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Lobar Distribution of Lesion Volumes in Late-Life Depression: The Biomedical Informatics Research Network (BIRN)

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White matter hyperintense lesions on T2-weighted images are associated with late-life depression. Little work has been carried out examining differences in lesion location between elderly individuals with and without depression. In contrast to previous studies examining total brain white matter lesion volume, this study examined lobar differences in white matter lesion volumes derived from brain magnetic resonance imaging. This study examined 49 subjects with a DSM-IV diagnosis of major depression and 50 comparison subjects without depression. All participants were age 60 years or older. White matter lesion volumes were measured in each hemisphere using a semiautomated segmentation process and localized to lobar regions using a lobar atlas created for this sample using the imaging tools provided by the Biomedical Informatics Research Network (BIRN). The lobar lesion volumes were compared against depression status. After controlling for age and hypertension, subjects with depression exhibited significantly greater total white matter lesion volume in both hemispheres and in both frontal lobes than did control subjects. Although a similar trend was observed in the parietal lobes, the difference did not reach a level of statistical significance. Models of the temporal and occipital lobes were not statistically significant. Older individuals with depression have greater white matter disease than healthy controls, predominantly in the frontal lobes. These changes are thought to disrupt neural circuits involved in mood regulation, thus increasing the risk of developing depression.
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INTRODUCTION

Depression in late life is associated with the occurrence of white matter hyperintense lesions (WMLs) detected on brain magnetic resonance imaging (MRI). These WMLs are bright regions, hyperintense on proton density (PD) and T2-weighted MRIs, seen in the parenchyma of the brain, and are associated with advanced age (Awad *et al*, 1986; Longstreth *et al*, 1996; Guttmann *et al*, 1998) and cardiovascular risk factors, particularly hypertension (Fazekas *et al*, 1988; Ylikoski *et al*, 1995; Longstreth *et al*, 1996; Liao *et al*, 1997; Veldink *et al*, 1998; Schmidt *et al*, 1999; Dufouil *et al*, 2001; Taylor *et al*, 2003a). Many reports associate hyperintense lesions with late-life depression. White and gray matter hyperintense lesions are more severe in older depressed subjects than nondepressed subjects (Krishnan *et al*, 1988; Dolan *et al*, 1990; Fujikawa *et al*, 1993; Krishnan, 1993; Greenwald *et al*, 1996; Steffens *et al*, 1999; Kumar *et al*, 2000; Tupler *et al*, 2002; Taylor *et al*, 2005), and are more severe in late-onset than early-onset elderly depressed subjects (Figiel *et al*, 1991; Hickie *et al*, 1995; Salloway *et al*, 1996; Krishnan *et al*, 1997; Lavretsky *et al*, 1998; de Groot *et al*, 2000; Tupler *et al*, 2002). Increases in WML severity over time are additionally associated with new onset of depression (Lavretsky *et al*, 1999; Nebes *et al*, 2002) and poorer outcomes to antidepressant therapy (Simpson *et al*, 1997; O'Brien *et al*, 1998; Taylor *et al*, 2003c), although some have not found a relationship between WML severity and treatment outcomes (Salloway *et al*, 2002).

This body of work led to the development of the vascular depression hypothesis (Alexopoulos *et al*, 1997; Krishnan *et al*, 1997) and the more specific description of subcortical ischemic depression.(Krishnan *et al*, 2004) This hypothesis posits that WMLs represent cerebrovascular injury to the brain that may disrupt mood regulation, thus increasing the risk of developing depression. Thus, WMLs hypothetically contribute to the pathogenesis of depression by disrupting

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the fiber tracts that connect cortical and subcortical structures involved in mood regulation, such as disruption of frontostriatal circuits (Tekin and Cummings, 2002) or connections with limbic structures as described using functional imaging studies (Seminowicz *et al*, 2004), both of which are implicated as contributing to mood disorders.

