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BRAIN MICROSTRUCTURE MAPPING IN MAJOR DEPRESSIVE DISORDER: A PILOT MR STUDY

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INTRODUCTION: Major depressive disorder is a common mental health disorder. Alterations in cortical structures have been identified in this disease, but findings have been variable and inconsistent. Previous studies have illustrated that the cingulate and prefrontal gyrus, along with the amygdala, are involved in emotional processing and the development of abnormal emotional responses in depression.

OBJECTIVE: Our research aims to investigate the neurological structural differences and alterations in ACC, bilateral amygdala, and dmPFC regions in patients with MDD using quantitative MRI (MPF and Diffusion parameters mapping (DPM), including diffusion kurtosis).

MATERIALS AND METHODS: In this study, we utilized advanced quantitative MRI techniques, specifically Diffusion Tensor Imaging, Diffusion Kurtosis Imaging, and Macromolecular Proton Fraction Mapping, to investigate microstructural differences and alterations in the specific regions in patients diagnosed with major depressive disorder.

RESULTS: Our findings revealed no significant interaction between Macromolecular proton fraction Mapping with depressive disorder. However, patients with major depressive disorder exhibited a statistically significant increase in apparent mean, axial and radial diffusivity ($F=6.3$, $p=0.01$, $F=5.0$, $p=0.03$, $F=7.08$, $p=0.01$, respectively) in the bilateral amygdala compared to healthy controls, as well as in mean and radial diffusivity in the anterior cingulate cortex ($F=5.61$, $p=0.02$, $F=7.08$, $p=0.01$, respectively).

DISCUSSION: These findings suggest that altered molecular diffusion characteristics in the amygdala and the anterior cingulate cortex may be specifically associated with major depressive disorder.

CONCLUSIONS: The importance of using new quantitative MRI methods to assess structural changes at the molecular level in the brain is shown, which, ultimately, expands the fundamental understanding of the pathophysiology of depression.

KEYWORDS: MRI, Macromolecular proton fraction, Diffusion Parameters Mapping, major depressive disorder

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КАРТИРОВАНИЕ МИКРОСТРУКТУРЫ ГОЛОВНОГО МОЗГА ПРИ БОЛЬШОМ ДЕПРЕССИВНОМ РАССТРОЙСТВЕ: ПИЛОТНОЕ МР-ИССЛЕДОВАНИЕ

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ВВЕДЕНИЕ: Большое депрессивное расстройство является распространенным нарушением психического здоровья. Изменения в структуре коры головного мозга при этом заболевании сегодня остаются малоизученными, а результаты иссле-

дований неоднозначны и противоречивы. Ранее было показано, что поясная и префронтальная извилины, а также миндалина участвуют в обработке эмоциональных сигналов и развитии аномальных эмоциональных реакций при депрессии.

ЦЕЛЬ: Изучение неврологических структурных различий и изменений в передней поясной коре, миндалине и области дорсомедиальной префронтальной коры у пациентов с БДР с помощью количественной МРТ (МПФ и картирование диффузионных параметров, включая куртозис диффузии).

МАТЕРИАЛЫ И МЕТОДЫ: В работе использовались современные количественные методы магнитно-резонансной томографии (МРТ), а именно диффузионно-тензорная томография, томография куртозиса диффузии и картирование макромолекулярной протонной фракции для изучения микроструктурных различий и изменений в специфических областях мозга у пациентов с большим депрессивным расстройством.

РЕЗУЛЬТАТЫ: Полученные в данной работе результаты не выявили значимой взаимосвязи между содержанием макромолекулярной протонной фракции и депрессивным расстройством. Однако у пациентов с депрессивным расстройством наблюдалось статистически значимое увеличение измеряемого коэффициента средней, осевой и радиальной диффузии ($F=6,3$, $p=0,01$, $F=5,0$, $p=0,03$, $F=7,08$, $p=0,01$ соответственно) билатерально в миндалинах по сравнению с контрольной группой здоровых людей, а также измеряемого коэффициента средней и радиальной диффузии в передней поясной коре ($F=5,61$, $p=0,02$, $F=7,08$, $p=0,01$ соответственно).

ОБСУЖДЕНИЕ: Полученные результаты дают основание полагать, что изменение характеристик молекулярной диффузии в миндалине и передней поясной коре может быть специфически связано с большим депрессивным расстройством.

