromal and syndromal depression, regardless of the age of onset. In addition, volumetric reductions in the temporal lobe structures such as hippocampus and amygdala (Sheline et al., 1996; Sheline et al., 1999; Steffens et al., 2000; Bell-McGinty et al., 2002; O'Brien et al., 2004; Andreescu et al., 2008) are reported mainly in geriatric major depression and not found in subclinical depressive syndromes. Late-onset depression (mostly defined as the first episode of depression after the age of 60), which may be a marker of incipient dementia, also is associated with smaller volumes in these frontal

and temporal lobe subregions (Kumar et al., 1998; Steffens et al., 2000; Andreescu et al., 2008). In addition, the depressed elderly with smaller hippocampal volumes are at increased risk of subsequent cognitive decline and incident dementia (Steffens et al., 2002; O'Brien et al., 2004). In the neuroimaging substudy of the Baltimore Longitudinal Study of Aging (BLSA), subthreshold DS were associated with orbitofrontal cortex and cingulate gyrus volume declines with advancing age, during a 9 year follow-up period (Dotson et al., 2009, a). In addition, the presence and the level of severity of white matter hyperintensities and subclinical strokes also have been associated with DS and late-life depression (Krishnan et al., 1997; Alexopoulos et al., 1997; Nebes et al., 2002; O'Brien et al., 2006). Some studies indicate that these white matter abnormalities are also associated with poorer cognitive outcomes and development of dementia (Kramer-Ginsberg et al., 1999; Steffens et al., 2007).

However, observations of reduced regional brain volumes (Pantel et al., 1997; Ashtari et al., 1999) and greater vascular lesion burden (Barnes et al., 2006) among individuals with late-life DS are not universal. Furthermore, there are no studies to our knowledge that have examined how late-life DS are related to *future* cerebrovascular lesion and regional brain volumes in postmenopausal women.

The Women's Health Initiative Memory Study (WHIMS), an ancillary study to the Women's Health Initiative Hormone Therapy (WHI-HT) trials, provides a unique opportunity to address the temporal relationship between elevated DS and both regional brain volumes and ischemic lesion burden (Resnick et al., 2009; Coker et al., 2009). In WHIMS, the presence of DS at baseline was independently associated with an increased incidence of mild cognitive impairment (MCI) and probable dementia in postmenopausal women 65 years of age and older (*unpublished observations; in review*).

The objective of the present study was to examine whether late-life higher DS were associated with increased cerebrovascular disease and smaller regional brain volumes among the WHIMS subjects who also participated in the WHIMS-MRI study. We hypothesized that postmenopausal women with elevated DS at WHIMS baseline will have smaller frontal and temporal lobe regional volumes and larger ischemic lesion volumes on brain MRI an average of eight years later, after controlling for potential confounding variables including sociodemographic characteristics, global cognitive function, cardiovascular disease and hormone therapy.

METHODS

WHIMS Study Design and Sample

WHIMS, an ancillary study to the WHI randomized clinical trials of hormone therapy, was designed to examine the effect of postmenopausal hormone therapy on risk for dementia and change in global cognitive function in generally healthy women who were 65 to 79 years of age and free of dementia at study baseline. From the thirty-nine of the 40 WHI clinical centers that participated in the WHIMS, 7479 community-dwelling postmenopausal women were enrolled. The study design, eligibility criteria, recruitment procedures and the results were previously published (Shumaker et al., 1998; Shumaker et al., 2003; Shumaker et al., 2004). Written informed consent was obtained, and the WHI, WHIMS and WHIMS-MRI protocols were approved by the NIH and institutional review boards at participating centers.

Baseline demographic information, medical history and lifestyle variables were primarily obtained by self-report and clinical measurements using standardized forms (Shumaker et al., 1998; Shumaker et al., 2003; Shumaker et al., 2004). Body mass index (BMI) was calculated as weight (kg)/height (m)². Baseline global cognitive function was assessed by

administering the Modified Mini-mental State (3MS) examination at baseline by centrally trained and certified technicians (Teng and Chui, 1987).