Although the basis of this hypothesis is that WMLs related to depression must occur in specific areas, there is only limited research investigating this question. Several studies have noted that frontal WMLs are particularly associated with depression (Greenwald *et al*, 1998; Taylor *et al*, 2003b; Firbank *et al*, 2004), particularly WMLs occurring in the orbital frontal cortex (MacFall *et al*, 2001); this supports theories that frontal lobe regions are critical in mood regulation. Unfortunately, many of these studies did not examine other regions, such as the temporal or parietal lobes. Involvement of regions beyond the frontal lobe is a critical question as a recent large-scale population study associated depression with severe WML disease in the frontal and parietal lobes, but WML disease also extended into temporal and occipital regions (Artero *et al*, 2004). This finding contrasts with work using Statistical Parametric Mapping (SPM99) analyses that did consider the entire brain, and reported that differences in depression predominantly are in the frontal lobe (MacFall *et al*, 2001; Taylor *et al*, 2003b). The SPM voxel-based morphometry approach is useful, but has been criticized because of the extensive processing involved to create lesion density maps from high-resolution segmented images that identify the lesions.

There are alternative approaches to addressing this question. One such alternative is to localize lesions by measuring the lesion volume in each of the anatomically defined lobes of the brain. This can be carried out by creating a lobar atlas that is applied to the images of each subject; this sophisticated image processing capability is available in only a few research laboratories. A recent National Institutes of Health initiative know as the Biomedical Informatics Resource Network has begun to make such tools available to be used by a wider group of research laboratories who have medical imaging data that could benefit from such image processing tools.

In this paper, we report on the use of the Biomedical Informatics Research Network (BIRN) network to create brain lobar atlases for this imaging data and their use to report on the white matter lesion volumes within each lobe. We hypothesized that when compared with elderly control subjects, elderly subjects with depression would exhibit greater total WML volume, and based on hypotheses implicating the frontal lobe in the pathogenesis of depression, that the difference in WML volume between depressed and nondepressed subjects would be greatest in the frontal lobe. We further hypothesized that this difference would persist over a 2-year period.

METHODS

Sample

All subjects participated in the NIMH-sponsored Longitudinal Study of Late-Life Depression at Duke University Medical Center. This study was approved by the Duke University Medical Center Institutional Review Board. After receiving an explanation of the study's purpose and procedures, subjects provided written informed consent.

Subjects were outpatients age 60 years or older with a diagnosis of nonpsychotic Major Depressive Disorder and a Center for Epidemiologic Studies-Depression Scale (Radloff, 1977) score $\geqslant$16. They were recruited from clinical referrals. Exclusion criteria included (1) other major psychiatric illnesses; (2) history of substance abuse or dependence; (3) primary neurological illnesses, including stroke and dementia; (4) medical illnesses impairing cognitive function; (5) metal in the body precluding MRI; and (6) Mini-Mental State Examination (Folstein *et al*, 1975) score below 25. This group included subjects both with early-onset recurrent depression as well as those individuals with the first episode of depression occurring later in life.

Control subjects were age-matched community volunteers recruited from the Aging Center Subject Registry at Duke University. They had a nonfocal neurological examination, no self-report of neurologic or depressive illness, and no evidence of depression based on the Diagnostic Interview Schedule (Robins *et al*, 1981).

The sample for this study was a subset of 50 depressed subjects and 50 age-matched control subjects from the larger cohort; these subjects have been included in previous reports of larger samples examining cross-sectional differences between groups (Taylor *et al*, 2005) and longitudinal changes (Taylor *et al*, 2003a, c). Subjects were selected by the database manager based upon age and sex matching of those individuals with complete clinical and MRI assessment data for their baseline evaluation and the follow-up evaluation 2 years later.

The data were anonymized for subject privacy protection in accordance with HIPAA regulations. All image files and tabular data were converted to a standardized format, SAS export files for tabular data and DICOM for image data, and uploaded to the BIRN storage resource broker (SRB—the BIRN database) where they could be accessed by participating sites.