ЗАКЛЮЧЕНИЕ: Показана важность использования новых количественных методов МРТ для оценки структурных изменений на молекулярном уровне в головном мозге, что расширяет фундаментальные представления о патофизиологии депрессии.

КЛЮЧЕВЫЕ СЛОВА: магнитно-резонансная томография, макромолекулярная протонная фракция, диффузионно-тензорная томография, томография куртозиса диффузии, большое депрессивное расстройство

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Introduction. More than 280 million people worldwide are affected by various degrees of depression [1]. Major depressive disorder (MDD) is one of the leading causes of disability, characterized by high prevalence and a chronic course. Alterations in cortical structures have been identified in MDD, but findings have been variable and inconsistent. To date, no reliable quantitative tools have been available to effectively characterize gray matter alterations in the default mode network. The identification of new quantitative markers of brain structure alterations could be crucial in the prediction of moderate or severe MDD.

It has been learned in previous studies, that medication-free patients with MDD showed a complex pattern of increased cortical thickness in the posterior cingulate cortex, ventromedial prefrontal cortex, and anterior cingulate cortex and decreased cortical thickness in others (gyrus rectus, orbital segment of the superior frontal gyrus, and middle temporal gyrus) [2]. It must be understood that the measurement of cortical thickness can only be a statement of some accompanied structural changes that lead to an increase in the volume effects. Some articles report on reductions in synaptic density and plasticity, dendritic spines, boutons, and glia associated with depression, specifically the arrangement and myelination of nerve fibers, which can be examined using microstructural MRI techniques such as DTI and MPF [3].

Previous studies have illustrated that the cingulate gyrus and amygdala are associated with emotional processing and can trigger abnormal emotional responses and cause disorders, such as depression [4–6]. The alterations of diffusivity in MDD patients were found in the amygdala [7, 8]. The anterior cingulate cortex (ACC) is attributed to dysfunctions in stress selfregulation and emotional processing [9]. Structure alterations, including a reduction of gray matter volume and differences in white matter integrity, have been observed in the anterior cingulate cortex of patients with MDD [10–13]. Important functions of the dorsal part of the medial prefrontal cortex are working memory, cognitive flexibility, and abstract thinking, involving reflective and hypothetical processing of information related to social interaction. Structural alterations of the prefrontal cortex cause deficits in executive functions, reduced decision-making abilities, and social behavior disorders [14]. A decrease in gray matter volume has been observed in the dmPFC region of patients with MDD, which is probably preceded or accompanied by microstructural changes that have not yet been detected/investigated [15].

The most promising structural MDD biomarkers include various neuroimaging, genetic, molecular and peripheral assays, for the purposes of determining susceptibility or presence of illness. Non-nvasive DTI and MPF biomarkers, based on MRI, are of particular interest for developing personalized approaches. This is not only because they are relevant to the pathophysiology of interest, but also because they may be

scalable and adoptable in the clinic in the near-term future [16].

Objective. Considering these factors, our research aims to investigate the neurological structural differences and alterations in ACC, bilateral amygdala, and dmPFC regions in patients with MDD using quantitative MRI (MPF and Diffusion parameters mapping (DPM), including diffusion kurtosis).

Materials and methods. Participants: In this cross-sectional study participants were recruited from the International Institute of Psychology and Psychotherapy, Novosibirsk. They were divided into two groups: 17 patients (age 19–51, average value=33 y.o., female=13, male=4) diagnosed with MDD and 19 healthy controls (HC) (age 21–55, average value=39 y.o., female). The MPF map reconstruction was made for 13 patients (age 21–43, average value=34 y.o., female=8, male=3) and 23 HC (age 21–55, average value=35 y.o., female). The group of healthy people is completely identical to the experimental group in terms of age criteria; a healthy test subject of the same year of birth is recruited for each patient. The inclusion criteria for all participants were as follows: aged over 18 years old, meeting diagnostic criteria — codes F32, F33 (except F32.3 and F33.3), F34.1, according to International Classification of Diseases, Tenth Revision (ICD-10), and stable medical treatment >6 weeks, with discontinuation of medications affecting brain function or cerebral blood flow for at least 3 weeks, the group exhibited homogeneity in pharmacotherapy, and all participants had a minimum of one year of disease experience. Besides, the assessments of patients confirmed to have depressive disorder were based on the following diagnostic criteria for the clinical definition of the disease: The structural interview of the Hamilton Depression Rating Scale (17-HAM-D>13 points), Montgomery-Asberg Depression Rating Scale (MADRS>7 points), Beck Depression Inventory-II (BDI-II>14 points) [17–19]. The exclusion criteria for all participants were pregnancy, history of severe brain damage, previous diagnosis with other mental disorders, psychotic symptoms, serious comorbid neurological, psychiatric, and somatic pathology, any abnormal findings on routine brain MRI, and MRI contraindications. If participants reported any discomfort during the scanning process, the scanning was halted, and they were excluded from the experiment. The study was approved by the Committee on Biomedical Ethics of the Federal Research Center for Fundamental and Translational Medicine (FRC FTM), decision No. 9 dated 12.05.2022. Written informed consent was obtained from the participants.