Assessment of Depression

Depression was measured using the Burnam screening algorithm that consists of six items from the 20-item Center for Epidemiologic Studies Depression Scale (CES-D) and two items from the National Institute of Mental Health's Diagnostic Interview Schedule (DIS) (Burnam et al., 1988).

As a part of CES-D questions, participants were asked about their feelings during the past week. The six items were:

1. You felt depressed (blue or down)
2. Your sleep was restless
3. You enjoyed life (reverse scored)
4. You had crying spells
5. You felt sad
6. You felt that people disliked you

Each item was scored as 0 (rarely or none of the time; less than 1 day), 1 (some or a little of the time; 1–2 days), 2 (occasionally or a moderate amount of time; 3–4 days), or 3 (most or all of the time; 5–7 days).

The two-item DIS was:

1. In the past year, have you had two weeks or more during which you felt sad, blue or depressed, or lost pleasure in things that you usually cared about or enjoyed? 0 (no); 1 (yes)
2. Have you had two or more years in your life when you felt depressed or sad most days, even if you felt okay sometimes? 0 (no); 1 (yes). If yes, have you felt depressed or sad much of the time in the past year? 0 (no); 1 (yes)

The Burnam screen, initially developed for the National Study of Medical Care Outcomes, uses a logistic regression algorithm and provides a composite score between 0 and 1. The Burnam cutpoints of 0.06 and 0.009 have been shown previously to have good sensitivity and specificity to detect depressive disorder (i.e., major depression and dysthymia) in the past month, in the primary care and mental health settings. The cutpoint of 0.009 showed superior sensitivity but slightly lower specificity compared to the 0.06 cut-off for both recent and lifetime prevalence of depressive disorder (Burnam et al., 1988). In previous work within the WHIMS cohort, both these Burnam cutpoints were associated with incident MCI and probable dementia (*unpublished observations; in review*). Only 107 women had Burnam scores below the 0.06 cutpoint; therefore, we chose to use the cut-off of 0.009, which more than doubled the number of women with elevated DS. For the purpose of this study, we will use the term *elevated DS* to describe women who score above this cut-off.

WHIMS-MRI study design and sample

WHIMS-MRI was designed to compare neuroradiologic outcomes post-trial among participants who were assigned to hormone therapy versus placebo arms at 14 of 39 WHIMS sites (Resnick et al., 2009; Coker et al., 2009). On average, scans were performed 8.0 years (for CEE + MPA) and 8.0 years (for CEE-alone) following randomization; 3.0 (for CEE+MPA) and 1.4 years (CEE-alone) after termination of the WHI-HT trials. Recruitment

occurred between January 2005 and April 2006. Women who provided consent were screened to determine eligibility for MRI scanning. Exclusion criteria included the presence of items or conditions contraindicated for MRI including pacemakers, metallic implants and other foreign bodies, shortness of breath or inability to lie flat.

MRI protocol

MRI scans were conducted using a standardized protocol developed by investigators at the MRI Quality Control Center in the Department of Radiology, University of Pennsylvania, Philadelphia (Resnick et al., 2009; Coker et al., 2009; Espeland et al., 2009). Scanning pulse sequences were performed as follows: *Series one*: three-plane gradient echo localizer for positioning; *Series two*: sagittal T1-weighted spin echo midslice image to demonstrate anatomic location of the anterior commissure/posterior commissure (AC/PC) for slice angle and slice position; *Series three*: oblique axial spin density/T2-weighted spin echo (3,200/0/30,120/3) images from the vertex to skull base parallel to the AC/PC plane; *Series four*: oblique axial FLAIR T2-weighted spin echo (8,000/2,000/100/3) images matching slice positions in series three; *Series five*: oblique axial three-dimensional T1-weighted gradient echo (flip angle 30; 21/0/8/1.5) images from the vertex to the skull base parallel to the AC/PC plane. The field of view was 22 cm and the acquisition matrix was 256×256 for series three, four, and five.