Assessment of Medical Comorbidity

Subjects completed a questionnaire that asked about the presence or absence of hypertension. These data were self-report only and were derived from questions included in the NIMH Epidemiological Catchment Area program (Regier *et al*, 1984).

Antidepressant Therapy

During their participation in the study, depressed subjects were treated according to a treatment algorithm, the Duke STAGED Approach (Steffens *et al*, 2002). This algorithm mimics 'real-world' treatment options rather than a more rigid clinical trial design by accounting for past treatments and current severity. Never-treated subjects are initially prescribed a selective serotonin reuptake inhibitor (SSRI). If adequate doses of the SSRI do not bring sufficient response after 8–12 weeks, the recommendation is to switch to venlafaxine or augment with bupropion. Options after a

continued, inadequate treatment response include tricyclic antidepressants and lithium augmentation. At each stage, doses are increased as tolerated or required, to the maximum approved dose. Electroconvulsive therapy is a treatment option at each algorithm level, dependent on subject severity, number of failed trials, and subject preference. Subjects were not routinely referred for psychotherapy, although some were already engaged in ongoing psychotherapy at study entry, while others were referred for individual and/or group psychotherapy, usually cognitive–behavioral psychotherapy.

MRI Acquisition and Image Segmentation

Subjects received brain MR imaging at baseline and then approximately 2 years later. At both instances, subjects were imaged with a 1.5 T whole-body, research-dedicated MRI system (Signa, GE Medical Systems, Milwaukee, WI) using a standard head (volumetric) radiofrequency coil. A dual-echo fast spin-echo acquisition was obtained in the axial plane for morphometry. The pulse sequence parameters were TR = 4000 ms, TE = 30, 135 ms, 32 kHz, (±16 kHz) full-imaging bandwidth, echo train length = 16, a 256 × 256 matrix, contiguous 3 mm section thickness, one excitation, and a 20 cm field of view.

The volumes of lesions, gray matter, white matter, and CSF were determined through the use of semiautomated segmentation and volume measurement computer programs in the Neuropsychiatric Imaging Research Laboratory at Duke University Medical Center (Byrum *et al*, 1996; Payne *et al*, 2002). Periventricular and deep white matter lesions were separately identified, but were combined in the results reported here. As this study specifically aimed to examine differences in WML volume, subcortical gray matter lesions were not included in the analyses. Additionally, due to image processing methods, brainstem lesions were not included.

All image analysts received extensive training. Reliability was established by repeated measurements on multiple MR scans before analysts processed study data. Intraclass correlation coefficients were left cerebral gray matter lesions = 0.995; right cerebral gray matter lesions = 0.996; left cerebral white matter lesions = 0.988; and right cerebral white matter lesions = 0.994.

Brain Template and Lobar Atlas Creation

Assignment of a given brain region to left or right frontal, temporal, parietal, or occipital lobes was accomplished using BIRN-enabled computer programs. A 'template' image that is essentially an average PD brain image for this population was first created using previously described methods provided to the BIRN by the Laboratory of Neuro Imaging (LONI), University of California, Los Angeles, CA (Rex *et al*, 2003). Similarly a T2-weighted template image was also created. Figure 1 shows the PD template.

The lobar atlas was created from this template via manual delineation (DER) of the subject atlas space utilizing intensity information from the average PD and average T2 volumes. The landmarks used were similar to those of the ICBM305 anatomic delineation (Evans *et al*, 1996) and are as found for the LONI sulcal delineation protocol (Luders *et al*, 2003; http://www.loni.ucla.edu/ad/AD_protocol/sulcal.html). An illustration of the atlas, superimposed on the template brain, is shown in Figure 1. Note that the atlas is somewhat larger than the template to avoid cutting off sections of the brain or CSF near the surface.

