ORIGINAL ARTICLE

Magnetic Resonance Imaging in Late-Life Depression

Multimodal Examination of Network Disruption

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Context: Disruption of frontal-subcortical and limbic networks is hypothesized to have a key role in late-life depression (LLD) and can be examined using magnetic resonance imaging (MRI) techniques. Gray matter can be examined using T1-weighted MRI, white matter using T2-weighted MRI and diffusion tensor imaging, and functional connectivity in resting-state networks using functional MRI. Although independent MRI studies have supported gray and white matter abnormalities in frontosubcortical and limbic networks and increased functional connectivity in the default-mode network in depression, no study has concurrently examined gray matter, white matter, and functional connectivity.

Objective: To examine whether results of different MRI techniques are complementary, multimodal MRI was used to compare gray matter, white matter, and resting-state networks between LLD and control groups.

Design: Cross-sectional, case-control, multimodal MRI analysis.

Setting: University research department.

Participants: Thirty-six recovered participants with LLD (mean age, 71.8 years) and 25 control participants (mean age, 71.8 years).

Main Outcome Measures: Gray matter was examined across the whole brain using voxel-based morphometry. Subcortical gray matter structures were also automatically segmented, and volumetric and shape analyses were performed. For white matter analysis, fractional anisotropy, axial diffusivity, and radial diffusivity values were examined using tract-based spatial statistics. For resting-state network analysis, correlation coefficients were compared using independent components analysis followed by dual regression.

Results: White matter integrity was widely reduced in LLD, without significant group differences in gray matter volumes or functional connectivity.

Conclusions: The present work strongly supports the hypothesis that white matter abnormalities in frontal-subcortical and limbic networks play a key role in LLD even in the absence of changes in resting functional connectivity and gray matter. Factors that could contribute to the lack of significant differences in gray matter and functional connectivity measures, including current symptom severity, medication status, and age of participants with LLD, are discussed.

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LATE-LIFE DEPRESSION (LLD), typically defined as depression in adults 60 years or older, is a common and disabling illness. Estimates of the prevalence of clinically relevant depressive symptoms in older adults typically range from 10% to 15% and rates of major depression from 1% to 5%.[1-3] With an aging population,[4] the number of older adults with depression is set to rise to unprecedented levels.

Disruption of frontosubcortical and limbic circuitry is hypothesized to have a key role in the pathogenesis of LLD[5] and may involve structural and functional abnormalities. Regarding structural abnormalities, there may be differences in the volume or shape of gray matter (GM) regions and also in the integrity of the connecting white matter (WM) tracts. In terms of functional connectivity, there may be differences in resting-state networks (RSNs), including the default-mode network (DMN), the affective network (AN), and the executive control network (ECN).

Magnetic resonance imaging (MRI) is an ideal tool for investigating network disruption in LLD in vivo, with different MRI sequences allowing various aspects of network disruption to be investigated. Gray matter is most commonly studied using T1-weighted MRI, WM hyperintensities (WMHs) using T2-weighted MRI, and WM integrity using diffusion tensor imaging (DTI). Resting-state functional MRI (fMRI) reflects functional connectivity in neural networks. Many studies have used MRI

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techniques to extract measures of GM, WM, or functional connectivity and have compared measures between depressed and control groups. Overall, the literature supports GM and WM abnormalities in frontosubcortical and limbic networks[6,7] and increased functional connectivity in the DMN in depression.[8-11] However, no study, to our knowledge, has examined GM, WM, and functional connectivity concurrently. To directly explore whether results gained from different techniques are complementary, we used multimodal MRI to examine group differences in GM, WM, and functional connectivity between mainly recovered participants with LLD and control participants.

We examined GM across the whole brain using voxel-based morphometry (VBM). Subcortical GM structures were also automatically segmented, and volumetric and shape analyses were performed. We investigated WM integrity using tract-based spatial statistics (TBSS). In regions that displayed significant differences in fractional anisotropy (FA), we examined differences in axial diffusivity (DA) and radial diffusivity (DR) to gain a greater understanding of what may underlie WM abnormalities in LLD. For example, reductions in FA accompanied by increased DR but no change in DA may represent decreased myelination.[12-16] In contrast, wallerianlike degeneration of WM resulting from GM abnormalities is characterized by reductions in FA accompanied by increases in DR and decreases in DA.[12,17] Also, in the case of wallerianlike degeneration, WM abnormalities would be expected to parallel the pattern of GM abnormalities. We also examined WM abnormalities by rating periventricular and deep WMHs. We examined functional connectivity in the DMN, ECN, and AN using independent components analysis (ICA) followed by dual regression. As there is evidence to support disconnection between anterior and posterior elements of the DMN in aging,[18] functional connectivity in anterior and posterior DMN components was also examined. Significant analyses were to be repeated, with GM maps as an additional covariate, to explore whether differences can be explained by differences in GM volumes.

In line with previous studies, we hypothesized that the LLD group would display (1) reduced GM volumes, particularly in the frontal cortex and the hippocampus[6]; (2) reduced FA in the frontosubcortical and frontolimbic tracts,[7] particularly in the anterior thalamic radiation, which connects the prefrontal cortex and the thalamus, and in the uncinate fasciculus, which connects the frontal and temporal lobes; (3) more severe WMHs[19]; and (4) increased functional connectivity in the DMN.[8-11]

METHODS

PARTICIPANTS

This study was conducted with approval from the Mid and South Buckinghamshire Local Research Ethics Committee. Informed written consent was obtained from all the participants.