MRI Outcomes

A. Regional brain volume measurements—The T1-weighted volumetric MRI scans were first preprocessed according to a standardized protocol for alignment to the AC-PC orientation, removal of extracranial material and segmentation of brain parenchyma into gray matter (GM), white matter (WM), and CSF. Regional volumetric measurements of GM, WM, and CSF were subsequently obtained via a validated, automated computer-based template warping method (Shen and Davatzikos, 2002). This technique is based on a digital atlas labeled for brain lobes and individual structures, including the hippocampus. Atlas definitions were transferred to MRI scans via an image-warping algorithm performing pattern matching of anatomically corresponding brain regions. The volumes of GM, WM, and CSF of each labeled brain region were obtained by summing the number of respective voxels within each region. Measures of regional volumes obtained by this approach show high test-retest stability over time (Driscoll et al., 2009). Volumes of GM and WM reported in this article refer to normal brain tissue only. Intracranial volume (ICV) was estimated as the total cerebral hemispheric volumes, including ventricular CSF and the CSF within the sulcal spaces.

B. Ischemic lesion volume assessment—Ischemic lesion volume defined and identified by this methodology generally corresponds to what has been called small vessel ischemic disease (ischemic white matter disease and lacunar infarctions). This process is now accepted as a non-necrotic, ischemic effect on myelin that is secondary to the effects of aging, hypertension, and other small vessel pathologic processes of the brain (Pantoni and Garcia, 1997). The methodology for detecting and quantifying ischemic tissue used in this report reflects the evolution in image processing from manual human observer (Bryan et al., 1994) to automatic, quantitative computerized digital image analytical techniques that are correlated with human observers and the semiquantitative scoring systems, and are very reproducible and offer a greater dynamic range (Mantyla et al., 1997; Anbeek et al., 2004). This methodology classifies all brain tissue into either normal or ischemic gray or white matter and assigns the tissue type to each of 92 anatomic regions of interest (ROIs) of the cerebrum.

The total ischemic lesion volume was based on a standardized imaging and reading protocol and measured in cubic centimeters by summing abnormal tissue across all labeled regions. Secondly, ischemic lesion volumes in the basal ganglia and the cerebral white and gray matter outside the basal ganglia were estimated by summing abnormal tissue across the respective regions (Lao et al. 2008). Finally, we also examined ischemic lesion volumes for a number of individual frontal and temporal lobe gyri, including precentral gyrus, superior, medial, middle and inferior frontal gyri, medial and lateral orbital gyri, and hippocampus and amygdala. The computer-assisted methodology for definition of abnormal tissue volumes used here has been validated against manual segmentation, i.e., manual drawing of regions of interest, by an experienced neuroradiologist (Lao et al., 2008; Driscoll et al., 2009).

Statistical Analysis

Women classified with and without elevated DS at baseline were compared with respect to demographic, lifestyle, cognitive, and clinical characteristics at the time of randomization to the WHI-HT trials, with chi-square tests and *t* tests. The outcomes of interest included the following regional brain volumes: hippocampal, amygdala, frontal lobe, and total brain volume. Areas of special interest within the frontal lobe were lateral orbital gyrus, medial orbital gyrus, medial frontal gyrus, inferior frontal gyrus, middle frontal gyrus, superior frontal gyrus, and precentral gyrus. Basal ganglia lesion volume and the combination of white and gray matter lesion volume (outside of the basal ganglia) constituted the ischemic brain lesion volumes, the other primary outcome for the current study. Because ischemic lesion volumes were highly skewed, a logarithmic transformation, i.e. Log (ischemic lesion volume + 1), was employed and back-transformed (geometric) means were calculated.

Analysis of covariance was used to contrast means of the MRI outcomes between women with and without elevated DS. Intracranial volume, WHI treatment assignment, clinic, and time between WHI baseline and the MR scan were included as covariates in the basic model. Additional models included adjustment for potential confounders (age, race/ethnicity, education, body mass index, 3MS score, smoking, prior use of hormone therapy, antidepressant therapy, prior cardiovascular disease, diabetes, and hypertension), which represented factors associated with depressive symptoms and cardiovascular risk/disease or affecting participation in WHIMS-MRI (Jaramillo et al., 2007). The consistency of relationships between elevated DS and regional brain volumes and ischemic lesion volumes was assessed using tests of interactions for subgroups defined by age, baseline 3MS score, and prior hormone therapy. The Burnam depression score was divided into quintiles and analyses of covariance were repeated. The adjusted mean brain volumes were plotted against the quintiles to reveal the brain volume patterns across the range of depression scores.