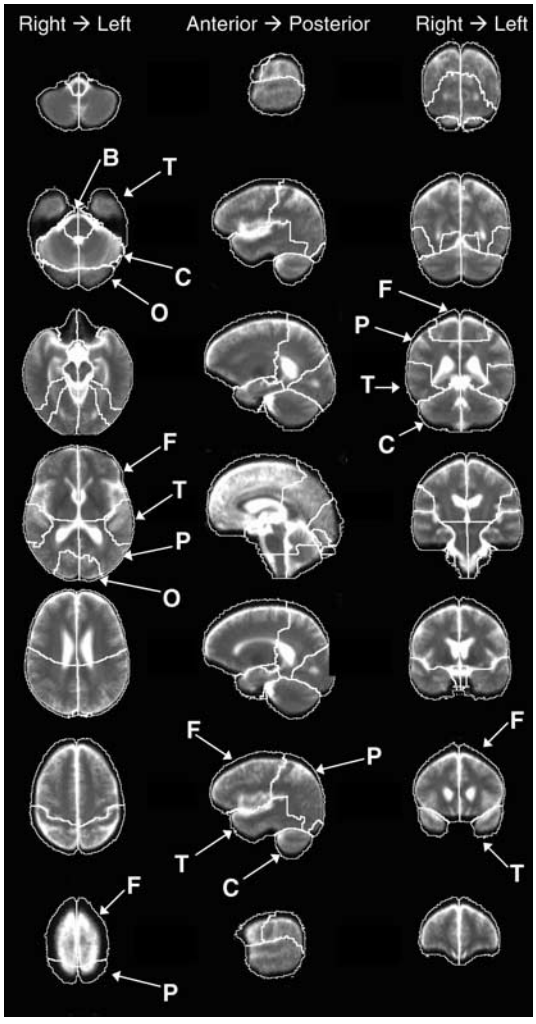

Figure 1 Diagram of the lobar atlas. The lobes are demarked by lines and the regions are labeled accordingly: F = frontal lobe; P = parietal lobe; O = occipital lobe; T = temporal lobe; C = cerebellum.

Study subjects' images had the skull removed for registration purposes using an automated skull-stripping method (Rex *et al*, 2004). The T2 template was aligned to each skull-stripped depressed and control subject via a fifth-order polynomial nonlinear alignment (Woods *et al*, 1998). The associated lobar atlas was then transformed to each subject using a nearest-neighbor interpolation, preserving the borders of the labeling, in order to define each lobe of each subject for regional analyses. This was performed in an automated manner utilizing the LONI Pipeline Processing Environment (Rex *et al*, 2003).

To calculate the lobar lesion volumes for each subject, voxels containing lesion (in the untransformed, original coordinate system) were classified as belonging to a given lobe using the atlas that was transformed to the subject's

original coordinate system. Then, the lesion volume for each lobe was calculated by summing up the number of such voxels in each lobe and multiplying by the (common) voxel volume.

Analytic Strategy

All analyses were completed using SAS (version 8.2; Cary, NC). Summary statistics for each group were derived for demographic and clinical variables, including MRI results. General linear models were created for the analysis of cross-sectional data at both baseline and follow-up; they were determined to reach statistical significance if the overall model had a p-value <0.05. These models examined lesion volume in each region as the dependent variable, with depression status, age, and the presence or absence of hypertension as independent variables. From these models, the least-squares mean of the WML volume in each region was calculated for both depressed and control subjects. As we have previously demonstrated that age and presence of hypertension are independently related to WML volume (Taylor *et al*, 2005), this approach provides an adjusted difference between the depressed and nondepressed groups, so may be more accurate than a report of unadjusted observed means. However, unadjusted observed means were calculated for lesion volumes in brain regions where the overall models were not statistically significant, and differences examined using Satterthwaite t-tests due to unequal variances.