Participants with LLD were identified from the general adult and old age psychiatric services of Oxford Health National Health Service Foundation Trust and also directly from the community by word of mouth and advertisements. Control participants were identified from the community. Eligible participants were older than 60 years, with no potentially confounding comorbid medical, psychiatric, or neurologic conditions (including diagnosis of stroke, bipolar disorder, schizophrenia, Alzheimer disease, Parkinson disease, and mild cognitive impairment) and no implanted metallic devices, as required by standard MRI protocols. Participants with controlled hypertension and diabetes were included. Participants with LLD met the *DSM-IV* criteria for major depression in the past, as assessed by an experienced psychiatrist (C.L.A., M.L.M., or K.P.E.) but were not necessarily currently depressed. Control volunteers with a history of memory impairment or psychiatric illness were excluded using the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Research Version, Non-Patient Edition.[20]

CLINICAL ASSESSMENT

All the participants underwent a clinical assessment to determine cognitive impairment (Mini-Mental State Examination and Addenbrooke Cognitive Examination Revised),[21,22] educational level, National Adult Reading Test estimate of Full-Scale Intelligence Quotient,[23] handedness,[24] and Framingham stroke risk.[25] Age at onset, medication status, and current symptom severity were also determined in participants with LLD. Current symptom severity was assessed using the 17-item Hamilton Depression Rating Scale (HAM-D)[26] and the Geriatric Depression Scale.[27] Medications were classified into the following categories: anticonvulsants, antidepressants, antipsychotics, anxiolytics, and lithium salts.

Statistical analysis was performed using a commercially available software program (PASW Statistics, version 18; IBM Corp). Continuous demographic variables were compared between groups using independent-samples *t* tests, and categorical demographic data were compared using χ^2 tests.

MRI ACQUISITION AND ANALYSIS

All the participants underwent MRI at the University of Oxford Centre for Clinical Magnetic Resonance Imaging using a 3.0-T scanner (Trio; Siemens AG) with a 12-channel head coil. High-resolution 3-dimensional T1-weighted MRIs were acquired using a magnetization-prepared rapid gradient-echo sequence (repetition time, 2040 milliseconds; echo time, 4.7 milliseconds; flip angle, 8°; field of view, 192 mm; and voxel dimension, 1-mm isotropic). Whole-brain DTI was performed using an echoplanar imaging sequence (repetition time, 7900/7800 milliseconds; echo time, 98/82 milliseconds; field of view, 240 mm; voxel size, 2.5-mm isotropic; b value, 1000; number of directions, 60; and number of acquisitions, 2). T2-weighted images were also acquired to characterize WMHs (repetition time, 6000 milliseconds; echo time, 91 milliseconds; field of view, 220 mm; and voxel size, $0.7 \times 0.7 \times 4.0$ mm). Whole-brain resting-state fMRI was performed using a gradient echoplanar imaging sequence (repetition time, 2500 milliseconds; echo time, 30 milliseconds; flip angle, 89°; field of view, 192 mm; and voxel dimension, 3.0-mm isotropic). During resting-state fMRI, participants were instructed to lie still in the scanner, keep their eyes open, and refrain from falling asleep. Image analysis was performed using tools from the Oxford Centre for Functional MRI of the Brain (FMRIB) software library (FSL, version 4.1[28]; http://www.fmrib.ox.ac.uk/fsl).

GRAY MATTER

Whole-Brain Volume and Tissue-Type Percentages

T1-weighted images were brain extracted using the Brain Extraction Tool (BET),[29] and partial-volume tissue segmentation

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was performed using the FMRIB automated segmentation tool v4.1 (FAST).[30] Whole-brain (WB) volume was obtained by summing the volumes of GM, WM, and cerebrospinal fluid. The WB volume and GM, WM, and cerebrospinal fluid percentages were compared between the LLD and control groups using a multivariate general linear model, with age and sex as covariates.

Subcortical Structures

Subcortical brain segmentation and shape (vertex) analysis of the amygdala, caudate, pallidum, putamen, and thalamus was performed using the FMRIB Integrated Registration and Segmentation Tool (FIRST).[31] The FIRST is an automated model-based subcortical segmentation tool trained using manually labeled images from the Center for Morphometric Analysis, Massachusetts General Hospital.

T1-weighted images were aligned to MNI152 space at 1-mm resolution using a 2-stage (amygdala, caudate, pallidum, putamen, thalamus) or 3-stage (hippocampus) affine registration. Next, based on the learned models, linear combinations of shape modes of variation were searched for the most probable shape instance given the observed intensities in the T1-weighted image. This search resulted in a mesh composed of a set of triangles, with the apex of adjoining triangles called a *vertex*. Each mesh is composed of a fixed number of connected vertices for each structure so that the spatial location of corresponding vertices can be compared between groups. A boundary correction method was used to classify boundary voxels in the volumetric output for each structure. The registrations and subsequent segmentations were manually checked for errors; none were found.