Because these analyses were not part of a formal hypothesis-testing plan, Type I error was not controlled for multiple outcomes. All *P* values were two-sided and *P* < 0.05 was considered significant. All statistical analyses were performed with SAS statistical software, version 9.1 (SAS Institute Inc., Cary, NC).

RESULTS

Of the total sample of 1403 participants that met study criteria for central MRI reading, the Burnam score could not be calculated for 31 women due to missing data. Therefore, 1372 participants were included in this analysis. At baseline, 18% (N=253) of women met the Burnam score cut-point of 0.009 for elevated DS. At baseline, depressed compared with non-depressed women had lower global cognitive function and were more likely to have a history of prior hormone therapy (Table 1).

Elevated Depressive Symptoms, Brain Volumes and Ischemic Lesions

After adjusting for intracranial volume, WHI treatment assignment arm, clinic site and time between WHI baseline assessment and MRI, elevated DS were associated with lower mean superior frontal ($p=0.02$), middle frontal ($p=0.008$), inferior frontal ($p=0.02$), and lateral orbital ($p=0.03$) gyri volumes relative to the reference cohort. There were no differences in the mean total brain, frontal lobe, amygdala and hippocampal volumes between depressed and non-depressed women (Table 2).

After controlling for demographic, lifestyle, baseline cognitive function, cardiovascular risk factors and disease, WHI-HT treatment assignment arm, clinical site, intracranial volume, antidepressant therapy, prior hormone use and time from randomization to MRI scan, the mean differences between the groups remained significant in the superior frontal ($p=0.008$), middle frontal ($p=0.006$) and inferior frontal ($p=0.03$) gyri volume measures (Table 3).

In addition to the dichotomous variable, quintiles of the Burnam score were calculated and their relationships with MRI volumes were examined. After controlling for potential confounding variables, the adjusted mean superior frontal gyrus and middle frontal gyrus volumes were lower for the highest quintile, which corresponded very closely to the Burnam cutpoint of 0.009 (Figure 1A and 1B).

There were no significant differences in the geometric mean total, basal ganglia, and total non-basal ganglia gray matter and white matter lesion volumes between the depressed and non-depressed cohort (Table 4).

We found no interactive effects of age, baseline 3MSE and prior hormone therapy history on the relationships between DS and regional brain volumes and ischemic lesion volumes ($p>0.05$).

DISCUSSION

This is the first study that has examined the relationship between elevated DS and regional brain volumes and subclinical cerebrovascular disease in a large cohort of postmenopausal women. Elevated DS were associated with lower superior, middle and inferior frontal gyral volumes after adjusting for several potential confounding variables. Highest depressive symptom severity was associated with the smallest volumes in these frontal lobe subregions. However, contrary to our hypotheses, we found no differences in the hippocampal and amygdala volumes and vascular lesion load between depressed and nondepressed women. These relationships were not significantly influenced by age, baseline cognitive function and prior hormone therapy in this older sample of women.

Our findings are consistent with prior observations of significant relationships between late-life depression and smaller superior and middle frontal gyri volumes (Ballmaier et al., 2004; Andreescu et al., 2008). However, frontal lobe volume reductions were more consistently observed in older depressed men than women in some studies (Lavretsky et al., 2004) and greater subclinical depressive symptoms were related to smaller frontal and temporal lobe volumes only at older ages in a recent study (Dotson et al., 2009,a). In the BLSA, higher depressive symptoms were associated with faster rate of longitudinal volume decline in the left frontal white matter across all ages (Dotson et al., 2009, a). Our results extend findings of smaller frontal lobe volumes to a depressed sample restricted to women, but we did not observe an effect of age on the DS associated reduction of brain volume. Frontal lobe involvement in depression is also supported by behavioral observations of executive dysfunction in the depressed elderly (Alexopoulos, 2005), which is dependent on intact frontal functioning. Furthermore, the presence of executive dysfunction in the depressed

elderly is associated with poor antidepressant treatment response and greater risk of relapse (Alexopoulos et al., 1993; Alexopoulos, 2005), and the persistence of executive deficits after remission of geriatric depression may be a sign of incipient dementia (Alexopoulos et al., 1993). Moreover, increased cerebral glucose metabolism in these frontal lobe subregions is reported in geriatric depression (Smith et al., 2009) and greater subclinical depressive symptoms were associated with decreased regional cerebral blood flow to these same structures in both men and women in the BLSA studies (Dotson et al., 2009, b). Therefore, our results lend further credence to the hypothesis of frontal lobe dysfunction in association with elevated DS among postmenopausal women.