All data were acquired on a 3T scanner (Ingenia; Philips Healthcare, Best, the Netherlands) equipped with a 16-channel head coil at the International Tomography Center Novosibirsk.

To reduce motion and scanner noise, cushions, and earmuffs were provided for participants. For diffusion imaging, a single-shot, fat-suppressed, diffusion-weighted spin echo-planar imaging sequence was performed. The image acquisition parameters were as follows: TR/TE=10500/73 ms, field of view (FOV)=224×224 mm^2, matrix size=96×94, voxel size=2.33×2.33×2.33 mm^3, parallel imaging (SENSE) factor=2, b-values=0, 1500 and 2500 s/mm^2 in 32 total non-collinear directions.

The whole-brain fast 3D MPF mapping protocol included three spoiled gradient-echo sequences providing T1, proton density, and magnetization transfer contrasts with non-selective excitation, FOV=230×230×180 mm^3, 1.4×1.4×1.4 mm^3 resolution, followed by B1 mapping sequence for exact flip angle determination. PD- and T1-weighted GRE images were acquired with TR/TE=20/4.6 ms and FA=4° and 20°, respectively. MT-weighted images were acquired with TR=50 ms and FA=10°. Off-resonance saturation was achieved by applying the single-lobe sinc pulse with Gaussian apodization and the following parameters: offset frequency 4 kHz, effective saturation FA=560°, and duration 12 ms. Parallel imaging (SENSE) was used for all scans in two phase encoding directions with acceleration factors 1.5 (anterior-posterior) and 1.2 (left-right). Scan times were 1 min 32 s for the T1- and PD-weighted images, 3 min 50 s for the MT-weighted, and 3 min 26 s for the B1 map, thus resulting in about 23 min acquisition time for the entire protocol. Additionally, standard anatomical high-resolution 3D T1-weighted images (TR/TE=7.7/3.8 ms, FA=8°, inversion time (TI)=900 ms, voxel size=1×1×1 mm^3, scan time 3 min 01 s) were acquired with same FOV for comparison purposes. Sample source images are illustrated in Fig 1.

Image Processing and Analysis

Image processing was performed using SPM 12 (Welcome Trust Centre for Neuroimaging, University College London, UK) [26]. MPF and DPM images were coregistered to corresponding high-resolution anatomical images. The right and left amygdala masks were generated using WFU PickAtlas [27]. The ACC and dmPFC rois were taken from the article of Amft et al. [28]. For each subject, all of the ROIs, defined in MNI space, were warped to the individual's space and used as masks to calculate ROI-average values of the analyzed maps. Two studies with heavily mispositioned DPM volume not covering left and right amygdala ROIs were excluded from the analysis. The ROI volumes were: 1.1±0.1 ml for the left amygdala, 1.7±0.1 ml for the right amygdala, 1.4±0.1 ml for ACC, and 0.8±0.1 ml for dmPFC. The scheme of ROI placement is illustrated in Fig 1.

DKI datasets were processed using the Diffusional Kurtosis Estimator software tool (DKE, Version 2.6) [29]. Kurtosis (mean, mean kurtosis tensor) and mean diffusivity parametric maps as well as FA maps were calculated with the DKI in 36 cases (17 MDD and 19 HC). Examples of DPM are shown in Fig 2.