A similar method was used for examining differences in change in WML volume between the two scans. These general linear models examined change in WML volume as the dependent variable, with depression status, age, and the presence or absence of hypertension as independent variables. The least-squares mean of the change in WML volume in each region was calculated for both depressed and control subjects. This issue was also examined using mixed measures models, where WML volume was the dependent variable, and depression status, time, age, and hypertension were independent variables. These models also included a depression status (group) by time interaction term.

RESULTS

Demographic and Clinical Differences

We examined 49 depressed and 50 control subjects; one depressed subject's MRI data could not be analyzed due to a nonconforming protocol. There were no significant differences between groups in mean age (depressed: 68.2 years, range = 60–82 years, SD = 6.4; control: 68.6 years, range = 60–81 years, SD = 5.7; 97 df, $t=0.37$, $p=0.709$) or sex (depressed: 63.3% female; control: 62.0% female; $\chi^2=0.02$, $p=0.897$). In the depressed group, one was Asian-Americans, three were African-Americans, and 46 Caucasians; in the control group, six were African-Americans and 44 Caucasians. There was no significant difference between groups in the ratio of minorities to Caucasians (Fisher's exact, $p=0.487$). The control group overall had a significantly higher mean level of education (control: 15.4 years, range = 12–17 years; depressed = 14.3 years, range = 8–17 years; 97 df, $t=2.56$, $p=0.010$).

Hypertension was more commonly reported in the depressed (in 24 of 49 subjects) than the control group (eight of 50 subjects; $\chi^2=12.30$, $p=0.0005$). Depressed subjects had a mean age of depression onset of 40.0 years (range = 7–71 years; SD = 18.0 years) and a depression severity, measured using the Montgomery–Asburg Depression Rating Scale (Montgomery and Asberg, 1979), of 27.1 (range = 16–53; SD = 7.8).

MR Hyperintense Lesion Volume Differences

All baseline lesion measurements found greater lesion volumes in depressed than control subjects (Table 1). General linear models tested for differences between groups while accounting for age and hypertension. Depression was associated with significantly greater WML volumes in total brain volume measurements, and all frontal lobe measures. There was also a statistical trend that did not reach a level of significance that depressed subjects exhibited greater WML volumes in the total and right parietal lobe. Age was significantly ($p<0.05$) associated with greater WML volumes in total brain, frontal, and parietal lobe analyses.

Table 1 Initial White Matter Lesion Volume by Lobe: Association with Depression Status

	Depressed (SE)	Control (SE)	Mean difference	Parameter estimate	*t*-value	*p*-value
Total brain WMH lesion volume	6.11 (0.90)	3.09 (1.02)	3.02	1.36	2.23	0.0283
Left hemisphere WMH lesion volume	2.95 (0.41)	1.63 (0.47)	1.32	0.62	2.12	0.0363
Right hemisphere WMH lesion volume	3.16 (0.50)	1.46 (0.56)	1.70	0.75	2.27	0.0254
Total frontal lobe WMH lesion volume	4.17 (0.46)	2.37 (0.52)	1.80	0.69	2.63	0.0101
Left frontal lobe WMH lesion volume	2.02 (0.21)	1.22 (0.24)	0.80	0.31	2.55	0.0123
Right frontal lobe WMH lesion volume	2.16 (0.26)	1.15 (0.29)	1.01	0.39	2.56	0.0120
Total parietal lobe WMH lesion volume	1.87 (0.46)	0.74 (0.45)	1.13	0.70	1.62	0.1084
Left parietal lobe WMH lesion volume	0.91 (0.21)	0.43 (0.21)	0.48	0.33	1.47	0.1451
Right parietal lobe WMH lesion volume	0.96 (0.25)	0.31 (0.28)	0.65	0.37	1.76	0.0814

WMH volumes (in ml) displayed are least-squares mean volumes, from models controlling for age, depression status, and hypertension; standard error for these volumes are reported rather than standard deviation as they were derived from these models. The statistical parameter estimate, standard error (SE), t-value, and p-value report the influence of depression on WMH lesion volume in general linear models, which also include age and hypertension and independent variables.

