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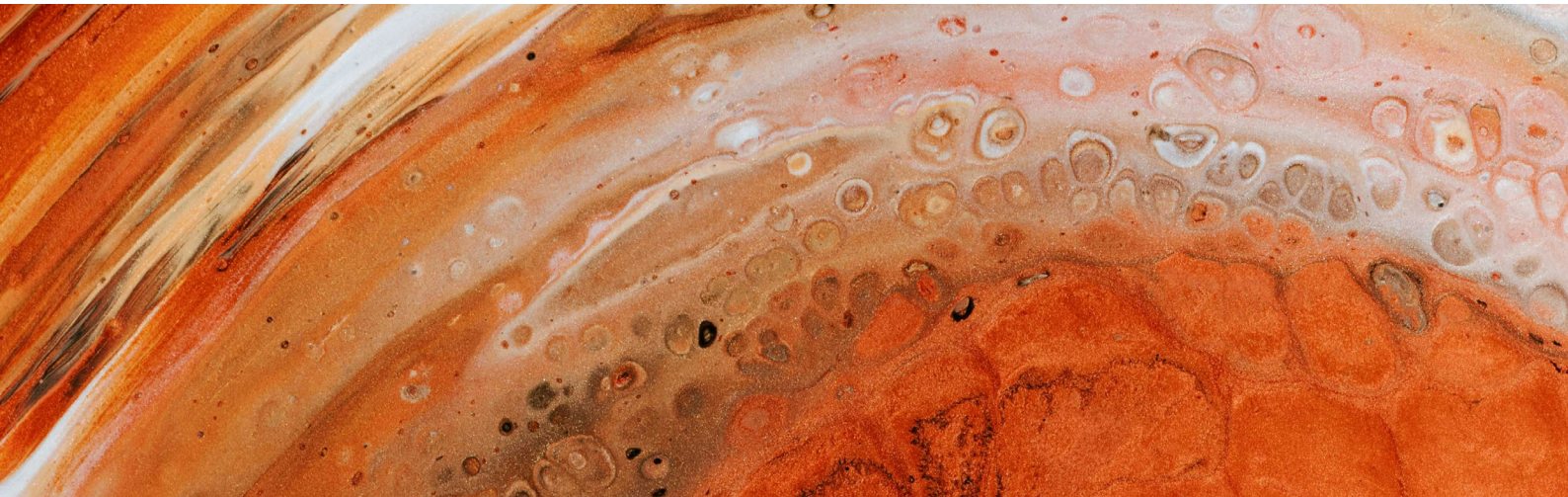
# The Modern Concept of Schizoaffective Disorder: A Narrative Review Page 42





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**Original research**

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**ABSTRACT**

**BACKGROUND:** Schizophrenia is a psychiatric disorder known to affect brain structure and functionality. Structural changes in the brain at the level of gross anatomical structures have been fairly well studied, while microstructural changes, especially those associated with changes in the molecular composition of the brain, are still being investigated. Of special interest are lipids and metabolites, for which some previous studies have shown association with schizophrenia.

**AIM:** To utilize a spatially resolved analysis of the brain lipidome composition to investigate the degree and nature of schizophrenia-associated lipidome alterations in the gray and white matter structures of two neocortical regions — the dorsolateral prefrontal cortex (Brodmann area 9, BA9) and the posterior part of the superior temporal gyrus (Brodmann area 22, posterior part, BA22p), as well compare the distribution of the changes between the two regions and tissue types.

**METHODS:** We employed Matrix-Assisted Laser Desorption/Ionization Mass Spectrometric Imaging (MALDI-MSI), supplemented by a statistical analysis, to examine the lipid composition of brain sections. A total of 24 neocortical sections from schizophrenia patients (*n*=2) and a healthy control group (*n*=2), representing the two aforementioned neocortical areas, were studied, yielding data for 131 lipid compounds measured across more than a million MALDI-MSI pixels.

**RESULTS:** Our findings revealed an uneven distribution of schizophrenia-related lipid alterations across the two neocortical regions. The BA22p showed double the differences in its subcortical white matter structures compared to BA9, while less bias was detected in the gray matter layers. While the schizophrenia-associated lipid differences generally showed good agreement between brain regions at the lipid class level for both gray and white matter, there were consistently more discrepancies for white matter structures.

**CONCLUSION:** Our study found a consistent yet differential association of schizophrenia with the brain lipidome composition of distinct neocortical areas, particularly subcortical white matter. These findings highlight the need for broader brain coverage in future schizophrenia research and underscore the potential of spatially resolved molecular analysis methods in identifying structure-specific effects.

## АННОТАЦИЯ

**ВВЕДЕНИЕ:** Шизофрения — это психическое расстройство, известное своим влиянием на структуру и функциональность мозга. Хотя изменения в архитектуре мозга на уровне крупных анатомических структур были исследованы достаточно подробно, микроструктурные изменения, особенно связанные с молекулярным составом мозга, остаются предметом интенсивного изучения. В последние годы особое внимание уделяется липидам и метаболитам, поскольку ряд предыдущих работ выявил их возможную связь с шизофренией. Понимание этих молекулярных изменений может помочь в раскрытии механизмов, лежащих в основе этого расстройства, и в разработке новых подходов к его диагностике и лечению.

**ЦЕЛЬ:** Исследовать степень и характер ассоциированных с шизофренией различий в пространственном распределении липидов в сером и белом веществе двух областей неокортекса — в дорсолатеральной префронтальной коре (область Бродмана 9, BA9) и задней части верхней височной извилины (область Бродмана 22, задняя часть, BA22p), а также сравнить распределение различий между двумя областями и типами тканей.

**МЕТОДЫ:** Проведена визуализация при помощи метода масс-спектрометрии с применением матрично-активированной лазерной десорбции/ионизации (MALDI-MSI). Всего было исследовано 24 среза, полученных от больных шизофренией (*n*=2) и от здорового контроля (*n*=2), представляющих две вышеупомянутых области неокортекса, что позволило проанализировать данные по 131 липидному соединению, измеренному по более чем миллиону пикселей MALDI-MSI.

**РЕЗУЛЬТАТЫ:** Обнаружено неоднородное распределение разницы в уровне липидов, связанных с шизофренией, в двух исследованных областях неокортекса. Белое вещество из BA22p показало больше различий по сравнению с белым веществом из BA9, в то время как в сером веществе дисбаланс количества различий менее выражен. Хотя изменения липидов, связанные с шизофренией, в целом, хорошо согласуются между областями мозга на уровне классов липидов как для серого, так и для белого вещества, было обнаружено значительно больше расхождений для структур белого вещества.

**ЗАКЛЮЧЕНИЕ:** Исследование выявило согласованную, но дифференцированную связь между шизофренией и составом липидома мозга в различных областях неокортекса, особенно в подкорковом белом веществе. Полученные результаты подчеркивают важность учета специфики мозговых структур в будущих исследованиях

шизофрении и демонстрируют перспективность методов молекулярного анализа с пространственным разрешением для выявления структурно-ориентированных изменений, связанных с этим расстройством.

**Keywords:** *schizophrenia; lipidomics; mass-spectrometry; MALDI-MSI; neocortex*
**Ключевые слова:** *шизофрения; липидом; масс-спектрометрия; MALDI-MSI; неокортекс*

## INTRODUCTION

Schizophrenia is a psychiatric disorder affecting 0.3 to 0.45% of the global population[1] [1, 2] and up to 4.7% in selected countries [3, 4], with a significant social and healthcare impact [2]. The molecular underpinnings of schizophrenia remain poorly understood due to the multifactorial nature of the disease and brain tissue heterogeneity. Recent advances in high-resolution molecular imaging techniques, such as Matrix-Assisted Laser Desorption/Ionization Mass Spectrometry Imaging (MALDI-MSI), offer unprecedented opportunities to elucidate the spatial distribution of molecules on tissue sections [5–7], thereby enabling a more comprehensive understanding of the biochemical changes associated with schizophrenia [8]. Studying molecular changes in other disorders using MALDI-MSI provides a powerful approach to identifying and localizing potential biomarkers [9], in an effort towards a better understanding of disease etiology [10, 11].