Although the lack of differences in the hippocampal and amygdala volumes between depressed and non-depressed women is consistent with some studies (Ashtari et al., 1999; Dotson et al., 2009, a), an increasing body of evidence supports the involvement of hippocampus and amygdala in geriatric depression (Steffens et al., 2000; Bell-McGinty et al., 2002; Ballmaier et al., 2004; Andreescu et al., 2008). Smaller hippocampal (Steffens et al., 2000; Bell-McGinty et al., 2002; Ballmaier et al., 2004; Andreescu et al., 2008) volumes are found in elderly depressed patients compared with normal subjects, but the direction of effect remains unclear. Younger age of onset and longer duration of untreated depression can result in hippocampal exposure to toxic levels of glucocorticoids leading to volume loss (Sheline et al., 1996; Sheline et al., 1999; Bell-McGinty et al., 2002; Frodl et al., 2008; Sapolsky, 2000). On the other hand, late-onset depression and DS may be non-cognitive manifestations of a neurodegenerative process that is also associated with smaller hippocampal volumes (Steffens et al., 2000; Andreescu et al., 2008). In contrast, the role of reduced amygdala volume in depression is less conclusive (Sheline et al., 1999; Frodl et al., 2008; Andreescu et al., 2008). Information on age of onset and the total duration of untreated depressive symptoms is unavailable for our sample. The older age of our sample may have limited our ability to identify any associations that hippocampal and amygdala volumes had with elevated depressive symptoms. In addition, we did not find an influence of baseline cognitive function on the depression-regional brain volume relationship. Despite slightly lower baseline global cognitive function in the depression group of our study, the cognitive scores were generally higher than previous studies that have shown depression associated hippocampal atrophy (Steffens et al., 2002; Andreescu et al., 2008). Unlike WHIMS-MRI and BLSA community-based samples, prior studies that have found late-life depression related hippocampal volume loss (Steffens et al., 2002; Andreescu et al., 2008) were conducted in tertiary care mental health centers and most likely enrolled treatment seeking elderly participants who may also have had severe symptoms, perhaps contributing to discrepant findings. It is possible that the depressed elderly with poorer cognitive performance may have smaller hippocampi and volume reductions in this medial temporal lobe region may be a neuroimaging marker for incident dementia in patients with geriatric depression (Steffens et al., 2002).

DS or greater depressive symptom severity were not associated with larger total ischemic lesion volumes, ischemic lesion volumes in the basal ganglia and cerebral white and gray matter outside of the basal ganglia in this study. These findings are in contrast to the well-established literature that has reported associations between late-life depression and subclinical cerebrovascular disease (Krishnan et al., 1997; Alexopoulos et al., 1997; Krishnan et al., 2004). Increased white matter hyperintensities (WMH) and subclinical strokes are more frequently found in patients with geriatric depression relative to normal control subjects (Krishnan et al., 1997; Alexopoulos et al., 1997; Nebes et al., 2002; O'Brien et al., 2006; Teodorczuk et al., 2007; Hermann et al., 2008). Increased severity of WMH is associated with a more chronic course of depression, poor treatment response to antidepressants, and worse cognitive outcomes (Kramer-Ginsberg et al., 1999; Taylor et al., 2003; Alexopoulos, 2005). Increased severity of subclinical cerebrovascular ischemic

changes in late-life depression is associated with several risk factors including advancing age, vascular risk factors and medical co-morbidity (Alexopoulos et al., 1997; Krishnan et al., 2004; Alexopoulos, 2005). These observations support the hypothesis of vascular depression and have emphasized the critical role of subclinical cerebrovascular disease in the pathogenesis of geriatric depression. The older age of our sample may have made it difficult to identify small differences in vascular lesions given their relative frequency in older adults.

