No Changes in Gray Matter Density or Cortical Thickness in Late-Life Minor Depression

To the Editor: Minor depression (MinD) is a subclinical depressive disorder affecting nearly 10% of the elderly population.[1] According to the fourth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM-IV*), a minor depressive episode requires 2 to 4 depressive symptoms that are present for at least 2 weeks. Minor depressive disorder is diagnosed when a lifetime history of major depressive disorder (MDD) is excluded.[2] Although MinD may seem transient, its consequences are often severe.[3,4] The pathophysiology of MinD remains largely unexplored.[1]

We analyzed structural magnetic resonance images (MRI) of 38 subjects with MinD and 80 healthy controls (aged 60–79 years) using voxel-based morphometry (VBM) and region-of-interest (ROI) analyses of gray matter density and cortical thickness.

According to meta-analyses[5–10] of structural brain changes in MDD, we hypothesized disease-specific decreases of gray matter density in the bilateral anterior cingulate cortex (ACC), hippocampus, and amygdalae and the right dorsomedial frontal cortex. In the ROI analysis, we expected decreased gray matter density within the meta-analytically derived[11] mask (Supplementary eFigure 1) (the largest cluster: left insula, temporal pole, inferior frontal, superior temporal gyrus) and cortical thinning bilaterally in the medial orbitofrontal cortex, fusiform gyrus, insula, rostral anterior, and posterior cingulate cortex and unilaterally in the left middle temporal, right inferior temporal gyrus, and right caudal ACC.[12]

Methods. We included 38 subjects with a MinD episode and 80 healthy subjects (aged 60–79 years) from the community-based LIFE-Adult study[13] (see Supplementary Methods). The study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethics Committee of the University of Leipzig. Subjects provided written informed consent prior to participation.

Participants underwent the Structured Clinical Interview for *DSM-IV* (SCID),[14] cognitive testing, and MRI. MinD episode was diagnosed on the basis of *DSM-IV* criteria.[2] High-resolution structural brain images were obtained with a 3T MAGNETOM Verio (Siemens; Erlangen, Germany) scanner using standard Alzheimer's Disease Neuroimaging Initiative protocol.[15]

Structural images were preprocessed using VBM in SPM8 (www.fil.ion.ucl.ac.uk/spm) as previously described.[16] Gray matter density across the whole brain was compared between MinD and control groups using 2-sample *t* test corrected for gender, age, and degree of white matter hyperintensities, measured on the Fazekas scale.[17] In a second analysis, we used a mask for reduced gray matter density in MDD, obtained from the recent meta-analysis.[11] Further analysis was performed using ROIs based on the meta-analysis of cortical thickness in MDD.[12] Structural images were preprocessed using Freesurfer segmentation (http://surfer.nmr.mgh.harvard.edu) and compared between the groups using analysis of covariance in SPSS version 21 (IBM; Chicago, Illinois).

Results. Demographic and clinical data of participants are presented in the Supplementary Results in Supplementary eTable 1. In VBM, we found a reduction of gray matter density in the bilateral precentral gyri, right superior frontal gyrus, and left thalamus using a voxel threshold of *P* < .001 (Figure 1). However, these differences did not reach statistical significance after correction for multiple comparisons.

Comparing gray matter density within the meta-analytically derived mask did not yield any significant differences between the groups. Reanalyses of the imaging data with sex or age as single covariate, with age- and gender-matched controls, or in subgroups with and without a history of depression compared to controls confirmed nonsignificant effects. The ROI analysis based on Freesurfer segmentation did not show any significant cortical thinning (Supplementary eTable 2).