Previous studies using mass spectrometry have indicated the presence of detectable metabolic alterations in the brains of schizophrenia patients: particularly in hydrophobic metabolites known as lipids [12–14]. Similarly, genetic studies have revealed associations linked to the genes involved in lipid metabolism in schizophrenia patients [15, 16]. Despite an increase in studies that investigate the metabolome, specifically the lipidome, of the schizophrenia brain, a comprehensive understanding of the metabolic alterations associated with this debilitating disorder is yet to be achieved. One reason for this lack of systemic understanding is the near-exclusive focus of most molecular studies on a specific brain area — the dorsolateral prefrontal cortex.

Another contributing factor to incomplete understanding of schizophrenia-associated alterations is the lack of spatial resolution in most of the methods used for molecular tissue examination. Traditional lipidomic studies often prepare samples for liquid or gas chromatography, combined with mass spectrometry, by homogenizing the biological sample, which often results in a loss of information about the lipids' spatial distribution. At the same time, the cerebral cortex possesses a complex multilayer structure that influences its functionality [17, 18]. Moreover, certain lipids and lipid classes have been shown to exhibit a distinctive spatial distribution within the cortex layers [19]. Collectively, these points underscore the need to employ methods that incorporate spatial resolution in order to examine the molecular composition of multiple brain regions in a schizophrenia brain, which has not been implemented previously.

The dorsolateral prefrontal cortex, which has been the focus of multiple schizophrenia studies, was associated with such negative symptoms as affected cognitive control [20], working memory dysfunction [21], and anhedonia [22–24]. Investigation of the spatial lipidome of the prefrontal cortex of schizophrenia has indicated some abnormalities in phospholipids but yielded limited data on other lipid classes. It also lacked statistical evaluations [8]. Variations in the volume of the left-side superior temporal gyrus have been consistently associated with auditory hallucinations, which are a primary positive symptom of schizophrenia [25]. Furthermore, gene expression studies that have examined multiple neocortical regions have reported the greatest number of gene expression alterations in this area [26–28]. However, no previous studies have focused on the spatial distribution of the lipids in this temporal region. Moreover, no comparative analysis has been conducted for the two regions.

Our study aimed to utilize a spatially resolved analysis of the brain lipidome composition to investigate the degree and nature of schizophrenia-associated lipidome alterations in the gray and white matter structure [27–29] of two neocortical regions — the dorsolateral prefrontal cortex (Brodmann area 9, BA9) and the posterior part of the superior temporal gyrus (Brodmann area 22, posterior part, BA22p). The focus on these two regions made it possible to establish a reference frame for the results obtained in the form of the well-studied region BA9, as well as the

[1] Available from: https://www.who.int/news-room/fact-sheets/detail/schizophrenia

opportunity to collect completely new data for a region that had not previously been studied using our chosen method. We further examined two histological areas within each region — one corresponding to subcortical white matter and the other to neocortical gray matter layers.

## METHODS

### Tissue samples

Healthy control (HC) and schizophrenia patient (SZ) brain samples (sex: M/F=0/2 and 1/1; age: 36, 63 and 62, 56; respectively) were obtained from the biospecimens of the contract research organization National BioService (Saint Petersburg, Russia). No subject in the control group had a history of psychiatric or neurodegenerative disease and no gross anatomical abnormalities were revealed during the pathoanatomical assessment. Brain donors were diagnosed with schizophrenia according to ICD-10 by psychiatrists during inpatient treatment at Mental-health clinic No. 1 named after N.A. Alexeev (Moscow, Russia). Each subject suffered sudden death with no prolonged agony state.

All the post-mortem brain samples were sectioned, placed on aluminum blocks, and frozen on dry ice. All sample transport was conducted on dry ice and long-term storage in –80°C freezers. There was no sample thawing or heating at any point. The two regions of interest (BA9 and BA22p) were located according to the Atlas of the Human Brain[2] by a neuroanatomist. A total of 24 samples were dissected. They covered two regions from two individuals from both the HC and SZ and were measured in three replicates, meaning that each region in each individual was represented by three brain tissue slices (Table S1 in the Supplementary).

### Tissue preparation

The brain samples were sectioned using the Leica CM1950 microtome cryostat (Leica Biosystems, China). Cutting was done at a chamber temperature of –18°C; sample temperature was –15°C. The thickness of the sections was set to 20 µm. The sections were placed on an ITO (indium tin oxide) coated glass slide without an adhesive medium (Hudson Surface Technology, Glass Slides for MALDI imaging, Republic of Korea) and attached to the glass by thaw-mounting. The sections were next placed in a desiccator for 90 minutes. Air was removed from the chamber using a MEMVAK 2x1 membrane pump to a 30-mbar pressure at room temperature. A solution of α-cyano-4-hydroxycinnamic acid (Sigma-Aldrich, USA), with a concentration of 5 mg/mL in a 50/50 water/acetonitrile mixture with 0.1% and trifluoroacetic acid (TFA, Sigma-Aldrich, USA), was diluted twice. No internal standards were added. The diluted solution was sprayed using an Iwata Micron CM-B2 airbrush (Anest Iwata, Japan) for two seconds and allowed to dry for 2.5 minutes. This process was repeated 20 times.

### MALDI experiment

MALDI images were obtained using a modified MALDI-Orbitrap mass spectrometer (Thermo Scientific Q-Exactive Orbitrap with MALDI/ESI Injector from Spectroglyph, LLC, USA) equipped with an 355 nm Nd:YAG Laser Garnet (Laser-export. Co. Ltd, Russia). For positive ion induction the laser power was set to a 20 J repetition rate to 1.7 kHz. The distance between the sample on a coordinate table and ion funnel was 0.5 cm. The produced ions were captured by ion funnel and transferred to a Q-Exactive Orbitrap mass spectrometer (Thermo). Mass-spectra were obtained in a mass range of m/z 500–1000, and the mass resolution was 140,000. No fragmentation was carried out. The scanning pattern was left-right. MALDI interface operated in the MALDI mode at a laser repetition rate of 1 kHz. The ion accumulation time per pixel was 250 ms. The tissue region to be imaged and the raster step size were controlled using the Spectroglyph MALDI Injector Software. No oversampling was performed. To generate images, the spectra were collected at 40-µm intervals in both the *x* and *y* dimensions across the surface of the sample. Ion images were generated from raw files (obtained from the Orbitrap tune software) and coordinate files (obtained from the MALDI Injector Software) by the Image Insight software from Spectroglyph LLC. MALDI raw mass spectra were converted to *.ibd and *.imzML formats using the Spectroglyph software, with the background noise threshold set to zero. All further processing was done using Cardinal 2.8.0 (Kylie A. Bemis, USA), an R package designed for mass spectrometry imaging data analysis [30].

For image analysis, duplicated coordinates were removed from the converted files. Peak intensity was evaluated as height, then the spectra were normalized by the total

[2] Acronym: A91. Name: lateral subdivision of area 9 [Internet]. [cited 2023 Dec 7]. Available from: https://atlas.brain-map.org/atlas?atlas=265297126#atlas=265297121023399 58&structure=10179&x=30131.805555555555&y=37587.999131944445&zoom=-7&resolution=138. 6&plate=71&z=3

ion current. We performed peak picking on the basis of a signal-to-noise ratio threshold equal to three to select peak centers for the downstream analysis. The signal-to-noise ratio was calculated based on the difference between the mean peak height in a window of predefined size and the mean height in a window of the manually selected flat part of the spectrum [31]. After the peak picking procedure, the spectra of each pixel were aligned to the average spectrum of the entire image, in accordance with the library functionality Cardinal 2.8.0 (Kylie A. Bemis, USA). Peaks present in less than 7% of the sample spectra were removed from further analysis. Images were generated with the peaks of interest centered around the measured m/z values.