Mechanisms that can explain the relationships between elevated DS and smaller volumes in the superior and middle frontal gyri are not clear. Previously, we found that the postmenopausal women with DS at baseline were more likely to progress to MCI and probable dementia during a mean follow-up of 5 years (*unpublished observations*). It is possible that the increased risk of incident cognitive impairment among depressed women is mediated by volume declines in specific frontal lobe subregions. The lower superior and middle frontal gyral volumes we observed are not due to subclinical cerebrovascular disease: we found comparable ischemic lesion load in depressed and non-depressed women. Rather, the reduced volumes are likely due to the elevated DS being a prodromal presentation of dementia (Steffens et al., 2000; Andreescu et al., 2008) or from DS related neurotoxic effects (Sheline et al., 1999; Frodl et al., 2008). Although the medial temporal lobe regions are most vulnerable to the AD neuropathology, amyloid and tau deposition are also seen in the frontal lobe structures in pre-clinical dementia states (Villemagne et al., 2008). In fact, amyloid deposition is found in prefrontal cortical regions in the cognitively normal elderly population and increased fibrillar amyloid correlates with episodic memory deficits and future cognitive decline (Mintun et al., 2006; Villemagne et al., 2008). Recent findings from in vivo imaging studies localize associations between amyloid deposition and longitudinal verbal memory decline to brain regions including prefrontal structures (Resnick et al., 2010). Moreover, AD subjects with depression had hypoperfusion in the frontal lobe and greater neurofibrillary tangle burden in the frontal, parietal and temporal cortices when compared with AD patients without depression (Rapp et al., 2008; Levy-Cooperman et al., 2008). Patients with remitted geriatric depression were found to have cortical amyloid accumulation comparable to AD, providing additional support to the theory that late-life depression may be the prodromal manifestation of AD, at least in some individuals (Butters et al., 2008).

Strengths and Limitations

The WHIMS-MRI provides a large diverse cohort of well-characterized women with standardized assessments of DS, brain volumes, and risk factors for dementia. As volunteers for a clinical trial of postmenopausal hormone therapy and brain MRI, these women do not reflect more general populations (Stefanick et al., 2003; Jaramillo et al., 2007). In order to address the possibility of selection bias, we examined whether there was differential enrollment to the WHIMS MRI study based on the depression status and found no differences between women with and without elevated DS. Because we have data from only a single MRI, we cannot determine the temporal sequence of observed relationships. However, our study groups had relatively well balanced baseline characteristics and the findings remained significant after controlling for several potential confounders. Currently, a second MRI scan is being collected on the same cohort approximately 4 years after the first scan, and this will allow assessment of temporal relationships. Another limitation is that assessment of depression and DS were not based on a semi-structured interview, and thus was not a clinical diagnosis. Therefore, even though the Burnam cutpoint of 0.009 has shown excellent sensitivity and good specificity for current depressive disorder diagnoses, we classified these women who scored above the cut-off as having elevated DS (Burnam et al., 1988). In addition, we did not have information on the age of onset of elevated DS and

total number of episodes and duration of each episode. Finally, in our descriptive analyses, we have not controlled type 1 error across brain regions, so that some chance findings may be included among our results.

In the largest study of postmenopausal women reported to-date, we found an association between elevated DS and volumes of certain frontal lobe subregions that are implicated in both geriatric depression and cognitive impairment. The associations between elevated DS and frontal lobe volumes were not mediated by subclinical cerebrovascular disease. Furthermore, there were no DS-related volume differences for the hippocampus and amygdala. Longitudinal studies should be conducted to further elucidate the effects of depression and DS on brain volumes and their relationship with conversion to dementia.

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Figure 1.