MPF maps were reconstructed from a single dataset in 36 cases (13 MDD and 23 HC). The example

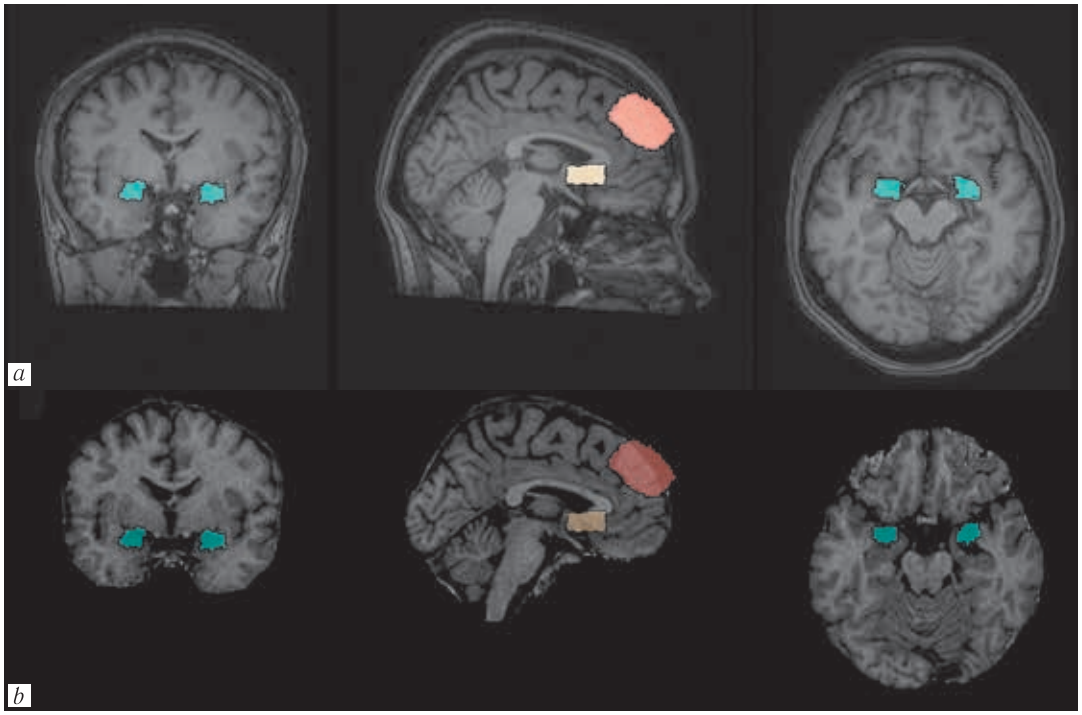

Fig. 1. Representation of the three ROI examined in this article obtained from one of MDD patients (37 y.o. female). Blue: bilateral amygdala; red: dorsomedial prefrontal cortex (dmPFC); yellow: anterior cingulate cortex (ACC) placed on the three-dimensional sample source images: (*a*) T1-weighted image and (*b*) macromolecular proton fraction (MPF) map

Рис. 1. Представление трех исследуемых в данной статье ROI, полученных от одного из пациентов с БДР (женщина 37 лет), расположенные на трехмерных изображениях: (*a*) T1-взвешенное изображение и (*b*) карта МПФ. Синий: миндалины; красный: дорсомедиальная префронтальная кора; желтый: передняя поясная кора