Peaks originating from the glass slide surface not covered by tissue and uninformative parts of the spectra containing no biologically relevant peaks were removed from each sample spectral data. To do that, the sample image area was divided into two parts using the spatial k-means algorithm; one of the clusters corresponding to the tissue sample, the other — to the sample-free matrix-covered surface of the glass slide. The mapping of the clusters to the sample and the surrounding area was manually curated by visual inspection of the slides. Mean feature intensities were calculated for the two clusters, and only peaks with 1.5 times greater mean intensities within the sample cluster compared to the surrounding sample-free area were kept. After these filtration steps, all sample spectra were aligned to the spectrum with the largest number of detected peaks.

For the clustering of pixels within the sample area into white and gray matter clusters, histological staining of the adjacent sample sections was used. Unsupervised clustering of gray matter (without preliminary peaks selection) was performed with the spatial Shrunken Centroids function from the Cardinal library. The following parameters were used: $s$=1, $k$=3, $r$=1, where $s$ is the sparsity parameters, $k$ is the number of clusters, and $r$ is the smoothing radius.

### Peaks annotation

The peaks were annotated as lipid species based on their mass-to-charge ratio with the mass difference threshold between the data and target values set to 20 ppm. For cases of multiple matches, the following rules were applied (also see Figure S1 in the Supplementary).

*One peak — one lipid — one adduct*. When a unique match occurred between the lipid annotation of a particular adduct and the m/z ratio in MALDI, this annotation was assigned to the MALDI peak.

*Several peaks — one lipid — different adducts*. If peaks with masses matching the same lipid were detected in MALDI but with different adducts, priority was given to annotating the lipid with a hydrogen adduct. If no hydrogen adduct was present, the sodium adduct took higher priority over the potassium adduct.

*One peak — several lipids — different adducts*. If one MALDI peak corresponded to the annotation of two different lipids, where one had a hydrogen adduct and the other had any other adduct, the peak was assigned with annotation of a lipid with a hydrogen adduct.

*One peak — several lipids — one adduct*. If one MALDI peak corresponded to the annotation of two different lipids, both of which contained a hydrogen adduct, the peak was assigned the annotation of both lipids.

The remaining lipids coincided with lipid classes characteristic of a given tissue and matrix [32–35][3].

### Histology of sections

The histology of the white and gray matter on the brain sections was revealed by luxol fast blue staining (blue color for lipid-rich compartments) and by eosin (pink color for protein-rich cytoplasm). Brain sections were briefly defated to increase dye penetration: they were placed gradually in ethyl alcohol (50%, 75%, 95% and 100%) and back to 95% for 1 min in each solution. Then, the sections were left in a 0.1% luxol fast blue solution (BioOptica, Italy) in ethyl alcohol with 0.5% glacial acetic acid in a 56°C oven for 12–14 h. Excess stain was rinsed off with 95% ethyl alcohol and then in distilled water. Staining was differentiated in a 0.05% lithium carbonate solution (BioOptica, Italy) in water for 30 seconds and rinsed in distilled water several times, with constant control by microscopic examination if gray matter was clear and white matter sharply defined. Then, the sections were counterstained with a 1% eosin solution (BioVitrum, Russia) in water for 30–40 seconds, rinsed in distilled water, dehydrated briefly in IsoPrep (BioVitrum, Russia), cleared in Bio Clear (Bio-Optica, Italy), and coverslipped with Bio Mount HM (Bio-Optica, Italy). Histology images were acquired with a Zeiss Axio.Observer. Z1 (ZEISS, Germany) transmitted light microscope system.

[3] Bemis K. Cardianl peakPick [Internet]. [cited 2023 Dec 7]. Available from: https://github.com/kuwisdelu/Cardinal/blob/devel/R/process2-peakPick.R

### Statistical analysis

Before performing statistical tests for the MALDI-MSI data, an image with lipids, intersected with González et. al [19] work, was generated, where the intensity of both lipids (PC 40:6 and SM d42:2) was normalized in 0 to 1 range. To explore the differences in the PC 40:6 lipid between the disease and control in each of the obtained layers in gray matter for both of the explored regions, intensities were normalized within layers for each region in a base-two log scale, followed by ANOVA between layers for each region and the disease.

All statistical tests were performed on base-two log transformed measured intensities. Mean values were calculated for gray matter and white matter clusters in each slide. Measured intensities from three replicates and all individuals in each group were averaged for further analysis. The difference (for base-two log transformed values) between the schizophrenia and control group was calculated for each lipid species within each region (BA9 and BA22p) and each histological cluster (gray matter and white matter). Groups of lipids with changes between the two groups were defined as having absolute changes of 0.25