Adjusted mean middle frontal gyrus (A) and superior frontal gyrus (B) volumes and 95% confidence interval after fully adjusting for potential confounding variables.*

Footnote: *Confounding variables: Women's Health Initiative clinical trial, arm, clinical site, age, race/ethnicity, education, body mass index, modified mini-mental state (3MS), smoking, prior use of hormone therapy, antidepressant therapy, cardiovascular disease history, diabetes, hypertension, intracranial volume, and time from randomization to magnetic resonance imaging (MRI) scan

Table 1

Associations Between Baseline Variables and Elevated Depressive Symptoms

Variable	Elevated depressive symptoms based on cut-point >0.009 N=number (%)		P value*
	Yes N=253 (18)	No N=1119 (82)	
Age, years (mean, standard deviation)	70.6, 3.9	70.5, 3.6	0.87
Ethnicity, n (%)			0.13 [†]
White	224 (89)	1033 (93)	
African American	16 (6)	43 (4)	
Hispanic	7 (3)	10 (1)	
Asian	4 (2)	18 (2)	
American Indian	0 (0)	3 (0)	
Unknown	1 (0)	9 (1)	
Education, n (%)			0.17
< high school graduate/GED	16 (6)	45 (4)	
High school graduate/GED	62 (25)	255 (23)	
Some college	104 (41)	442 (40)	
College graduate	70 (28)	375 (33)	
3MS at baseline (mean, standard deviation)	95.7, 3.5	96.2, 3.4	0.04
Years from randomization to MRI scanning (mean, standard deviation)	8.0, 0.6	8.0, 0.6	0.52
Body mass index, n (%)			0.11
< 25	75 (30)	334 (30)	
25–29	101 (40)	412 (37)	
30–34	41 (16)	252 (23)	
35+	34 (14)	118 (11)	
Smoking, n (%)			0.35
Never	135 (54)	655 (59)	
Past	103 (41)	411 (37)	
Current	12 (5)	45 (4)	
Prior hysterectomy, n (%)			0.07
No	146 (58)	714 (64)	
Yes	107 (42)	405 (36)	
History of diabetes, n (%)			0.68
No	238 (94)	1060 (95)	
Yes	15 (6)	59 (5)	
Hypertension, n (%)			0.31

Variable	Elevated depressive symptoms based on cut-point >0.009 N=number (%)		P value [*]
	Yes N=253 (18)	No N=1119 (82)	
None	143 (57)	574 (51)	
Current/controlled	36 (14)	172 (15)	
Current/uncontrolled	74 (29)	373 (33)	
History of cardiovascular disease, n (%)			0.31
No	233 (92)	1050 (94)	
Yes	20 (8)	69 (6)	
Hormone therapy assignment, n (%)			0.54
Active	130 (51)	551 (49)	
Placebo	123 (49)	568 (51)	
Prior hormone therapy, n (%)			0.001
No	146 (58)	772 (69)	
Yes	107 (42)	347 (31)	
Antidepressant therapy, n (%)			0.06
No	236 (93)	1074 (96)	
Yes	17 (7)	45 (4)	

3MS = modified mini-mental state; MRI = magnetic resonance imaging; % = percentage.

^{*} P value for categorical variables is based on Chi-Square test and for continuous variables, t test.

[†] Based on collapsing to three categories (White, African American, and other)

Table 2

Mean brain volumes for women with and without elevated depressive symptoms after adjustment for intracranial volume, WHI* treatment assignment, clinic, and time between enrollment and MRI†

Regional volume, ml	Elevated depressive symptoms based on cut-point >0.009		P value
	Yes N=253 (18%)	No N=1119 (82%)	
Total brain volume, mean (SE‡)	799.1 (2.3)	800.2 (1.1)	0.661
Hippocampal volume, mean (SE)	5.73 (0.06)	5.74 (0.03)	0.932
Amygdala volume, mean (SE)	1.86 (0.02)	1.89 (0.01)	0.307
Frontal lobe volume, mean (SE)	283.6 (1.0)	283.9 (0.5)	0.762
Superior frontal gyrus, mean (SE)	13.22 (0.15)	13.63 (0.07)	0.017
Middle frontal gyrus, mean (SE)	27.94 (0.24)	28.65 (0.11)	0.007
Inferior frontal gyrus, mean (SE)	17.79 (0.15)	18.16 (0.07)	0.023
Medial frontal gyrus, mean (SE)	18.144 (0.15)	18.35 (0.07)	0.199
Lateral orbital frontal gyrus, mean (SE)	16.54 (0.11)	16.79 (0.05)	0.034
Medial orbital frontal gyrus, mean (SE)	4.03 (0.04)	4.04 (0.02)	0.808
Precentral gyrus, mean (SE)	19.15 (0.15)	19.28 (0.07)	0.416

* WHI=Women's Health Initiative;

† MRI = magnetic resonance imaging;

‡ SE = standard error.