Volumes of each of the subcortical structures were extracted and compared using a multivariate general linear model, with age, sex, and WB volume as covariates. Vertex-wise statistics were performed using the FIRST, with age, sex, and WB volume included as confound regressors. The FIRST uses a multivariate general linear model to test differences in mean vertex location between groups, using the Pillai trace to derive F statistic values. False discovery rate correction for multiple comparisons was then applied to obtain thresholded F statistics.

Voxel-Based Morphometry

The VBM analysis was performed using FSL-VBM.[32,33] Gray matter partial-volume images were aligned to MNI152 standard space using the affine registration tool FMRIB Linear Image Registration Tool (FLIRT),[34,35] followed by nonlinear registration using the FMRIB Nonlinear Image Registration Tool (FNIRT),[36,37] which uses a b-spline representation of the registration warp field.[38] The resulting images were averaged to create a study-specific template, to which the native GM images were then nonlinearly reregistered. The registered partial-volume images were then modulated (to correct for local expansion or contraction) by dividing by the Jacobian of the warp field. The modulated segmented images were smoothed using an isotropic gaussian kernel with a sigma of 3 mm. Finally, voxelwise statistics were performed using "randomize," a permutation-based inference tool for nonparametric statistical thresholding that corrects for multiple comparisons across space.[39] The significance threshold for between-group differences was set at $P < .05$ using the threshold-free cluster enhancement (TFCE) option, with age and sex included as confound regressors.[40] As modulation in FSL-VBM is based only on the nonlinear registration stage, rather than on the affine and nonlinear stages of registration, it was not necessary to also include WB volume as a confound regressor.

WHITE MATTER

The DTI data were manually checked, and artifacts were removed before eddy-current correction was run to correct for eddy-current–induced distortions and head motion.

Tract-Based Spatial Statistics

Analysis of the DTI data was performed using TBSS.[41] The FA images were created by fitting a tensor model to the raw diffusion data using the FMRIB Diffusion Toolbox and then were brain extracted using the Brain Extraction Tool.[29] All the participants' FA data were then aligned into a common space using the FMRIB Nonlinear Image Registration Tool.[36,37] Next, the mean FA image was created and thinned to create a mean FA skeleton that represents the centers of all tracts common to the group. Each participant's aligned FA data were then projected onto this skeleton. The nonlinear warps and skeleton projection stages were then repeated using DA and DR values.

All voxelwise statistics were performed using "randomize,"[39] with age and sex included as confound regressors. The significance threshold for between-group differences was set at $P < .05$ using the TFCE option.[40] Group differences in FA were investigated across the whole skeleton, and group differences in DA and DR were examined in regions where FA was significantly different.

To aid in the localization of significant differences in FA, skeleton masks (tracts of interest [TOIs]) were created for the anterior thalamic radiation; genu, body, and splenium of the corpus callosum; cingulum; corticospinal tract; fornix; inferior longitudinal fasciculus; superior longitudinal fasciculus; and uncinate fasciculus. The TOI were based on the ICBM-DTI-81 white-matter labels atlas and the JHU (Johns Hopkins University) white-matter tractography atlas in the FSL atlas tool and on the *MRI Atlas of Human White Matter*.[42] The percentage of mask voxels that were significantly different in FA was calculated for each TOI. To aid in the display of results, mean FA, DA, and DR in voxels significantly different in FA in each TOI were converted to standardized z scores based on the mean and standard deviation of the control group. Signs were reversed for DA and DR so that reduced z scores represented increased DA and DR values in LLD.

WM Hyperintensities

Periventricular and deep WMHs were rated using the modified Fazekas scale,[43] which ranges from 0 to 3. Scans were assessed independently by 2 raters blinded to diagnosis, and differences were resolved by consensus. For periventricular and deep WMHs, the number of scans rated 2 or 3 was below 5 for the control and LLD groups. As a result, scores of 1 to 3 were collapsed into a single group before χ^2 tests were performed.

Voxel-Based Morphometry

A VBM analysis using WM partial-volume images was performed using FSL-VBM.[32,33] Voxelwise statistics were performed using "randomize,"[39] with age and sex included as confound regressors. The significance threshold for between-group differences was set at $P < .05$ using the TFCE option.[40]

FUNCTIONAL CONNECTIVITY

The FMRI data were manually checked, and volumes with major artifacts were replaced by the mean of the preceding volume and the following volume. Group-averaged RSNs were de-

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Table 1. Demographic Data by Group

Characteristic	Control Group (n = 25)	LLD Group (n = 36)	*P* Value
Sex, F/M, No.	16/9	24/12	.83
Age, mean (SD) [range], y	71.76 (7.30) [60 to 89]	71.83 (7.71) [61 to 89]	.97
Years of education, mean (SD) [range]	14.56 (3.08) [10 to 22]	13.94 (3.74) [9 to 24]	.56
FSIQ score, mean (SD) [range]	122.35 (5.08) [103 to 128]	119.85 (7.91) [88 to 128]	.17
Cognitive impairment, mean (SD) [range]			
ACE-R score	95.20 (5.04) [77 to 100]	91.50 (6.26) [71 to 100]	.02[a]
MMSE score	29.48 (0.71) [28 to 30]	28.97 (1.36) [25 to 30]	.09
Framingham stroke risk score, mean (SD) [range]	10.48 (4.16) [5 to 19]	10.64 (4.11) [4 to 19]	.97
Handedness score, mean (SD) [range]	21.32 (9.59) [–24 to 24]	20.33 (9.86) [–24 to 24]	.70
Age at onset, mean (SD) [range], y	NA	45.39 (18.97) [10 to 78]	NA
Severity, mean (SD) [range]			
HAM-D score	NA	4.19 (4.77) [0 to 18]	NA
GDS score	NA	3.83 (3.47) [0 to 11]	NA
Current medication			
No. of medications, mean (SD) [range]	NA	1.44 (0.77) [0 to 3]	NA
Medication free, No.	NA	1	NA
Anticonvulsants, No.	NA	33	NA
Antidepressants, No.	NA	7	NA
Antipsychotics, No.	NA	5	NA
Anxiolytics, No.	NA	4	NA
Lithium salts, No.	NA	0	NA