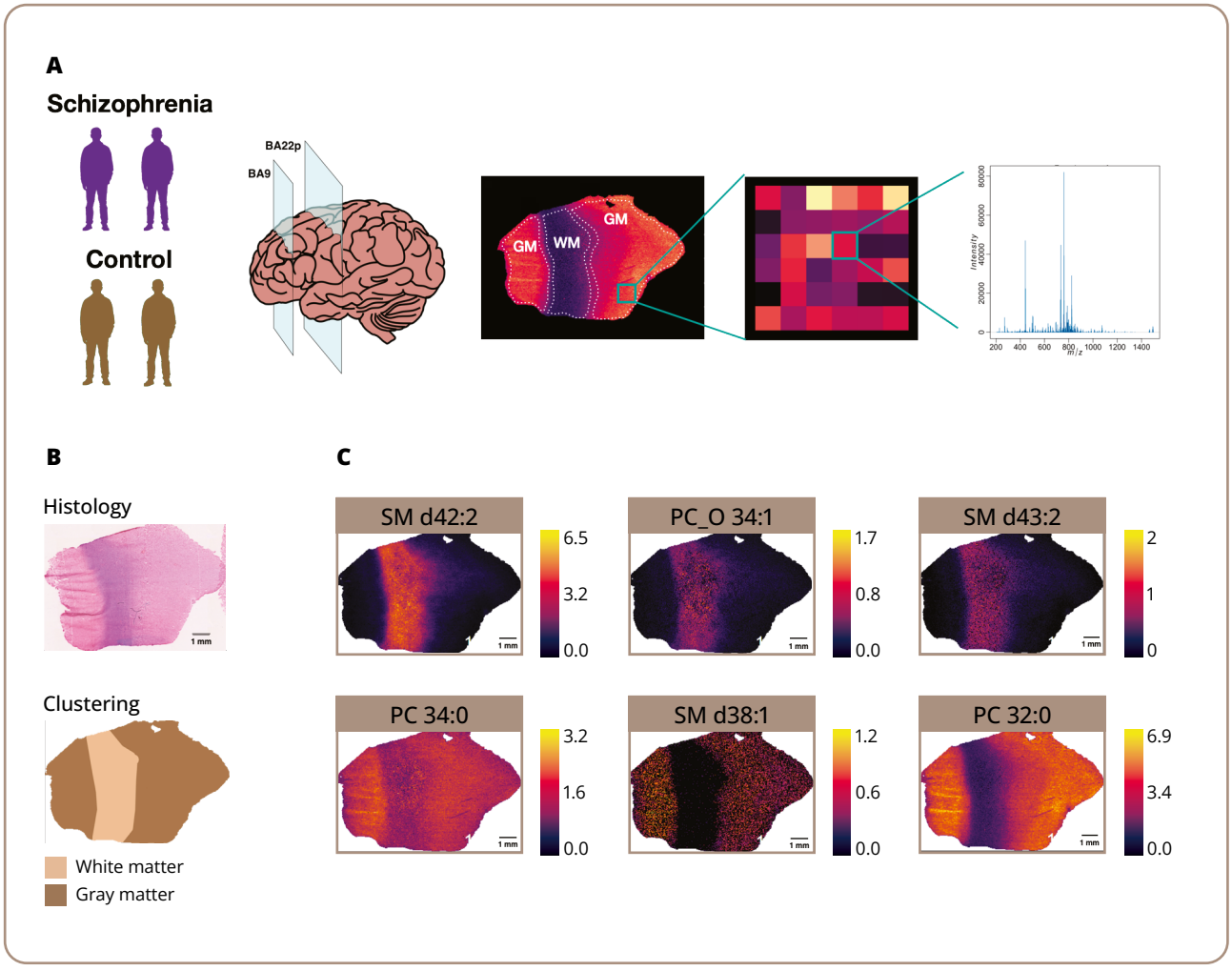


**Figure 1. Application of the MALDI-MSI method to brain region analysis.**

*Note:* (A) A schematic representation of the sample analysis. From left to right: sample set, thin sections dissection from two brain regions (BA9 and BA22p), and spatial distribution of the intensity levels of a particular mass spectrometric peak, representing a specific molecular ion, measured as a portion of a mass spectrogram collected for each pixel of the tissue section. (B) Histological staining and MALDI-MSI signal-based clustering of the pixels of one of the 24 examined neocortical sections. (C) Examples of lipids showing evident intensity distribution differences between gray and white matter areas of the neocortical section.
BA9 — Brodmann area 9; BA22p — Brodmann area 22 posterior; SM — sphingomyelin; and PC — phosphatidylcholine.
*Source:* Osetrova et al., 2024.

and more in log-scale. To assess the statistical significance of the difference in the number of lipid changes, the two sample one-sided proportion t-test was used. Pearson's correlation coefficients were calculated on the changes, averaged within lipid classes. To compare the correlation coefficients between the groups, Fisher transformation was applied to Pearson's correlation coefficients, followed by the two-sample one-sided Z-test. The analysis was performed using the R programming language and its publicly available libraries [36]. Analysis results were visualized using the ggplot2 version 3.4.3 package.

### Ethical approval

No ethics committee meeting was held. The data provided for the brain samples obtained from National BioService contained no personal information or any other information that could allow donors identification. Informed consent forms for the use of the biomaterial for research purposes were obtained from individuals or from the next-of-kin at the respective clinical organizations that provided the samples to National BioService in accordance with international regulations.

## RESULTS

Our analysis of mass spectrometric profiles for BA9 and BA22p derived from over a million pixels across 24 tissue section images yielded intensity data for 153 computational annotations for 131 MALDI peaks detected across the sections, which represented 16 lipid classes (Table S2 and Table S3 in the Supplementary). Clustering analysis of these pixels based on lipid intensities resulted in a reproducible patterning of the neocortical sections into two main areas, which was in alignment with the histologically defined gray and white matter regions, respectively (GM and WM clusters; Figures 1A, 1B). The images generated with specific lipids illustrate differences in distribution across distinct regions (Figure 1C).

In a primary visual cortex study [19], differences in lipid profiles across layers in two neighboring regions, primarily corresponding to a known variation in cortical layer architecture, were described. Visualization of the spatial distribution of two histologically associated lipids from the abovementioned article (SM d42:2, PC 40:6) in our cortical sections indeed revealed specific intensity gradients (Figure 2A). Unsupervised clustering of gray matter resulted in a segmentation of the cortex into three layers (Figure 2B). One-way ANOVA revealed a significant difference in PC 40:6 lipid mean values across the obtained layers for HC both in BA9 ($p$-value=0.004) and in BA22 ($p$-value=0.02) and for SZ in BA22 ($p$-value=0.002), but none in BA9 ($p$-value=0.1). The number of observations in each comparison was 4 per group.

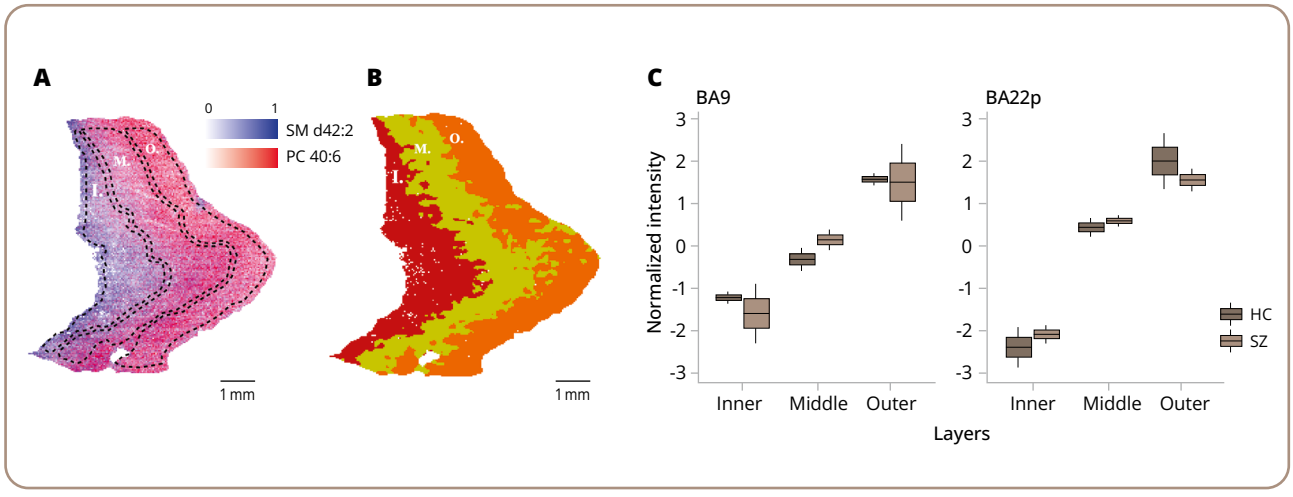


**Figure 2. Investigation of the gray matter microstructure.**

*Note:* (A) Superposition of the SM d42:2 and PC 40:6 intensity distribution across the gray matter (I — inner layer, M — middle layer, O — outer layer). (B) Unsupervised clustering of gray matter based on all peaks. (C) Distribution of the cluster mean value of all donors for PC 40:6 [H+] in BA9 and BA22. Color indicates disease. Information presented with a box-plot graph, where the box represents the interquartile range (IQR), with the median marked inside. The whiskers extend to the minimum and maximum values.
BA9 — Brodmann area 9; BA22p — Brodmann area 22 posterior; HC — healthy control; and SZ — schizophrenia patient.
*Source:* Osetrova et al., 2024.