Table 3

Mean brain volumes for women with and without elevated depressive symptoms after full adjustment*

Regional volume, ml	Elevated depressive symptoms based on cut-point >0.009		P value
	Yes N=253 (18)	No N=1119 (82)	
Total brain volume, mean (SE ^{**})	799.6 (2.2)	800.5 (1.0)	0.728
Hippocampal volume, mean (SE)	5.74 (0.06)	5.74 (0.03)	0.977
Amygdala volume, mean (SE)	1.86 (0.02)	1.89 (0.01)	0.385
Frontal lobe volume, mean (SE)	283.8 (1.0)	284.0 (0.5)	0.846
Superior frontal gyrus, mean (SE)	13.18 (0.15)	13.63 (0.07)	0.008
Middle frontal gyrus, mean (SE)	27.92 (0.24)	28.65 (0.11)	0.006
Inferior frontal gyrus, mean (SE)	17.81 (0.15)	18.17 (0.07)	0.026
Medial frontal gyrus, mean (SE)	18.12 (0.15)	18.35 (0.07)	0.168
Lateral orbital frontal gyrus, mean (SE)	16.56 (0.11)	16.78 (0.05)	0.057
Medial orbital frontal gyrus, mean (SE)	4.04 (0.04)	4.04 (0.02)	0.952
Precentral gyrus, mean (SE)	19.19 (0.16)	19.30 (0.07)	0.538

* fully adjusted for intracranial volume, WHI treatment assignment, clinic, time between enrollment and MRI and potential confounders: age, race/ethnicity, education, 3MS, BMI, smoking, prior use of hormone therapy, antidepressant therapy, history of cardiovascular disease, diabetes, and hypertension

[†] MRI = magnetic resonance imaging;

[‡] WHI = Women's Health Initiative;

[§] 3MS = modified mini-mental state;

[¶] BMI = body mass index;

** SE = standard error

Table 4

a. Geometric mean ischemic brain volumes for women with and without elevated depressive symptoms after adjustment for intracranial volume, WHI[*] treatment assignment, clinic, and time between enrollment and MRI[†]			
Lesion volume (ml)	Elevated depressive symptoms based on cut-point >0.009		P value
	Yes N=253 (18)	No N=1119 (82)	
Basal ganglia lesion volume, geometric mean (SE [‡])	0.67 (0.02)	0.67 (0.01)	0.990
White and gray matter (outside of basal ganglia) lesion volume, geometric mean (SE)	5.02 (0.28)	4.45 (0.12)	0.109
Total lesion volume, geometric mean (SE)	5.56 (0.32)	5.00 (0.13)	0.157

b. Geometric mean ischemic brain volumes for women with and without elevated depressive symptoms fully adjusted[*]			
Lesion volume (ml)	Elevated depressive symptoms based on cut-point >0.009		P value
	Yes N=253 (18)	No N=1119 (82)	
Basal ganglia lesion volume, geometric mean (SE ^{**})	0.66 (0.02)	0.67 (0.01)	0.794
White and gray matter (outside of basal ganglia) lesion volume, geometric mean (SE)	5.00 (0.28)	4.48(0.12)	0.138
Total lesion volume, geometric mean (SE)	5.53 (0.31)	5.03 (0.13)	0.196

^{*} WHI = Women's Health Initiative;

[†] MRI = magnetic resonance imaging;

[‡] SE = standard error.

^{*} fully adjusted for intracranial volume, WHI[†] treatment assignment, clinic, time between enrollment and MRI[‡] and potential confounders: age, race/ethnicity, education, 3MS[§], BMI[¶], smoking, prior use of hormone therapy, antidepressant therapy, history of cardiovascular disease, diabetes, and hypertension

[†] WHI = Women's Health Initiative;

[‡] MRI = magnetic resonance imaging;

[§] 3MS = modified mini-mental state;

[¶] BMI= body mass index