We used 3 methods to assess structural brain changes in later life MinD. However, we obtained no evidence for structural gray matter abnormalities similar to those in MDD or in previously reported MinD samples.[18,19] Major limitations of the study are our exceptional inclusion of subjects in late life, with an age of 60 years or older, and inclusion of subjects having a depressive episode in anamnesis. Nevertheless, our sample was larger than those in previous studies,[18,19] deeply phenotyped, and recruited from a representative population-based study. A further reason for the

Figure 1. Reduction of Gray Matter Density in Patients With Minor Depression Compared to Healthy Controls[a]
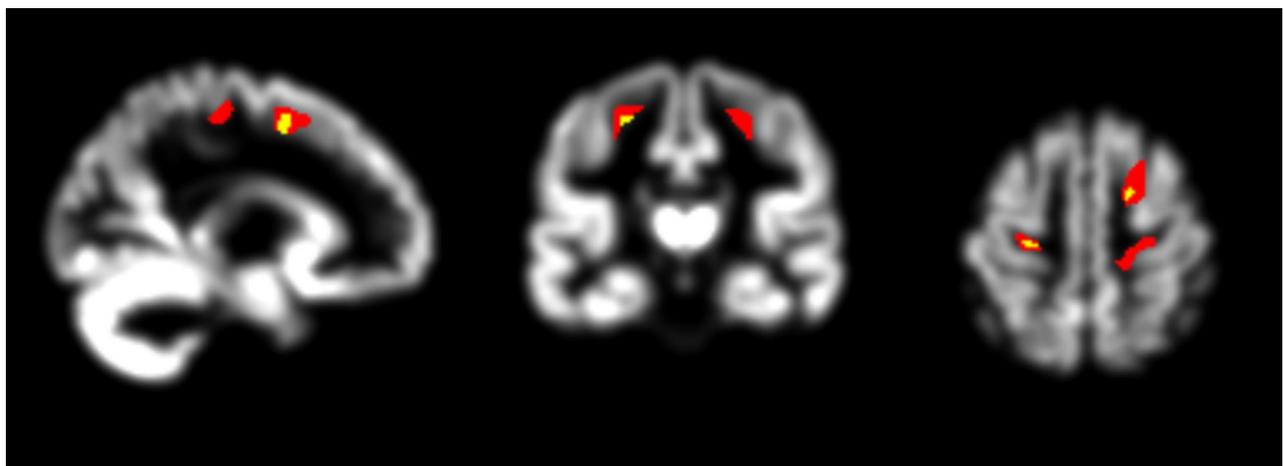
[a]Corrected for age, sex, and Fazekas score. Regions of decreased gray matter density in minor depression are displayed in red for voxelwise threshold of *P* < .01 (*t* > 2.4) and yellow for voxelwise threshold of *P* < .001 (*t* > 3.3).

absence of evidence for structural brain alterations in MinD might be its heterogeneity. Before MinD is hypothesized as a functional syndrome or adjustment disorder, it should be further investigated with respect to endophenotypes of MDD, such as a glutamatergic deficit in the ACC,[20] or in combination with disease-specific biomarkers.[21–23]

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Supplementary material follows this letter.

Supplementary Material

Letter Title: No Changes in Gray Matter Density or Cortical Thickness in Late-Life Minor Depression

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List of Supplementary Material for the letter

Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published letter. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary material

2. METHODS

2.1 Study Participants and selection criteria

Thirty-eight subjects with minor depressive episode and eighty healthy participants were selected from the Leipzig Population based study of adults (LIFE-adult) database. All participants gave written informed consent to participate in the study. The study was approved by the Ethics committee of the Leipzig University. All participants were over 60 years of age (range 60–79 years) and underwent thorough neuropsychiatric assessment using Structured Psychiatric Interview for DSM-IV (SCID), cognitive testing, and MRI scans (for the description of all assessments see Loeffler et al.[1]).

MinD episode was diagnosed according to DSM-IV criteria if the participant exhibited two to four depressive symptoms, including either depressed mood or loss of interest. Depressive symptoms had to be present for at least two weeks prior to the study[2]. Participants with a history of major depression were also included in the study. Using the data from neuropsychological testing, we excluded the subjects with cognitive impairment (mild and major neurocognitive disorder in accordance with DSM-5). Clinical and demographical data were compared using independent sample t-tests or Mann-Whitney U-test, based on the data distributions.