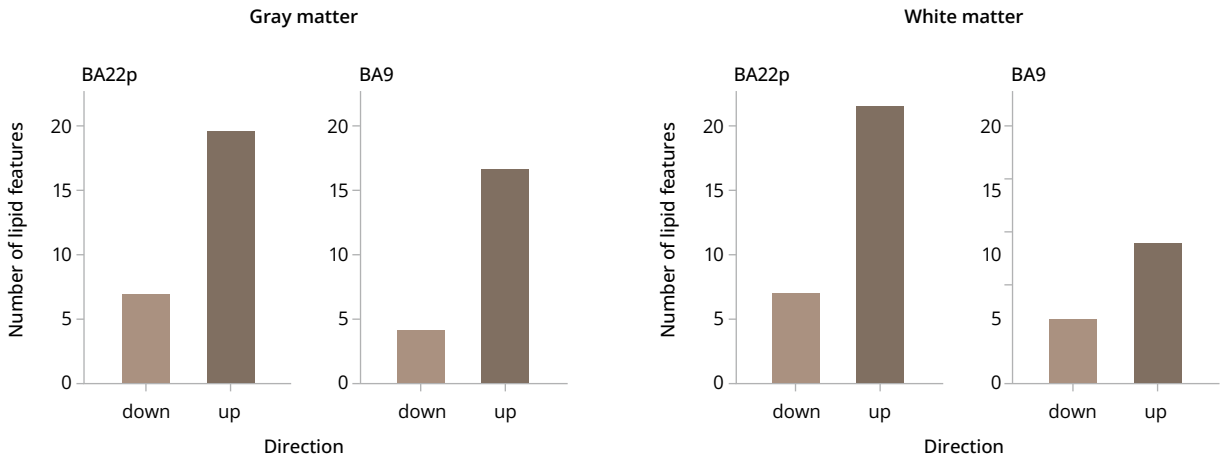


**Figure 3. The distribution of lipid differences between the schizophrenia and healthy groups in two specific brain regions.**

*Note:* The boxplots show the number of lipid species that exceeded fold-change thresholds of –0.25 and 0.25 in gray and white matter within the regions of interest (BA9 and BA22p). Lipids with a fold-change range between the –0.25 and 0.25-fold-change distribution are not included in the plot.
BA9 — Brodmann area 9; BA22p — Brodmann area 22 posterior.
*Source:* Osetrova et al., 2024.

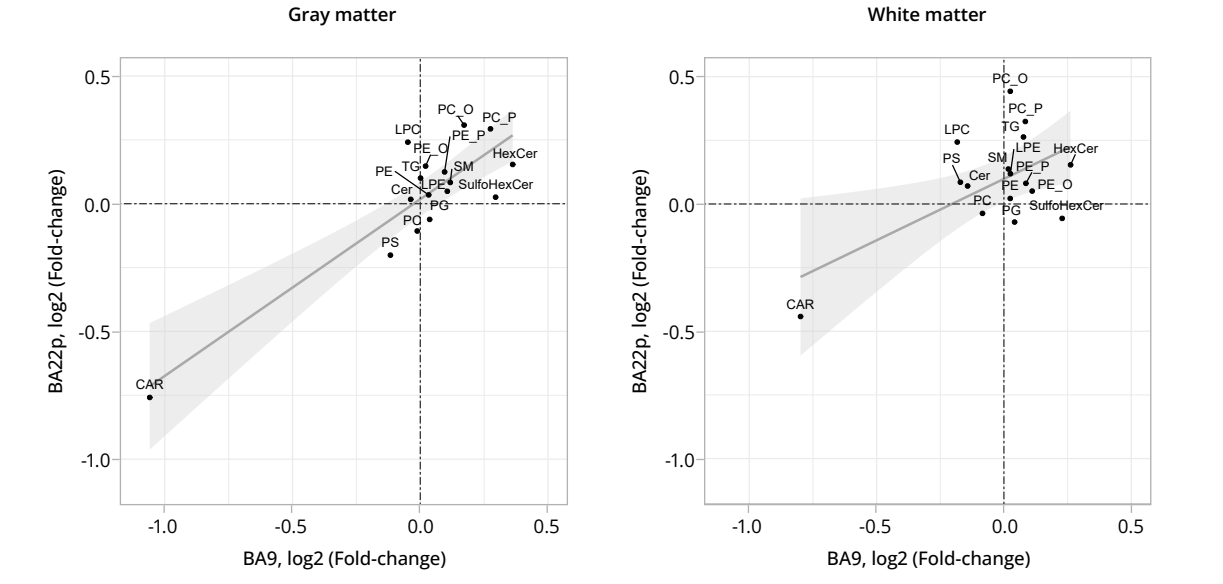


**Figure 4. Comparison of the schizophrenia-associated differences detected either in gray or white matter across the two brain regions under investigation.**

*Note:* Each point signifies the average difference (fold-change) in lipid intensity levels between the schizophrenia and control samples, calculated for all lipids within a specific lipid class in either the BA9 (x-axis) or BA22p (y-axis) brain region section. Linear regression lines are drawn with 95% confidence intervals represented by gray shaded areas.
BA9 — Brodmann area 9; BA22p — Brodmann area 22 posterior; SM — sphingomyelin; PC — posphatidylcholine; LPC — lysophosphatidylcholine; CAR — carnitine; PS — phosphoserine; Cer — ceramide; HexCer — hexoceramide; SulfoHexCer — sulfohexoceramide; TG — triglyceride; PC_O and PC_P — ether-linked phosphatidylcholine.
*Source:* Osetrova et al., 2024.

Analysis of compound intensity differences between the SZ and HC sections using the 131 annotated MALDI peaks yielded twice as many schizophrenia-associated differences in the BA22p region compared to BA9 in the WM: 31 and 17 lipid intensity differences, respectively (one-sided proportion t-test, $p$=0.019) (Figure 3). However, this disconnect was not statistically significant for the GM, where we had identified 27 and 21 lipid intensity differences, respectively (one-sided proportion t-test, $p$=0.212) (Figure 3).

In order to directly compare the lipid intensity differences associated with SZ between the two neocortical regions under investigation, we computed and contrasted the average fold-change values for each of the 16 lipid classes within each histological cluster. The differences associated with SZ showed a significant positive correlation between BA22p and BA9 in both the gray matter and white matter areas (Figure 4 and Table S4 in the Supplementary). As predicted from the greater discrepancy between the two brain regions in the number of schizophrenia-affected lipids in the white matter shown in Figure 3, correlation of the schizophrenia-associated differences between BA22p and BA9 in the white matter (Pearson correlation, $r$=0.57, $p$=0.017) compared to the gray matter (Pearson correlation, $r$=0.87, $p$=0.00001) was also significantly lower (one-sided two-sample Z-test on Fisher transformed Person's R, $p$=0.040).

Our analysis further highlighted certain lipid classes that demonstrated the most significant amplitude of schizophrenia-associated differences in both neocortical regions. Specifically, acyl-carnitines showed notably lower intensities in both BA22p and BA9 across both histological clusters. If acyl-carnitines were removed from the sample of lipid classes being analyzed, the correlation between regions would decrease in both tissue types, remaining positive and statistically significant for gray matter (Pearson's R=0.49, $p$=0.03194) and disappearing in the case of white matter (Pearson's R=−0.05, $p$=0.57).

## DISCUSSION

### Key results

The present study utilized MALDI-MSI to analyze the cortical sections corresponding to BA22p and BA9 in schizophrenia patients and healthy controls. Our findings suggest that schizophrenia is associated with alterations in lipid composition for the two regions investigated. Notably, we observed approximately twice as many differences in the white matter section of BA22p compared to BA9. This underscores the differential association of schizophrenia in these two functionally and structurally distinct cortical regions. While our results show significant agreement of schizophrenia-associated alterations between the two examined brain regions both in gray and white matter, they also indicate a stronger correlation of schizophrenia-associated differences in the gray matter than in the white matter between these two examined brain areas. This implies that, while the dorsolateral prefrontal cortex (BA9), a commonly investigated region in schizophrenia research, shares most of the schizophrenia-associated alterations with the anatomically distinct temporal lobe region (BA22p), it exhibits fewer differences in the infracortical white matter.

### Limitations

Our study had several limitations. First, the number of schizophrenia and control samples used for the analysis was limited to 24, with each condition represented by six samples in each of the two brain regions. Second, our lipid compound annotation was restricted to computational predictions and did not rely on the compound fragmentation spectrum, which would have allowed for more precise identification. Nonetheless, despite these limitations, we observed a positive correlation of schizophrenia-associated differences between two independently measured brain regions. Furthermore, although computational annotation might be imprecise at the individual compound level, it is much more reliable at the lipid class level, as confirmed by the alignment of our results between brain regions. Lastly, our study design did not exclude the potential influence of confounding variables on the lipid composition of the examined brain regions — such as the use of antipsychotic medication, which has been shown to have an impact on the rodent brain [37].