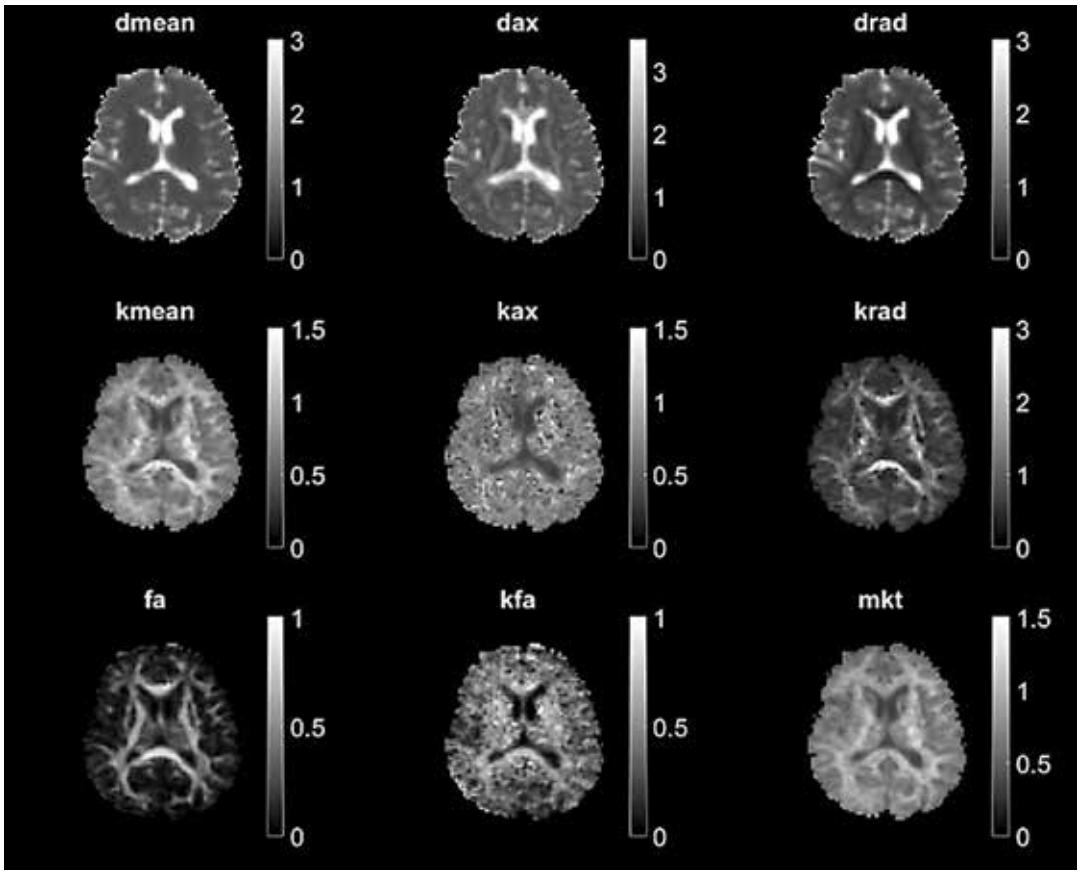

Fig. 2. Example images of diffusion parameter maps calculated by Diffusion Kurtosis Estimator; same axial slice depicted on all maps (37 y.o. female MDD patient)

Рис. 2. Примеры изображений карт параметров диффузии, рассчитанных с помощью Diffusion Kurtosis Estimator; на всех картах изображен один и тот же аксиальный срез (пациентка с БДР, 37 лет)

of a reconstructed fast whole-brain 3D MPF map with a standard region of interest set is illustrated in Fig 1.

MPF maps were reconstructed according to the single-point synthetic reference image method [22] using custom-written C-language software. MPF maps were registered to the images of standard T1 sequence.

Results. We did not reveal significant age differences (p=0.128) between MDD and HC groups. The two-sample t-test comparing the values of the left and right amygdala in the MDD and HC groups for each metric did not reveal any significant differences between the left and right amygdala values. Consequently, we combined the values of the left and right amygdala for each group in each metric.

ROI-based Analysis

The mean, radial, and axial diffusivity values were increased in the bilateral amygdala in MDD patients comparing HC (F=6.3, p=0.01, F=5.0, p=0.03, F=7.08, p=0.01, respectively) (Fig 3, *b*). In the ACC statistically significant increases were observed in the mean and axial diffusivity in MDD patients compared with HC (F=5.61, p=0.02, F=7.08, p=0.01, respectively) (Fig 3, *c*). The radial diffusivity in MDD patients appeared to be higher compared with HC, but did not reach statistical significance (Fig 3, *c*). There were no group differences in other metrics, including MPF (Fig 3, *a*), mean, radial and axial kurtosis, and MKT.

Discussion. In recent years, there has been growing evidence from neuroimaging studies suggesting that functional and structural changes in the brain may be associated with depression [30]. Diffusion MRI is a non-invasive method for mapping a brain microstructure and providing quantitative parameters, making it a valuable tool in neuroscience research, particularly in the context of psychiatric disorders. Among the various diffusion MRI techniques, DTI has been widely used to characterize gross fiber orientations and visualize brain networks by imaging the organization of white matter bundles. One of the most commonly studied variables in DTI is FA, which reflects the degree of directionality of water molecule movement in tissues and provides insights into the status of white matter tracts. Lower FA values are often associated with abnormalities in fiber density, myelination, or tract coherence, while values closer to 1 indicate highly directional movement and stable connectivity [31–33]. Zou, K. et al. [30] indicate reduced FA values in the left hemisphere in patients with major depressive disorder (MDD), associated with increased disease duration and severity. Hassan et al. [27] found a significant reduction in the FA values of the cingulum, uncinated fasciculus, and the fornix. However, other variables commonly used for DTI analyses include axial diffusivity, radial diffusivity, and mean diffusivity. Axial and radial diffusivity parameters pair provide the same information about diffusion ellipsoid as mean diffusivity+FA and may be used interchangeably.