Hypertension was not associated with lesion volume in any analysis.

The least-squares mean WML volumes in the follow-up assessment increased from baseline, and depressed subjects continued to exhibit greater lesion volumes than control subjects (Table 2). Similar to the analysis of baseline data, after controlling for age and hypertension, depression was significantly associated with greater WML volumes in total brain and frontal measures. The statistical trend for differences in the total and right parietal lobe also remained. Likewise, age continued to be associated with greater total, frontal, and parietal WML volume, while hypertension was not associated with WML volume in any analysis.

Analyses of occipital and temporal lobe WML volumes were also attempted. These models failed to reach an overall level of statistical significance using either the baseline or follow-up data. Unadjusted means and univariate analyses demonstrate that depressed subjects exhibited greater WML volumes in these lobes, although the differences between groups do not reach a level of statistical significance. In the baseline analyses of the occipital lobe, depressed subjects exhibited a mean WML volume of 0.0381 ml (SD = 0.179), while control subjects exhibited a mean WML volume of 0.0008 ml (SD = 0.004; Satterthwaite $t = 1.42$, 48 df, $p = 0.161$). In follow-up scan analyses of the occipital lobe, depressed subjects exhibited a mean WML volume of 0.0513 ml (SD = 0.248), while control subjects exhibited a mean WML volume of 0.0132 ml (SD = 0.179; Satterthwaite $t = 0.95$, 53.2 df, $p = 0.348$). In baseline analyses of the temporal lobe, depressed subjects exhibited a mean WML volume of 0.018 ml (SD = 0.084), while control subjects exhibited a mean WML volume of 0.002 ml (SD = 0.006; Satterthwaite $t = 1.29$, 48.5 df, $p = 0.204$). In follow-up scan analyses of the temporal lobe, depressed subjects exhibited a mean WML volume of 0.057 ml (SD = 0.273), while control subjects exhibited a mean WML volume of 0.005 ml (SD = 0.014, Satterthwaite $t = 1.35$, 48.3 df, $p = 0.184$).

Analysis of WMH Lesion Volume Change between MRI Scans

There was a mean time of 734 days (SD = 23.6; minimum = 680 days, maximum = 806 days) between MRI scans for the entire group. There was no statistically significant difference in time between scans and between the depressed (mean 730 days, SD = 27.5) and control groups (mean 737 days, SD = 18.5; Satterthwaite t-test, 83.9 df, $t = 1.67$, $p = 0.0982$).

After controlling for age and hypertension, depressed subjects exhibited larger least-squares mean change in WMH lesion volume over the study period than did control subjects, but this did not reach a level of statistical significance (Table 3). Age, but not hypertension, was positively associated with WMH lesion volume change in total, frontal, and parietal measures. In mixed measures models, no WMH lesion volume measure exhibited a statistically significant group by time interaction.

DISCUSSION

The main finding was that depressed subjects exhibited greater white matter lesion volumes in the frontal lobe than do control subjects. This finding remained statistically significant even after controlling for age and reports of hypertension. These findings were consistent between the baseline and follow-up scans. We did not detect any statistically significant change in WML volume in any lobe over the study period between the two groups.