Moreover, due to the limited number of samples analysed in this study, individual effects might interfere with the results, as well as a slight disbalance in sex and age between the two sample sets. However, the fact that the extent of schizophrenia-associated differences in the subcortical white matter of schizophrenia patients is substantially greater in the temporal lobe compared to the prefrontal cortex, while there is no such bias for gray matter, would require an anatomically and histologically dependent effect of these confounding variables on the brain lipidome. This is less likely than a true biological effect, considering previous observations of a higher level

of alterations associated with BA22p in gene expression [29] and structural MRI studies [38].

### Interpretation

Our observation of the greater extent of lipidome alterations associated with BA22p aligns well with existing knowledge regarding this region. Numerous neuroimaging studies have previously demonstrated substantial structural abnormalities in the superior temporal gyrus, which encompasses BA22p, in schizophrenia patients [39]. Moreover, variations in the superior temporal gyrus volume have been directly associated with the severity of auditory hallucinations in schizophrenia patients [40–42]. More recently, a study conducted on first-episode treatment-naive schizophrenia patients using structural MRI reported significant alterations in the myelin content in the superior temporal gyrus, but not in the dorsolateral prefrontal cortex [43]. Similarly, molecular studies of BA22 have identified multiple alterations in the transcriptome and proteome in schizophrenia that affect cell adhesion, synaptic transmission, axon guidance, and energy metabolism pathways [26, 44]. Notably, gene expression studies of schizophrenic brains examining 12 and 15 different neocortical regions, including the dorsolateral prefrontal cortex, have consistently found the highest number of alterations in BA22 [29, 45].

Our study aimed to assess whether the lipidome differences associated with schizophrenia, detected in the commonly studied neocortical brain region, BA9, are reflective of the differences present in other neocortical regions. Furthermore, we explored whether incorporating a spatial resolution dimension could reveal additional schizophrenia-associated features within the lipidome alterations. Our findings demonstrate that the spatial lipidomics approach is indeed capable of detecting subtle differences in schizophrenia-associated effects between the two examined higher level association regions of the neocortex. In addition to identifying a generally weaker association of schizophrenia with the white subcortical matter lipid composition of BA9 compared to BA22p, we observed substantial differences in a number of lipid classes with respect to the amplitude of schizophrenia-associated effects between the two regions. Interestingly, the changes were closer for the gray matter clusters of the two investigated regions rather than the white matter ones. Among the most lipid classes with conserved differences for both regions were plasmalogens, previously shown to be associated with schizophrenia in terms of the plasma lipidome [46–48]. Of special interest were acyl-carnitines that demonstrate highly conserved changes with the greatest amplitude in both regions and both types of tissues, being also responsible for the statistically significant correlation in the case of white matter. Schizophrenia patients demonstrated decreased levels for the majority of acyl-carnitines in blood plasma [47, 49], while studies that focused on a brain transcriptome analysis of the dorsolateral prefrontal cortex highlighted acyl-carnitines biosynthesis impairment, as well as an association of changes in the lipid content with cognitive symptoms of schizophrenia [15]. Thus, our results fit into the overall picture of the brain lipid differences associated with schizophrenia.

## CONCLUSION

Collectively, our findings suggest that including other neocortical regions beyond the dorsolateral prefrontal cortex into a schizophrenia-associated molecular study might yield promising new insight into the pathology of this disease. Moreover, our results underscore the value of a spatial resolution analysis, which allows for the separation of neocortical sections into gray and white matter areas for data analysis. Through such separation, we were able to identify substantial differences between these two brain regions with respect to schizophrenia-associated alterations in the subcortical white matter, but not in the cortical gray matter. This insight highlights the need for further spatial resolution studies to better understand the molecular alterations associated with complex brain phenotypes such as psychiatric disorders, including schizophrenia.


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## Supplementary data

Supplementary material to this article can be found in the online version:

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Table S2: https://doi.org/10.17816/CP15488-145327

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# Mechanisms and Functions of the Cerebral-Cognitive Reserve in Patients with Alzheimer's Disease: A Narrative Review

## Механизмы и функции церебрально-когнитивного резерва при болезни Альцгеймера: нарративный обзор литературы

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**Review**

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**ABSTRACT**

**BACKGROUND:** The need for scientific knowledge about aging is predicated on the demand of modern society to extend the active life of a person. To maintain intellectual longevity, it is necessary to take into account not only the pathological, but also compensatory mechanisms that arise during aging. The cerebral-cognitive reserve (CCR) influences the rate of transition from pre-phenomenological stages to the clinical stage of the disease, thereby changing the prognosis of Alzheimer's disease (AD).

**AIM:** The aim of this work was to review meta-analyses from studies that have examined the principles and functions of the CCR in people with AD.

**METHODS:** The work included 83 scientific publications devoted to the issues of the CCR in neurodegenerative diseases such as AD. The Results and Discussion sections of this article provide reviews of the results of 12 meta-analyses published from 2012 to 2024 and selected from the PubMed and eLibrary databases using the following keywords in English and Russian: "cerebral reserve", "cognitive "reserve", and "Alzheimer's disease". The scope of the definition was not limited, since the goal here was to determine the terminological boundaries of the concepts of "cognitive reserve" and "single brain reserve".

**RESULTS:** The modern understanding of AD as a biological continuum covering the preclinical, prodromal, and clinical phases of the disease makes it possible to infer that insufficiency of protective factors underlies the progression of AD. The cognitive reserve is involved in the sanogenetic protective mechanism during neurodegeneration. The cognitive reserve is a theoretical concept that reflects modern research's understanding of how the integrative functioning of the brain (cerebral) and cognitive reserves extend the period of active intellectual longevity through energy-saving mechanisms. It considers these mechanisms as central to healthy mental activity and in slowing the progression of neurodegenerative diseases. At some point, an increase in excess interneuronal activity that reflects the hypercompensatory function

of the reserve would accelerate the depletion of brain structures and contribute to clinical and psychopathological manifestations of AD.

**CONCLUSION:** The concept of the CCR puts the spotlight on the need to determine the compensatory indicators of cognitive deficit in AD, assess the architecture and volume of the reserve, and develop and follow protocols for its maintenance. It appears just as crucial to adopt measures to prevent the Reserve's depletion as early as at the preclinical stages of the disease. Elaborating protective and compensatory mechanisms that help to maintain the functional activity of the brain in conditions of neurodegeneration, that is, CCR, require further research and can form a conceptual basis for the prevention of AD, starting from the preclinical stages of the disease.

**АННОТАЦИЯ**

**ВВЕДЕНИЕ:** Необходимость научного познания старения мозга обусловлена запросами современного общества на продление активной жизни человека. Для поддержания интеллектуального долголетия необходимо учитывать не только патологические, но и компенсаторные механизмы, участвующие в старении. Церебро-когнитивный резерв (ЦКР) оказывает влияние на скорость перехода дофеноменологического этапа к клиническому этапу болезни, тем самым изменяя прогноз болезни Альцгеймера (БА).

**ЦЕЛЬ:** Произвести обзор научных публикаций, посвященных изучению механизмов и функций ЦКР у лиц, страдающих БА.

**МЕТОДЫ:** В работу было взято 83 публикации по проблеме ЦКР при нейродегенеративном заболевании на примере БА. В обзор вошли 12 метаанализов, опубликованных с 2012 по 2024 год, отобранных в базе данных PubMed и электронной библиотеке eLIBRARY по следующим ключевым словам на русском и английском языке: «церебральный резерв», «когнитивный резерв», «болезнь Альцгеймера». Глубину поиска не ограничивали, поскольку одной из задач работы было определение терминологических границ понятий «когнитивный резерв» и «церебральный резерв».

