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Supplementary Material

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

Author(s): Maryna Polyakova; Karsten Mueller, Dr.rer.nat; Christian Sander, Dr.rer.nat; Frauke Beyer, Msc; Veronica Witte, Dr.rer.nat; Leonie Lampe, MD; Francisca Then, Dr.rer.nat; Steffi Riedel-Heller, PhD; Karl-Titus Hoffmann, Dr; Arno Villringer, MD; Matthias Leopold Schroeter, MD, PhD; and Peter Schoenknecht, MD

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List of Supplementary Material for the letter

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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).

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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).

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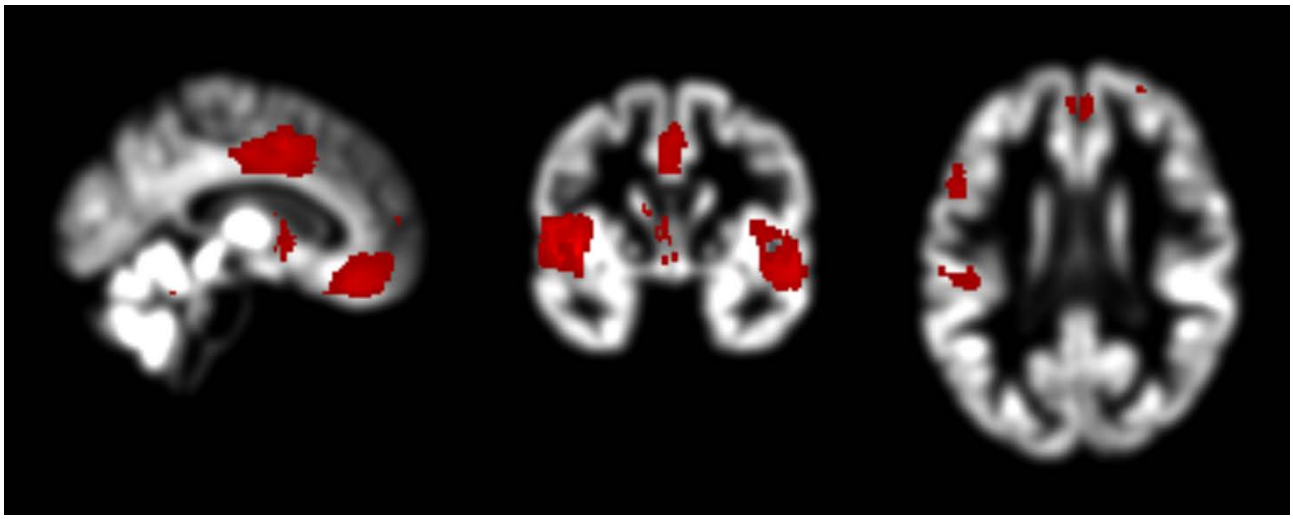

2.5 Region of interest (ROI) analysis based on Freesurfer parcellation

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.

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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.

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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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