Abbreviations: ACE-R, Addenbrooke Cognitive Examination Revised; FSIQ, Full-Scale Intelligence Quotient; GDS, Geriatric Depression Scale; HAM-D, Hamilton Depression Rating Scale; LLD, late-life depression; MMSE, Mini-Mental State Examination; NA, not applicable.
[a] Data shown indicate statistical significance ($P < .05$).

fined using probabilistic ICA[44] as implemented in Multivariate Exploratory Linear Decomposition into Independent Components (MELODIC) Version 3.09, part of the FSL. The following data preprocessing was applied to the input data: masking of nonbrain voxels, voxelwise de-meaning of the data, and normalization of the voxelwise variance. Preprocessed data of 25 participants with LLD and 25 control participants were whitened and projected into a 25- or 70-dimensional subspace using principal component analysis. Twenty-five– and 70-dimensional subspaces were chosen to identify the major networks and subnetworks, respectively, in line with previous studies.[45-47] The whitened observations were decomposed into sets of vectors that describe signal variation across the temporal domain (time courses), the participant domain, and the spatial domain (spatial maps) by optimizing for nongaussian spatial source distributions using a fixed-point iteration technique.[48] Estimated component maps were divided by the standard deviation of the residual noise and were thresholded by fitting a mixture model to the histogram of intensity values.[44] The RSNs of interest were identified based on previously defined maps.[10,49]

Dual regression was then used to identify individual temporal dynamics and associated spatial maps of RSNs of interest in all the participants.[46] First, spatial regression was performed using ICA spatial maps in a linear model fit against each participant's fMRI data set, resulting in matrices that describe temporal dynamics for each component in each participant. Second, temporal regression was performed using each participant's time-course matrices in a linear model fit against his or her fMRI data set, resulting in participant-specific spatial maps.

Voxelwise statistics were performed using "randomize,"[39] with age and sex included as confound regressors. The significance threshold for between-group differences was set at $P < .05$ using the TFCE option.[40] Group differences were subsequently spatially masked using a binary image of group activation maps of the network under investigation.

DEPRESSION SEVERITY

Partial correlation analyses were performed between depression severity and WB volume, with age and sex as covariates, and between depression severity and subcortical volumes, with age, sex, and WB volume as covariates. For FSL-VBM, TBSS, and RSN analyses, the significance threshold with symptom severity was set at $P < .05$ using the TFCE option in "randomize," with age and sex included as confound regressors.

RESULTS

No significant differences were noted between the LLD and control groups for sex, age, educational level, Full-Scale Intelligence Quotient score, Mini-Mental State Examination score, Framingham stroke risk, or handedness (**Table 1**). The LLD group had significantly lower Addenbrooke Cognitive Examination Revised scores compared with the control group. Twenty-seven participants with LLD had HAM-D scores indicative of remission (HAM-D score ≤7), 8 had scores indicative of mild depression (HAM-D score, 8-13), and 1 had a HAM-D score indicative of moderate depression (HAM-D score, 18). Most participants with LLD were currently receiving antidepressant drug treatment.

GRAY MATTER

The WB volume was significantly reduced in the LLD group (**Table 2**). There were no significant differences between groups in the percentage of GM, WM, or cerebrospinal fluid or in the volume of any subcortical struc-

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Table 2. Volumetric Results[a]

Region	Control Group	LLD Group	*P* Value
Whole brain, mean (SD), cm^3	1522 (140)	1457 (140)	.03[b]
GM, mean (SD), %	37.2 (1.7)	37.3 (2.0)	.91
WM, mean (SD), %	36.0 (1.6)	35.9 (1.9)	.76
CSF, mean (SD), %	26.8 (2.6)	26.9 (3.1)	.91
Amygdala, mean (SD), mm^3			
Left	1243 (243)	1132 (184)	.36
Right	1157 (338)	1088 (271)	.86
Caudate, mean (SD), mm^3			
Left	3375 (300)	3171 (427)	.14
Right	3553 (326)	3379 (493)	.45
Hippocampus, mean (SD), mm^3			
Left	3640 (490)	3539 (453)	.71
Right	3735 (548)	3602 (494)	.69
Pallidum, mean (SD), mm^3			
Left	1837 (307)	1724 (435)	.81
Right	1781 (254)	1740 (481)	.69
Putamen, mean (SD), mm^3			
Left	4470 (424)	4279 (792)	.54
Right	4487 (407)	4273 (708)	.39
Thalamus, mean (SD), mm^3			
Left	7286 (687)	6968 (827)	.44
Right	7034 (702)	6721 (807)	.48

Abbreviations: CSF, cerebrospinal fluid; GM, gray matter; LLD, late-life depression; WM, white matter.