**РЕЗУЛЬТАТЫ:** Современное представление о БА как о биологическом континууме, охватывающем доклиническую, продромальную и клиническую фазу заболевания, позволяет понять, что недостаточность протективных механизмов лежит в основе прогредиентности БА. Когнитивный резерв является примером саногенетического защитного механизма при нейродегенерации. Когнитивный резерв — это теоретическая концепция, отражающая представления современных исследователей об интегративном функционировании мозгового (церебрального) и когнитивного резервов, пролонгирующих период активного интеллектуального долголетия за счет энергосберегающих стратегий, лежащих в основе здоровой психической активности и снижающих прогредиентность нейродегенеративной болезни. На этапах развернутого заболевания чрезмерная межнейронная активность, отражающая гиперкомпенсаторную функцию резерва, способствует ускоренному истощению мозговых структур, облегчая клинико-психопатологические проявления БА.

**ЗАКЛЮЧЕНИЕ:** Концепция ЦКР делает актуальным вопрос поиска компенсаторных механизмов когнитивного дефицита при БА, а также оценку структуры и объема резерва, разработку и реализацию программ его поддержания, профилактику его истощения, начиная с доклинического этапа болезни. Защитно-компенсаторные механизмы поддержания функциональной активности головного мозга в условиях нейродегенерации, то есть ЦКР, требуют дальнейшего изучения и могут составить концептуальную основу профилактики БА, начиная с доклинических стадий заболевания.

**Keywords:** *cerebral reserve; cognitive reserve; Alzheimer's disease*
**Ключевые слова:** *церебральный резерв; когнитивный резерв; болезнь Альцгеймера*

## INTRODUCTION

The need for a scientific understanding of how the brain ages is rooted in the current demands in society for an extended active life. Researchers are convinced that not only the pathological, but also compensatory mechanisms of aging should be taken into account in order to maintain intellectual longevity [1]. According to Stern et al., the cognitive reserve (CR) is one of the protective mechanisms against clinically significant cognitive decline, even in the presence of neurodegeneration [2]. Not only Stern, but other authors as well note that the CR increases brain efficiency and intellectual productivity [3]. Individuals with a high CR are resistant to clinical manifestations of Alzheimer's disease (AD) and other neurodegenerative diseases [4, 5]. Advanced brain studies have shown that some elderly people retain their cognitive capacity through life despite suffering significant cerebral atrophy and degeneration [6]. Such significant differences between degrees of brain damage and severity of clinical signs (or absence thereof) stand at the basis of the CR concept [7].

It is now recognized that pathophysiological changes begin many years prior to the appearance of clinical manifestations of the disease and that the spectrum of AD spans from clinically asymptomatic to severely impaired individuals [8]. Advances in biomarker research have furthered our understanding of AD as a structurally complex process moving along an unbroken continuum [9, 10]. The pathophysiological basis of the AD continuum is the multifactorial etiology and pathogenesis of the disease [11]. Biomarkers such as gene mutations, amyloid and tau pathology [12, 13], neuroinflammation, mitochondrial dysfunction, and other pathological processes become involved in the multifactorial pathogenesis of AD decades before the onset of the first clinical symptoms of the disease and are responsible for the stepwise, gradual disease progression [14, 15]. Some of these factors are currently considered AD biomarkers, appearing decades before the onset of clinical symptoms [16, 17].

Transition from the preclinical (latent) stage to symptomatic AD depends on the interaction between pathological and protective factors. The CR may prevent the transition of AD to the clinical stage in some carriers of AD biomarkers [18]. In other words, individuals differ in their ability to cope with changes associated with aging, disease, or brain injury. However, AD patients with similar disease manifestations and a comparable degree of cognitive decline may be experiencing different changes in brain morphology. The question then arises: "What is the degree of brain resistance to pathogenic stimuli?" The significance of brain repair mechanisms and the role of the brain and CR at the latent and clinically apparent stages of the disease also remain unclear.

The aim of our work was to review scientific publications that have investigated the mechanisms and functions of the brain and cognitive reserve (BCR) in AD patients.

## METHODS

### Eligibility criteria

Inclusion criteria:

- full-text publications (meta-analyses, original studies, descriptive reviews) selected using the keywords "cognitive reserve", "Alzheimer's disease", "brain reserve";
- publications selected for review had to contain a description, analysis, or results of studies that enrolled patients with AD diagnosed according to the criteria of the International Classification of Diseases, 10$^{th}$ revision (ICD-10), or the Diagnostic and Statistical Manual of Mental Disorders, 5$^{th}$ edition (DSM-5).

Exclusion criteria:

- participants included in the selected studies were not verified as AD patients according to the ICD-10 and DSM-5 criteria.

### Information sources

Using the combination of the above-mentioned keywords, which provides a high-quality description of the content and increases the efficacy of the publications search, we carried out a descriptive review of 83 scientific publications. The aim of this review was to investigate the mechanisms and functions of the BCR in patients with AD. Publications were selected using the inclusion criteria (see above). The study materials were publications included in PubMed, the biomedical literature search engine, and eLIBRARY, the electronic library.

The scope of the search was not limited, since one of the objectives of this work was to define the terminological boundaries of the concepts of "cognitive reserve" and "brain reserve". Therefore, the list of references includes works published 10 or more years ago.

A review of 12 meta-analyses published from 2012 to 2024 and identified in the PubMed database using the

above-stated keywords is presented in the Results and Discussion sections of this work.

### Search strategy

Publications were searched step by step. The search sequence is shown in Figure 1.

### Selection process

Each publication was selected using a manual search. Several of the authors involved in this work performed the search and selection of publications (see "Authors' contributions"). Some publications selected at the screening stage were subsequently excluded from further analysis, because they did not meet the inclusion criteria.

### Analysis of the results

Each publication was analyzed. A synthesis of the information obtained from the selected scientific sources was performed. The results of the synthesis are presented in structured text, tables, and figures.

## RESULTS

### Concept of cognitive reserve

Some researchers working on neurodegenerative disorders seek to determine why some individuals retain their normal cognitive functions despite experiencing significant cerebral degeneration and to identify the mechanisms that trigger CR involvement. To answer this question, it appears necessary to clearly outline the terminological boundaries of the concept of CR (Table 1).

In our opinion, an exhaustive definition of CR has not yet been formulated, though the view of CR as a set of processes resisting neurodegeneration from its earliest preclinical stages allows us to answer the question of why some individuals successfully cope with progressive brain disorders, while others cannot tolerate the same level of brain damage.

To study and evaluate the brain repair mechanisms in neurodegeneration, it is necessary to know the features of its pathogenesis. An executive summary of current models of AD development is presented in Table 2.