A previous study used DTI for research on white matter integrity to evaluate the value of FA in patients with suicidal ideation. DTI is not able to distinguish branching or crossing fibers [34]. To address this limitation, we turned to diffusion kurtosis imaging (DKI), which offers additional metrics closely related to tissue microstructure. These metrics not only enhance the accuracy of fiber tracking but also provide improved quantitative and directional information in both white and gray matter [20, 21].

Despite the strong correlations observed in DKI metrics, it's noteworthy that there was no significant relationship between MPF values and depressive symptoms, even after we controlled for age. Our hypothesis that the disruption of cortical-subcortical circuit integrity may be accompanied or caused by some focal or diffuse myelin loss of structural alterations is not sufficiently sensitive. It doesn't detract from a diagnostic value of a new quantitative imaging method, MPF-mapping that already proved its value for quantitative neuro tissue characterization in vivo fetal and adult brain studies [24, 25]. Quantitative Assessment of Subcortical Gray Matter Demyelination using the Macromolecular Proton Fraction revealed a close association between Multiple Sclerosis phenotype and disability [23].

In terms of diffusion properties, mean and axial (as well as radial in the case of the amygdala) diffusivity values showed a statistically significant increased effect associated with major depressive disorder in the bilateral amygdala and ACC. Mean diffusivity is hypothesized to reflect tissue degeneration and may provide subtle indicators of neuropathology. This corresponds to the fact that the amygdala is the exception across all subcortical regions which perform a familial mean diffusivity aggregation, explained by additive genetic factors [33]. Previously, the reduction in gray matter volume and differences in white matter integrity were investigated in the ACC, which were associated with depressive symptoms in women [12]. Our work complements these previous findings by providing evidence of altered diffusion properties in gray matter in the ACC associated with MDD.

It is important to acknowledge the limitations of our study. Firstly, the cross-sectional design restricts our ability to make causal inferences or determine the temporal sequence of the observed alterations. Longitudinal studies are needed to establish the dynamics and progression of these microstructural changes over time. Secondly, our sample size was relatively small, which may have limited the statistical power to detect subtle differences. Future studies with larger sample sizes are warranted to confirm our findings. Our study only included adult participants at the strong age frame and were mostly females — therefore, the findings may not generalize to other age or sex groups, although studies and statistical results have shown that the rates of depression are universally higher in females [35]. Future studies could recruit more participants with male predominance to balance