2.2 Magnetic resonance imaging

Structural T1-weighted images were acquired with a 3-Tesla TIM Verio Scanner (Siemens Healthcare, Erlangen, Germany) using three-dimensional magnetization-prepared rapid gradient-echo imaging (3D MP RAGE) sequence (with the following parameters: inversion time, 900 ms; repetition time, 2300 ms; echo time, 2.98 ms; flip angle, 9°; band width, 240 Hz/pixel; image matrix, 256 × 240; 176 partitions; field of view, 256 × 240 × 176 mm^3; sagittal orientation; voxel size, 1 × 1 × 1 mm^3; no interpolation).

2.3 Voxel-based morphometry (VBM)

Gray matter density was assessed using the VBM8 toolbox in SPM8 (www.fil.ion.ucl.ac.uk/spm). Briefly, T1-weighted images were normalized to Montreal Neurological Institute (MNI) space, segmented into three tissue types (gray matter, white matter, and cerebrospinal fluid). Segmented gray matter images were then modulated by Jacobian determinants and smoothed with a Gaussian kernel of 8 mm full width half maximum (FWHM). Smoothed images were then compared between the groups using a two-sample t-test implemented by a general linear model with age, sex, and degree of white matter hyperintensities (Fazekas score) as nuisance covariates. Non-linearly modulated images were compared, therefore, controlling for total intracranial volume was not mandatory. Significant clusters were detected using a voxel-threshold of $p<0.001$. In addition, we tried to detect significant clusters correcting for multiple comparisons using the family-wise error approach with $p<0.05$.

2.4 VBM analysis within the mask

A mask for reductions of gray matter density in major depressive disorder was obtained from the meta-analysis of Wise et al.[3] (Figure 1). Gray matter density within this mask was compared between minor depression and control groups using two-sample t-test corrected for gender, age, and degree of white matter hyperintensities, measured according to Fazekas scale[4] .

Supplementary eFigure 1. Brain mask for decreased gray matter density in Major Depressive Disorder (MDD), derived from the meta-analysis of Wise et al. (2016).
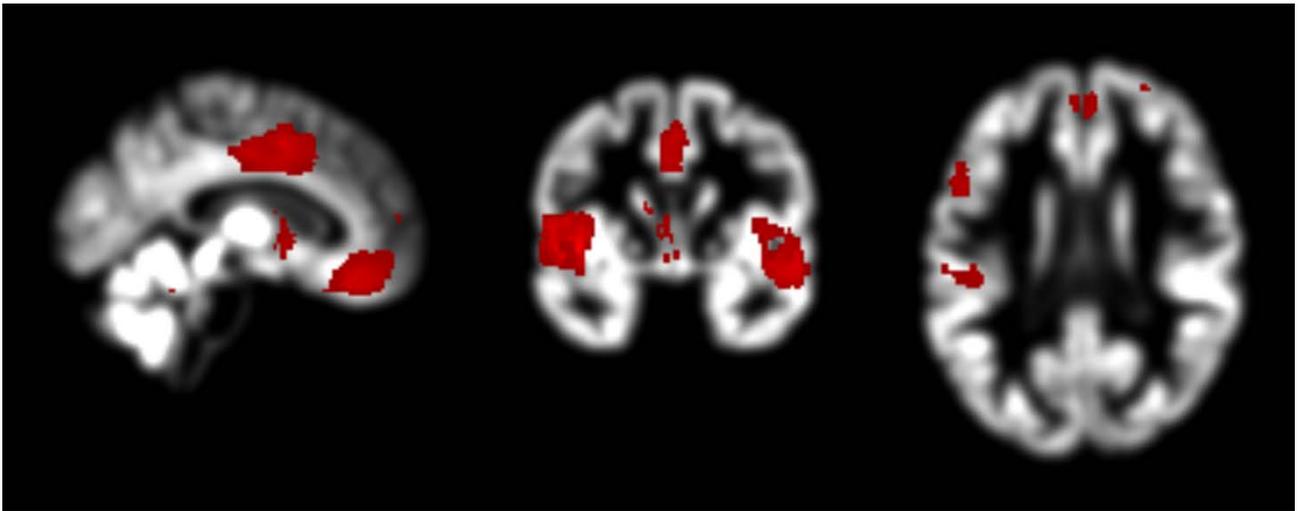
2.5 Region of interest (ROI) analysis based on Freesurfer parcellation