[a] Age and sex were included as covariates for comparisons of whole-brain volume and GM, WM, and CSF percentage. Age, sex, and whole-brain volume were included as covariates for comparisons of subcortical volumes.

[b] Data shown indicate statistical significance ($P < .05$), with *P* values obtained using a multivariate general linear model.

ture (Table 2). No differences in vertices survived multiple comparison correction in any subcortical structure. No significant differences in GM were detected between the LLD and control groups using FSL-VBM.

WHITE MATTER

There were widespread differences in FA, with 36% of skeleton voxels significantly lower in the LLD group at $P < .05$ and 16% at $P < .01$ (**Figure 1**). There were no regions where FA was significantly higher in the LLD group.

Both DA and DR were then examined in regions of decreased FA. Eighty-three percent of voxels that exhibited a decrease in FA in LLD exhibited a significant increase in DR at $P < .05$ (Figure 1). In contrast, no voxels that exhibited a decrease in FA also exhibited a significant difference in DA.

To aid in the localization of significant differences in FA, TOIs were created for the anterior thalamic radiation; genu, body, and splenium of the corpus callosum; cingulum; corticospinal tract; fornix; inferior longitudinal fasciculus; superior longitudinal fasciculus; and uncinate fasciculus. The results of the TOI analysis are presented in **Table 3**. At least 20% of voxels were significantly reduced in FA at $P < .05$ in all tracts. At least 50% of voxels were significantly reduced in FA at $P < .05$ in the anterior thalamic radiation, corticospinal tract, splenium of the corpus callosum, superior longitudinal fasciculus, and uncinate fasciculus. Standardized *z* scores of mean FA, DR, and DA in voxels significantly reduced in FA in LLD are shown in **Figure 2**.

Fazekas scores for periventricular and deep WMHs are presented in **Table 4**. There were no significant differences between groups in periventricular WMH scores ($\chi^2 = 2.698$, $P = .10$) or deep WMH scores ($\chi^2 = 0.259$, $P = .61$). No significant differences in WM were detected between the LLD and control groups using FSL-VBM.

FUNCTIONAL CONNECTIVITY

The DMN, ECN, and AN components were identified from 25-component ICA (**Figure 3**). The DMN component included medial prefrontal cortex, posterior cingulate cortex, precuneus, and lateral parietal activation. The ECN component included superior and middle frontal gyri and paracingulate activation. The AN included medial prefrontal cortex, subgenual and subcallosal anterior cingulate cortex, and caudate activation.

Posterior and anterior DMN components were identified from 70-component ICA (Figure 3). The posterior DMN component included posterior cingulate cortex, precuneus, and lateral parietal activation. The anterior DMN component included medial prefrontal cortex and anterior cingulate cortex activation. No significant differences in functional connectivity were detected between the LLD and control groups in the DMN, anterior DMN, posterior DMN, ECN, or AN.

DEPRESSION SEVERITY

Depression severity was not significantly correlated with WB volume; percentage of GM, WM, or cerebrospinal fluid; or subcortical volume (eTable; http://www.archgenpsychiatry.com). No significant correlations between symptom severity and GM were detected using FSL-VBM, between symptom severity and FA using TBSS, or between symptom severity and functional connectivity in the DMN, ECN, or AN.

POSSIBLE CONFOUNDERS

The number of participants with LLD, combined with the number of MRI measures, prevented thorough analyses of all possible factors that may have influenced the results. Such measures include current symptom severity, age at onset, medication status, and age of participants with LLD. We did, however, perform a preliminary analysis of group differences in FA with the patient group divided into early-onset depression (first episode of major depression before age 60 years, n = 23) and late-onset depression (first episode of major depression at or after age 60 years, n = 13) and into remitted depression (HAM-D score ≤7, n = 27) and nonremitted depression (HAM-D score >8, n = 9). Although the early- and late-onset depression groups displayed significant reductions in FA compared with the control group, differences were much more widespread for the late-onset depression group (eFigure). As early- and late-onset depression may have different etiologies, we explored the relationships between age at onset and MRI measures in greater detail elsewhere. The remitted and nonremitted depression sub-