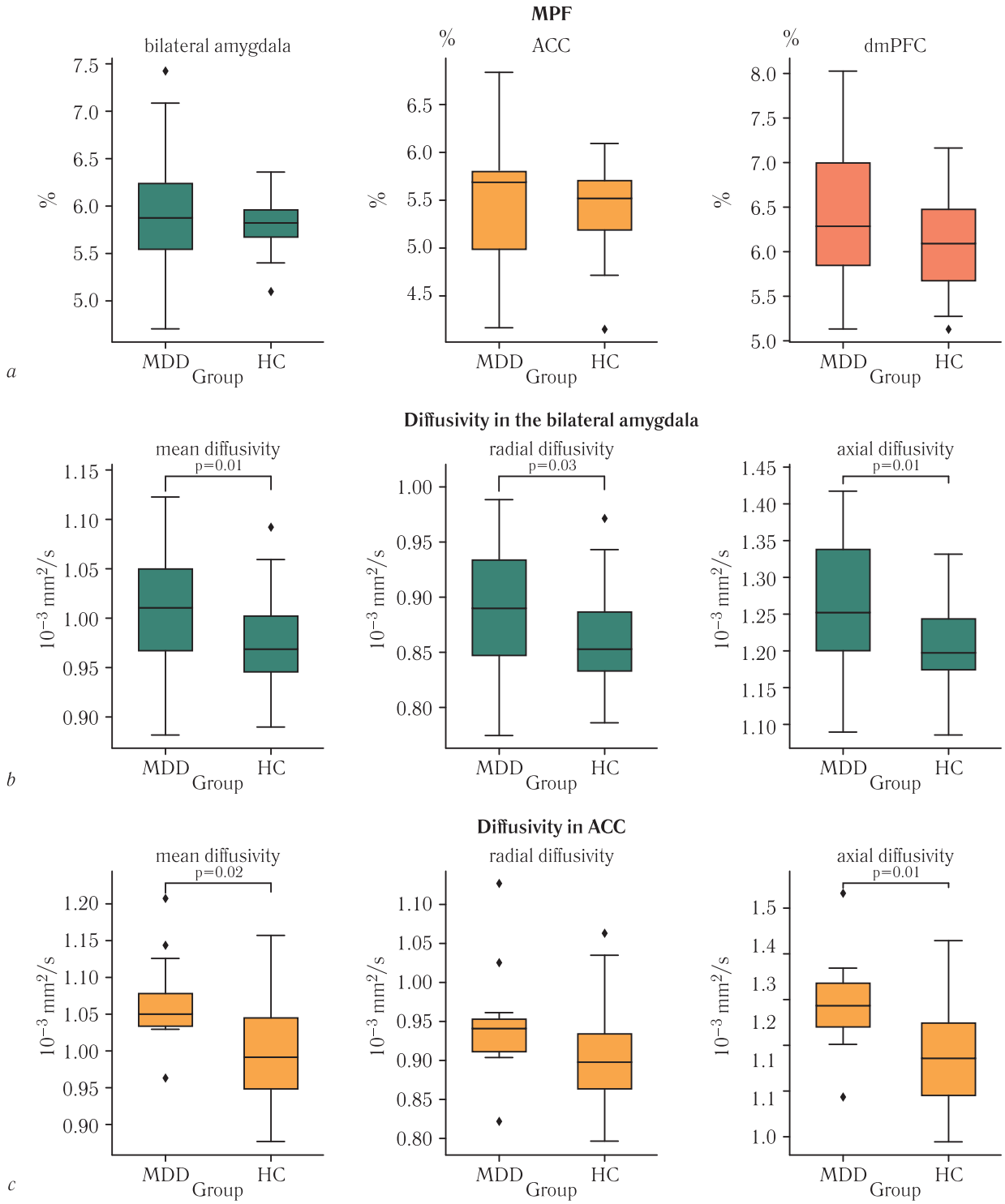

Fig. 3. Boxplots show the two-way ANCOVA comparisons of patients with MDD and HC (*a*) measured by MPF in the investigated regions and (*b*) in the bilateral amygdala measured by DTI (*c*) in the ACC measured by DTI

Рис. 3. Боксплоты показывают двусторонние ANCOVA-сравнения пациентов с БДР и ГК (*a*) по МПФ в исследуемых областях и (*b*) билатерально в миндалинах по ДТ МРТ (*c*) в передней поясной извилине по ДТ МРТ

the numbers. Additionally, our study focused on specific brain regions based on previous research that have consistently demonstrated the involvement of these regions in major depressive disorder [5, 8, 9, 15]. However, it is crucial to recognize that depression is a complex disorder that involves widespread neural networks and may be associated with microstructural alterations in other brain regions that were not examined in our study. By exploring a broader range of regions, future studies can provide a more comprehensive picture of the neurobiological mechanisms involved in depression.

Our study demonstrates the utility of diffusivity metrics in investigating microstructural alterations associated with depression. The findings enhance the fundamental understanding of the complexity of tissue microstructure and its relationship to depressive disorder. Further research employing larger sample sizes

and longitudinal designs will help confirm and extend our findings, which will ultimately contribute to a deeper theoretical understanding of the neurobiology of depression, and the development of practical technologies for various aspects of the diagnosis of this disease.

Conclusions. Accumulated evidence has shown that diffusion associated brain abnormalities are related to patients with major depressive disorder. In our study, we analyzed both neurological structural variations in healthy controls and depressed patients using Diffusion kurtosis imaging and Macromolecular proton fraction-mappings that improved the accuracy, integrated, and diversified approach of analysis MDD. Our results demonstrate that Macromolecular proton fraction mapping may not exhibit sensitivity to the earliest stages of myelin structural disturbance in the major depressive disorder brain or further studies may be required to explore potential clinical applications. We determined the effect of major depressive disorder and age on the differences between two groups in the values of Macromolecular proton fraction, mean diffusivity, fractional anisotropy, mean kurtosis, and kurtosis anisotropy. Diffusivity in the bilateral amygdala was found to have a significant increase in patients with major depressive disorder compared with healthy controls ($p<0.05$). In addition, we revealed structural changes in the form of an increase in the mean, radial and axial values of the diffusion coefficient ($p=0.01$) in the amygdala, which is consistent with the results of most previous studies [7, 8].

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