Our finding of greater WML volumes in the frontal lobe is concordant with previous studies. Numerous other reports have also found greater total WML volumes in elderly depressed subjects (Krishnan *et al*, 1988; Dolan *et al*, 1990; Fujikawa *et al*, 1993; Krishnan, 1993; Greenwald *et al*, 1996; Steffens *et al*, 1999; Kumar *et al*, 2000; Tupler *et al*, 2002), but few of these studies examined the location of WMLs. Using an objective method of quantifying WML volume within each lobe, we have confirmed reports (Greenwald *et al*, 1998; MacFall *et al*, 2001; Taylor *et al*, 2003b; Firbank *et al*, 2004) that the preponderance of WMLs that are different between depressed and control populations occur in the frontal lobe. Although others have proposed there may be differences between groups in other lobes, we did not confirm this finding (Artero *et al*, 2004). Our current approach has several advantages over that used in previous studies, including a larger sample, objective WML volume

Table 2 Follow-Up White Matter Lesion Volumes by Lobe: Association with Depression Status

	Depressed (SE)	Control (SE)	Mean difference	Parameter estimate	t-value	p-value
Total brain WMH lesion volume	7.52 (1.10)	3.82 (1.25)	3.70	3.70	2.23	0.0280
Left hemisphere WMH lesion volume	3.64 (0.51)	2.03 (0.57)	1.61	1.61	2.11	0.0375
Right hemisphere WMH lesion volume	3.87 (0.60)	1.79 (0.68)	2.08	2.08	2.29	0.0242
Total frontal lobe WMH lesion volume	4.95 (0.56)	2.86 (0.63)	2.09	2.09	2.49	0.0145
Left frontal lobe WMH lesion volume	2.38 (0.25)	1.49 (0.29)	0.89	0.89	2.34	0.0214
Right frontal lobe WMH lesion volume	2.58 (0.32)	1.37 (0.36)	1.21	1.21	2.52	0.0135
Total parietal lobe WMH lesion volume	2.47 (0.55)	0.97 (0.63)	1.50	1.50	1.79	0.0763
Left parietal lobe WMH lesion volume	1.22 (0.26)	0.54 (0.30)	0.68	0.67	1.69	0.0938
Right parietal lobe WMH lesion volume	1.25 (0.29)	0.43 (0.33)	0.82	0.82	1.86	0.0653

WMH volumes displayed are least-squares mean volumes, from models controlling for age, depression status, and hypertension; standard error for these volumes are reported rather than standard deviation as they were derived from these models. The statistical parameter estimate, standard error (SE), t-value, and p-value report the influence of depression on WMH lesion volume in general linear models, which also include age and hypertension and independent variables. Models of occipital and temporal WML volumes are not included as the models did not reach statistical significance.

Table 3 Change Over Time in WMH Lesion Volume between Groups

	Depressed (SE)	Control (SE)	Mean difference	Parameter estimate	*t*-value	*p*-value
Total brain WMH lesion volume	1.41 (0.37)	0.73 (0.42)	0.68	0.56	1.21	0.2291
Left hemisphere WMH lesion volume	0.69 (0.19)	0.40 (0.22)	0.29	0.28	1.02	0.3093
Right hemisphere WMH lesion volume	0.71 (0.19)	0.33 (0.2)	0.38	0.28	1.36	0.1779
Total frontal lobe WMH lesion volume	0.78 (0.24)	0.49 (0.27)	0.29	0.36	0.81	0.4217
Left frontal lobe WMH lesion volume	0.36 (0.12)	0.27 (0.14)	0.09	0.18	0.50	0.6168
Right frontal lobe WMH lesion volume	0.42 (0.12)	0.22 (0.14)	0.20	0.19	1.07	0.2878
Total parietal lobe WMH lesion volume	0.60 (0.14)	0.25 (0.16)	0.35	0.22	1.65	0.1027
Left parietal lobe WMH lesion volume	0.32 (0.08)	0.13 (0.09)	0.19	0.12	1.60	0.1134
Right parietal lobe WMH lesion volume	0.28 (0.07)	0.12 (0.08)	0.16	0.10	1.61	0.1102

WMH volumes displayed are least-squares mean volumes of the difference between scans, derived from models controlling for age, depression status, and hypertension; standard error for these volumes are reported rather than standard deviation as they were derived from these models. The statistical parameter estimate, standard error (SE), *t*-value, and *p*-value report the influence of depression on WMH lesion volume in general linear models, which also include age and hypertension and independent variables. Models of occipital and temporal WML volumes are not included as the models did not reach statistical significance.

measurements, and using an atlas-defined definition of lobes. These findings also support the body of evidence implicating frontal lobe regions as being particularly important in the pathogenesis of depression.