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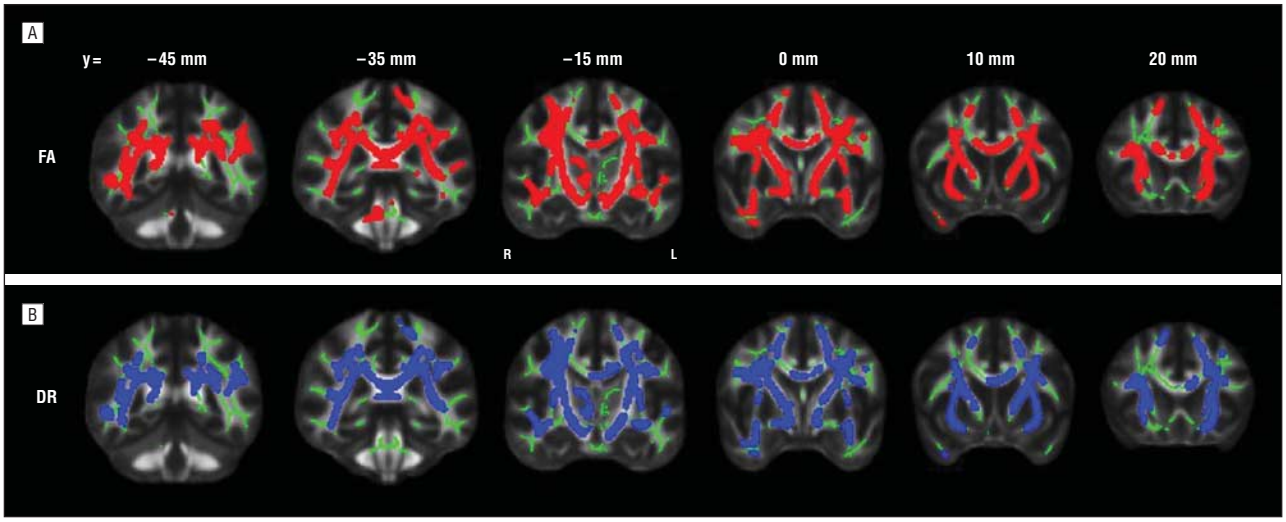

Figure 1. Localization of group differences in fractional anisotropy (FA) and radial diffusivity (DR). A, Regions significantly reduced ($P<.05$) in FA in late-life depression are shown in red, overlaid on a green skeleton. B, Regions significantly increased ($P<.05$) in DR, in addition to being significantly reduced in FA, are shown in blue, again overlaid on a green skeleton. Significant regions are dilated for illustrative purposes.

groups displayed a similar pattern of FA changes (eFigure, C and D).

COMMENT

We used multimodal MRI to compare GM, WM, and functional connectivity in 36 participants with LLD and 25 controls. Volumetric and shape analyses were used to assess subcortical GM structures; global analysis of GM was performed using VBM. No significant differences in subcortical GM structures were detected with either volumetric or shape analysis. Also, VBM did not identify any significant differences in GM between the LLD and control groups. Although the lack of significant findings is in contrast to the hypotheses of GM reductions in LLD and some of the literature, it is not unprecedented. For example, several studies[50-56] have not detected significant differences in hippocampal volume between LLD groups or subgroups and control groups. Also, Koolschijn et al[57] did not detect any regions significantly different in GM between the LLD and control groups using VBM.

Integrity of WM in LLD and control participants was investigated using TBSS. As hypothesized, LLD was associated with reduced FA in the frontosubcortical and limbic tracts, with more than 60% of voxels in the anterior thalamic radiation and uncinate fasciculus significant at $P<.05$. In addition, reductions in FA were detected in several other tracts, including the corticospinal tract, superior longitudinal fasciculus, and corpus callosum, thus supporting the existence of diffuse WM damage in depression, albeit with a frontosubcortical emphasis.[58] Reductions in FA were largely accompanied by significant increases in DR but no change in DA, a pattern that has been interpreted as indicative of decreased myelination.[12-16] Although neurobiological interpretations of DTI findings should be made with caution, postmortem studies support the notion of decreased myelination and have identified decreased oligodendrocyte density[59,60] and less intense myelin staining[61] in depression. In addition, microarray studies of postmortem tissue have revealed decreased expression of myelination and myelination-related genes and transcription factors in depression.[62] Given the absence of GM abnormalities, the results do not support the hypothesis that reductions in FA result from wallerianlike degeneration. Also, secondary Wallerian degeneration is characterized by reductions in FA accompanied by increases in DR and decreases in DA,[12,17] a pattern not displayed in the present findings.

Table 3. Localization of Group Differences in Fractional Anisotropy

Tract of Interest	Voxels Decreased Significantly, %	
	$P<.05$	$P<.01$
Whole Skeleton	36	16
Anterior thalamic radiation	62	39
Cingulum	20	10
Corpus callosum		
Body	45	12
Genu	48	0
Splenium	66	34
Corticospinal tract	59	37
Fornix	23	6
Inferior longitudinal fasciculus	38	14
Superior longitudinal fasciculus	60	24
Uncinate fasciculus	64	40

In contrast to the hypotheses, an increase in WMHs in LLD was not detected. Although this finding differs from much of the literature (reviewed by Herrmann et al[19]), several studies[53,58,63,64] of LLD in which groups were matched for vascular risk factors have not found increases in WMH scores or volume. There are a variety of possible explanations; for example, it may be that it is the regional specificity of WMHs, rather than the overall volume or severity rating, that is important in LLD. In support of this hypothesis, Sheline et al[64] found that