T1-weighted images were preprocessed with Freesurfer Image Analysis Suite (http://surfer.nmr.mgh.harvard.edu). ROIs were selected based on the meta-analysis of cortical thickness data in major depression[5]. The following regions showed cortical thinning in major depression: bilateral medial orbitofrontal cortex, fusiform gyrus, insula, rostral anterior and posterior cingulate cortex and unilaterally in the left middle temporal gyrus, right inferior temporal gyrus, and right caudal ACC. Cortical thickness was compared between the groups using analysis of covariance (ANCOVA) in SPSS version 21 (IBM, Chicago, IL, USA). Due to significant differences in gender distribution between the groups, gender was included in the model as a covariate.

3. RESULTS

3.1 Characteristics of the sample

In this study we included 38 subjects with minor depressive episode and 82 healthy subjects. Demographical and clinical data are presented in Supplementary Table1.

Supplementary eTable 1. Clinical and demographical data of participants.

	Subjects with minor depression	Healthy subjects	p-value
Number of subjects (with a history of depression)	38 (26)	80	
Age (years)	69.9 (4.4)	70.1 (4.2)	0.381
Sex (male/female)	7/31	49/31	<0.001
Fazekas score (0/1/2/3; number of subjects)	8/23/7/0	21/31/11/0	0.292
BMI (kg/m^2)	28.0 (4.9)	28.1 (4.7)	0.430

Data are presented as means (standard deviations, SD). BMI body mass index.

3.2 VBM analysis

In VBM analysis we observed decreased gray matter density in the bilateral prefrontal gyri, right superior frontal gyrus, and left thalamus using a voxel threshold of $p<0.001$ (Figure1). These regions were not significant when family-wise error correction (FWE) or false discovery rate were applied to correct for multiple comparisons.

3.3 Region of interest analysis

Based on Freesurfer image parcellation, we compared cortical thickness in meta-analytically defined regions between the groups. Results of the analysis are depicted in Supplementary Table 2.

Supplementary eTable 2. Comparison of cortical thickness between minor depression and healthy controls.

Region of interest	Cortical thickness in subjects with minor depression Mean (SD), mm	Cortical thickness in healthy subjects Mean (SD), mm	Group effect*, p-value
Left medial orbitofrontal cortex	2.3 ± 0.1	2.3 ± 0.1	0.9
Left fusiform gyrus	2.6 ± 0.1	2.6 ± 0.1	0.6
Left insula	2.8 ± 0.1	2.9 ± 0.1	0.2
Left rostral ACC	2.8 ± 0.2	2.8 ± 0.2	0.4
Left posterior cingulate cortex	2.4 ± 0.1	2.4 ± 0.2	0.8
Left middle temporal gyrus	2.6 ± 0.1	2.7 ± 0.1	0.1
Right medial orbitofrontal cortex	2.2 ± 0.1	2.3 ± 0.1	0.7
Right fusiform gyrus	2.7 ± 0.2	2.7 ± 0.1	0.9
Right insula	2.8 ± 0.2	2.8 ± 0.2	0.2
Right rostral ACC	1.8 ± 0.3	2.7 ± 0.2	0.9
Right posterior cingulate cortex	2.7 ± 0.5	2.3 ± 0.1	0.8
Right inferior temporal gyrus	2.7 ± 0.1	2.7 ± 0.1	0.7
Right caudal ACC.	2.4 ± 0.2	2.4 ± 0.3	0.2

*Analysis of covariance controlled for gender effects.

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