We did not demonstrate a statistically significant difference in the change of WML volumes between groups over the study period. However, our point estimates of volume change in the total brain, and frontal and parietal lobes were persistently higher in the depressed group. The inability to demonstrate a statistically significant difference was likely due to a relatively short follow-up period and a sample size insufficient to detect a difference over the study period; however, the change we report is comparable to that found in other longitudinal studies investigating either total (Taylor *et al*, 2003a) or deep white matter lesion volume (Cook *et al*, 2004). Other studies have demonstrated that WMLs do increase in severity and volume over time, and that greater change is associated with depression outcomes (Nebes *et al*, 2002; Taylor *et al*, 2003c).

Although there was a trend that depressed subjects may also exhibit greater WML volumes in the parietal lobe, this did not reach a level of statistical significance. Although this may reflect that WMLs in the parietal lobe do not contribute to the pathogenesis of depression, the trend we observed may instead indicate that this study was underpowered to detect a real difference between groups. Although some have associated parietal WMLs with depression (Artero *et al*, 2004), others have not found such an association (Firbank *et al*, 2004). However, given reports of reductions in parietal gray matter in depression (Ballmaier *et al*, 2004), and an association between parietal lobe volume and cognitive deficits in depression (Simpson *et al*, 2001), more research is needed into the role of the parietal lobe in depression.

Our models of WML volumes in the occipital and temporal lobes did not reach levels of statistical significance. This may be due to the same reasons discussed above, or due to only a small number of subjects exhibiting WMLs in these lobes. However, other possibilities exist, such as how factors other than age, depression, or hypertension may contribute to their development.

Although large compared with other imaging studies, sample size is a limitation of the study, particularly when considering the longitudinal analyses. Additionally, other studies have used FLAIR (fluid-attenuated inversion recovery) MR imaging to detect WMLs, which were not available for use when the presently reported data was gathered. While WMLs were detected reliably in this study, other studies that used FLAIR may have greater sensitivity to smaller lesions and different criteria for classification of WML. Another limitation is our measure of hypertension, which was a simple self-report of the presence or absence of a diagnosis; such an approach may underestimate true disease prevalence, and provides no objective measure of disease severity. This limitation, along with the smaller sample size, may have contributed to why we did not find an association between hypertension and WML volume, which may be a false-negative result as it is different from studies examining larger samples (Taylor *et al*, 2005). Finally, we did not examine other potential risk factors such as smoking or hyperlipidemia, although these may not contribute to lesion development (Uehara *et al*, 1999; Saitoh *et al*, 2002). Of note, questions of medical comorbidity are particularly important for questions of etiology, or when investigating overall differences between groups. When considering issues of WML volume within specific locations, they may be less important. However, given that depressed elders may have higher levels of medical comorbidity than do nondepressed elderly samples (Taylor *et al*, 2004), it is important to adjust for this difference, and future studies should have more comprehensive and objective measures of medical burden.

Another important avenue for future research is further investigation of lobar change in WML volume over time, and how it may be related to type and intensity of antidepressant therapy. Over the 2-year study period, depressed subjects generally had greater change in WML volume in the frontal and parietal lobes than did control subjects, although likely due to the small sample size, this did not reach a level of statistical significance. In addition to including comprehensive measures of medical burden, adequacy of medical treatment should be considered as

well as type and intensity of antidepressant treatment. Any of these factors may hypothetically affect WML progression. This is an important avenue for further research, particularly when combined with advanced MR techniques, such as diffusion tensor imaging fiber tract mapping, which can better describe neural connectivity and identify critical sites where lesion development may directly contribute to the pathogenesis of depression.

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