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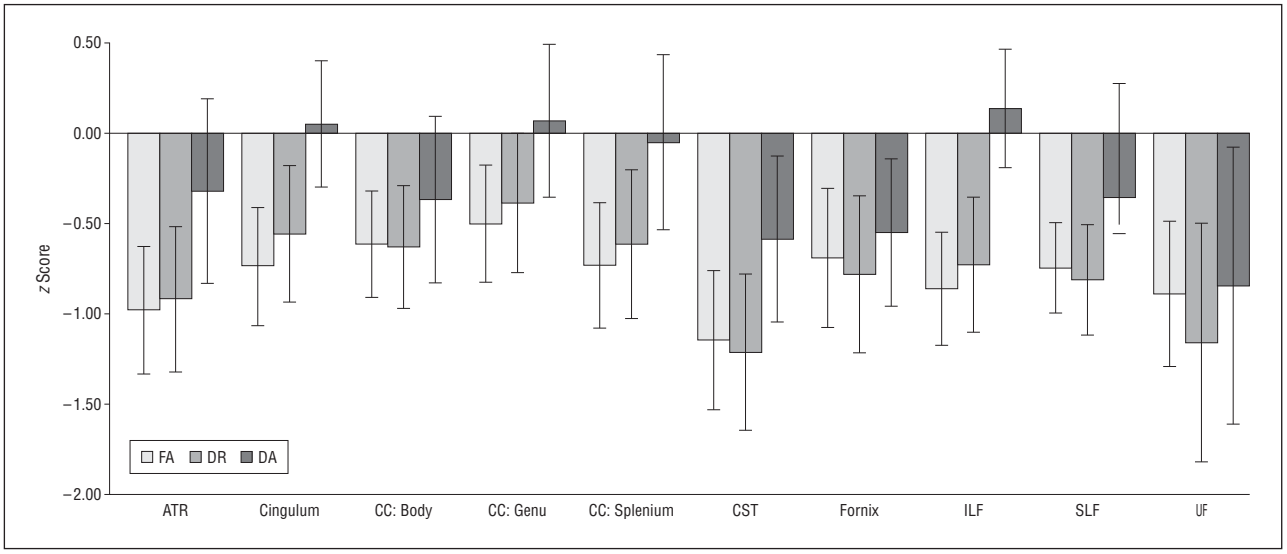

Figure 2. *z* Scores of fractional anisotropy (FA), radial diffusivity (DR), and axial diffusivity (DA) in voxels significantly reduced in FA in late-life depression (LLD). Data are given as mean *z* score ±2 SEs of the LLD group. Negative *z* scores represent reductions in FA and increases in DR and DA in LLD. By definition, *z* scores for the control group are zero. ATR indicates anterior thalamic radiation; CC, corpus callosum, CST, corticospinal tract; ILF, inferior longitudinal fasciculus; SLF, superior longitudinal fasciculus; and UF, uncinate fasciculus.

Table 4. Fazekas Scores

Fazekas Score	Participants, No. (%) Control (n = 25)	LLD Group (n = 31)
Periventricular WMHs		
0	9 (36)	18 (58)
1	14 (56)	12 (39)
2	1 (4)	1 (3)
3	1 (4)	0
Deep WMHs		
0	12 (48)	17 (55)
1	12 (48)	11 (35)
2	0	3 (10)
3	1 (4)	0

Abbreviations: LLD, late-life depression; WMH, white matter hyperintensities.

although the total volume of WMHs was equal between the LLD and control groups, the LLD group had more WMHs in tracts of the dorsolateral prefrontal cortex circuit. Also, in a postmortem study, Thomas et al[65] found that ischemic deep WMHs were more frequently located in the dorsolateral prefrontal cortex compared with the anterior cingulate cortex and occipital cortex in participants with LLD. However, in addition to failing to find overall differences in WMH volume, Shimony et al[58] also found no differences between groups in WMH volume in any subregion despite widespread reductions in FA. As a result, the authors suggested that WMHs represent a small portion of the overall WM abnormality in depression, with DTI metrics being far more sensitive measures of WM abnormalities compared with WMHs.

Differences in functional connectivity in the DMN, ECN, and AN between the LLD and control groups were investigated using ICA followed by dual regression. No significant differences in functional connectivity were detected between the LLD and control groups in the DMN. Although this finding is in contrast to the hypothesis and findings from several previous studies,[8-11] 2 other studies[66,67] also have not found differences in connectivity between depressed and control groups in the DMN. Differences in functional connectivity were also not detected in the anterior DMN, posterior DMN, ECN, or AN.

METHODOLOGICAL CONSIDERATIONS

The strengths of this study include the data acquisition parameters and analysis techniques: DTI acquisition entailed 2 repeats of 60-direction DTI. These parameters exceed the suggested minimum of 30 directions estimated to be necessary for robust estimation of FA and mean diffusivity[68] and are in contrast to many of the DTI studies of depression performed to date.[7] This study also represents the first TBSS study of LLD. Using TBSS in the analysis of DTI data allowed examination of the extent and spatial localization of differences in FA compared with region-of-interest approaches and minimized registration errors compared with VBM. Assessment of WMHs using the Fazekas scale did not allow direct comparison with the anatomy of WMHs and is a limitation of this study.

The main limitation of this study, however, is the small number of participants. Also, although all voxelwise image analyses contained correction for multiple comparisons, we did not correct for multiple comparisons across different modalities.

The relatively low HAM-D score of the LLD group in this study compared with that of many previous studies is a key factor that may have contributed to the lack of significant differences in GM and functional connectivity. A recent meta-analysis[69] found that patients during depressive episodes had significantly smaller hippocampal volume than did patients during remission. Increased severity has been associated with reduced volume in the hippocampus[50] and orbitofrontal cortex,[70]

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although several negative results exist.[51,57,71-73] Also, increases in DMN activity in depression have been attributed to increases in self-referential focus,[74,75] which may be evident only in participants who are currently depressed. Although 2 studies[10,11] have detected a significant correlation between functional connectivity and HAM-D score in depression, 3 studies[67,76,77] did not find any significant correlations between functional connectivity and symptom severity. Symptom severity was not associated with MRI measures of GM, WM, or functional connectivity in this study. However, as the LLD group did not include participants with HAM-D scores higher than 18, representing severe or very severe depression, the analyses may have been insufficiently powered. This study also assessed only current symptom severity. The cross-sectional nature of this study meant it was impossible to accurately determine the duration of remission or the current episode, which may have also influenced the results. Thus, it remains a possibility that the symptom severity of the LLD group contributed to the absence of significant differences between the LLD and control groups in GM and functional connectivity measures.

Intertwined with current symptom severity is the issue of medication status. As most participants with LLD were receiving antidepressant medications, severity of symptoms will have been confounded to a point by treatment resistance; that is, participants with LLD and higher HAM-D scores may have been more treatment resistant. Thus, any ostensible relationships between symptom severity and MRI measures would have been difficult to interpret. The limited number of participants with LLD in this study, combined with only 2 participants being currently medication free, prevented meaningful analyses of the influence of medication on MRI measures. However, a thorough investigation of medication by Versace et al[78] that divided medications by class and also examined total medication load reported no association between DTI measures and current medication.

The age of the participants may also impact functional connectivity results. This is the first study, to our knowledge, of the DMN, AN, and ECN in LLD; in all 4 previous studies[8-11] that detected increased connectivity in the DMN, the average age of the depressed group was younger than 40 years. Because there is evidence of disconnection between the anterior and posterior DMN components with aging,[18] anterior and posterior DMNs were examined separately, but this also did not identify any regions significantly different in functional connectivity.

Note that the lack of differences in GM and functional connectivity measures may be interrelated. For example, differences in GM may contribute to differences in functional connectivity. Future studies using multimodal analysis techniques, such as linked ICA, to simultaneously model and discover common features across different modalities[79] will be able to further clarify the relationships among GM, WM, and functional connectivity in LLD. Also, longitudinal studies that scan medication-free participants at first diagnosis and again after treatment would allow greater examination of the role of structural and functional abnormalities in the pathogenesis of LLD and would also allow assessment of whether structural and functional abnormalities in LLD represent state or trait characteristics. Finally, a key issue for future studies to address is the specificity of WM changes to LLD. Although DTI has been widely used to detect WM abnormalities in various psychiatric illnesses,[80] studies that have directly compared patients with a diagnosis of major depression with patients with diagnoses of other psychiatric illnesses[78] remain rare.

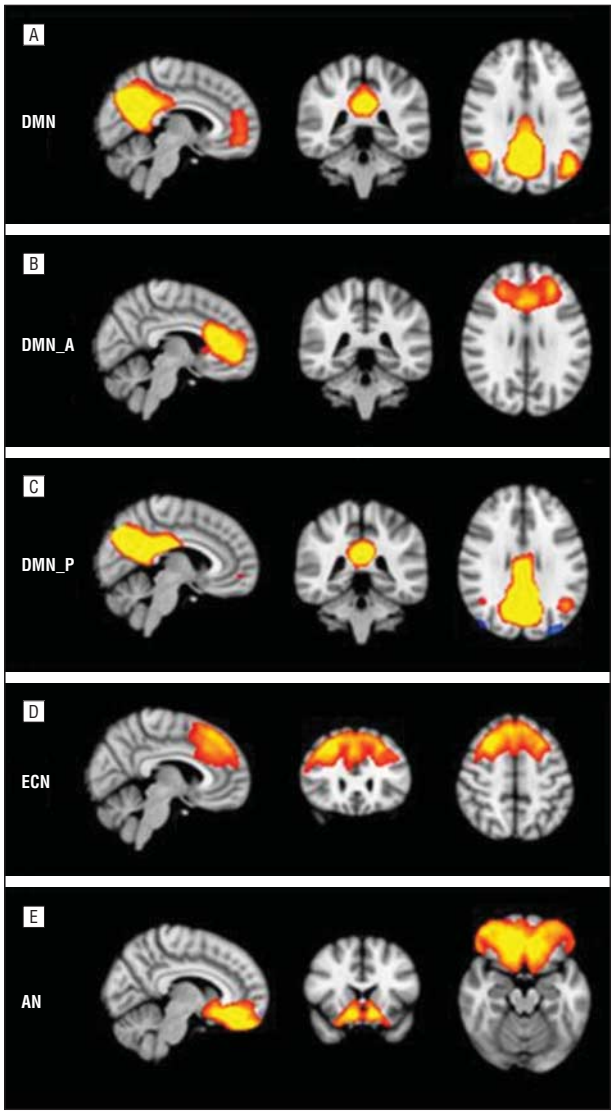

Figure 3. Independent components analysis–defined networks: default-mode network (DMN) (A), anterior DMN (B), posterior DMN (C), executive control network (ECN) (D), and affective network (AN) (E).

In conclusion, overall, these results strongly support the hypothesis that WM abnormalities in frontal-subcortical and limbic networks have a key role in mainly recovered LLD, even in the absence of changes in resting functional connectivity and GM.

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