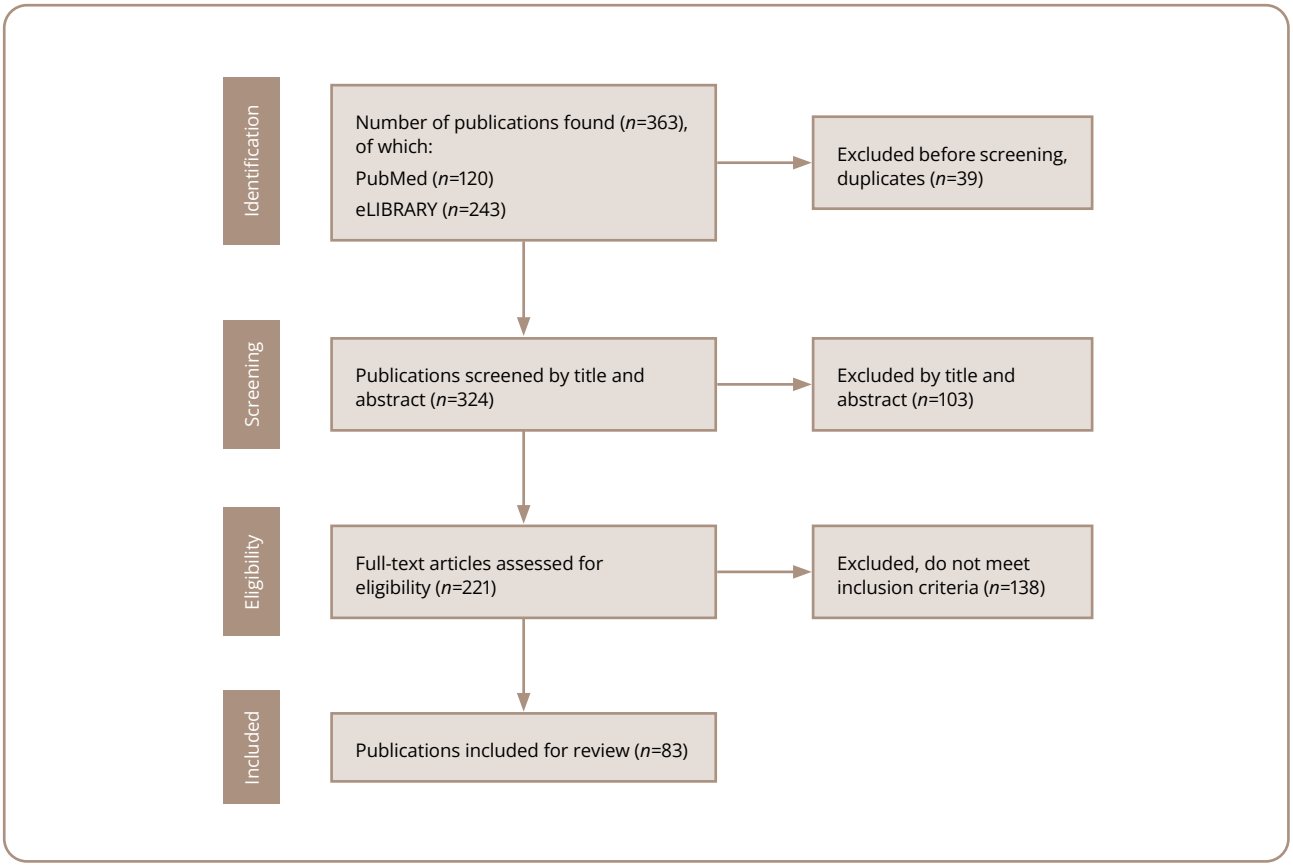


**Figure 1. Steps in the search for publications to be analyzed.**

*Source*: Sidenkova et al., 2024.

**Table 1. Formation of the cognitive reserve concept**

| Authors | Year of publication | Definition of cognitive reserve (CR) |
|---|---|---|
| Stern [19] | 2002 | CR is a combined factor that is influenced by the accumulated life experience. It cannot be measured directly due to its multifactorial and dynamic nature. |
| Soldan et al. [20] | 2017 | CR is a theoretical, abstract concept suggesting that greater engagement in cognitively stimulating activities throughout life modifies the brain, thus reducing the negative impact of brain disorders on cognitive function. |
| Stern et al. [21] | 2019 | CR is an individual's ability to optimize cognitive function through differential recruitment of brain structures or neural networks in brain activity. |
| Soldan et al. [22] | 2020 | CR is an ability of the brain to mitigate the sequelae of brain disorders or cognitive function impairment. |
| Stern et al. [23] | 2022 | The definition of CR includes two independent components:<br>1) assessment of brain damage affecting cognitive functions;<br>2) assessment of cognition;<br>3) measurement of the variable that affects steps (1) and (2). |

**Table 2. Dynamic models of Alzheimer's disease**

| Authors | Year of publication | Description of an AD model |
|---|---|---|
| *Hypothetical model of dynamic biomarkers of the AD pathological cascade* | | |
| Jack et al. [24] | 2010 | The sequential change of preclinical, prodromal, and dementia stages of Alzheimer's disease is caused by the interaction of 2 types of biomarkers:<br>- biomarkers associated with the presence of disease;<br>- biomarkers associated with the stage (i.e. progression) of disease. |
| *Biomarker model of preclinical AD* | | |
| Sperling et al. [25] | 2011 | This model reflects the cumulative nonlinear dynamics of several biomarker types:<br>- reductions in Aβ42 in the cerebrospinal fluid and increased amyloid tracer retention on PET imaging are biomarkers of brain Aβ amyloidosis;<br>- elevated CSF tau protein is a biomarker of neuronal injury;<br>- decreased fluorodeoxyglucose 18 uptake on PET with a temporoparietal pattern of hypometabolism is a biomarker of synaptic dysfunction;<br>- atrophy of medial temporal lobes, paralimbic and temporoparietal cortices on structural MRI is a biomarker of neurodegeneration. |
| *AD model of the National Institute on Aging and the Alzheimer's Association Workgroup (NIA-AA), 2018* | | |
| Jack et al. [26] | 2018 | AD diagnosis should be based on combined (clinical and biomarker) diagnostic criteria. According to these criteria, the early preclinical (presymptomatic) AD stage is diagnosed if Aβ biomarker is positive *in vivo.* Symptomatic AD is confirmed by *in vivo* detection of Aβ and pathological tau, as well as neurocognitive impairment. |
| *Multi-marker model of AD (A/T/N)* | | |
| Lodder et al. [27] | 2021 | This model takes into account the profiles of several biomarkers detected in evaluated patient:<br>- "A" refers to amyloid pathology and is determined by the presence of Aβ42 or Aβ42/Aβ40 in the CSF or Aβ in the brain structures on PET imaging;<br>- "T" refers to tau pathology and is determined by the presence of phospho-tau in the CSF or detection of abnormal tau filaments (intracellular thread-like tau structures) in the brain parenchyma on PET imaging);<br>- "N" refers to neurodegeneration and is confirmed by the presence of tau in the CSF and in the brain parenchyma on MRI or 18F-fluorodeoxyglucose PET. |

*Note:* AD — Alzheimer's disease; PET — positron emission tomography; MRI — magnetic resonance imaging; CSF — cerebrospinal fluid.

The authors of a meta-analysis of 17 functional MRI (fMRI) cohort studies reported a high probability of dementia in individuals with localized, increased activation of the left anterior cingulate cortex during cognitive tasks, compared with older adults who activate a broad network of brain regions during intellectual workload, including the medial and lateral frontal areas and the precuneus. That is, AD affects the frontoparietal network responsible for the cognitive control associated with general tasks. Detection of certain biomarkers, e.g. changes in specific fMRI activity

and tauopathies, increases the probability of dementia by a factor of 2 [28]. The probability of dementia increases in neurodegeneration carriers. This finding has been confirmed in different study cohorts; for example, the probability of dementia stood at 54% in a cohort with brain damage confirmed by neuroimaging, compared with 26% in the control group [29]. However, clinical and neuropsychological assessments do not always identify dementia in patients with signs of neurodegeneration. Indeed, studies have shown that a significant proportion of community-dwelling older adults with advanced neurodegeneration do not develop dementia. This apparent disconnect is explained by the combined influence of several factors: genetic polymorphism, other brain disorders, slow disease progression, lifestyle factors, CBR volume, and premature mortality from concomitant diseases [30]: that is, the multimarker dementia model based on the risks of AD in a probabilistic aspect.

## Concept of brain and cognitive reserves

Some researchers suggest distinguishing the brain (passive) reserve and the cognitive (active) reserve [21]. However, not all researchers agree with this approach and prefer the general concept of a single reserve, using the term CR [31]. We will nevertheless describe the mechanisms underlying the brain and cognitive reserves, according to different authors (Table 3).

A multicenter observational study on predementia Alzheimer's disease performed at the German Center for Neurodegenerative Diseases demonstrated that large volumes of hippocampal subfields, particularly CA1, may serve as a brain backup system that ensures normal cognition and absence of subjective cognitive decline in patients with amyloid pathology [36]. The study also showed that this effect does not depend on the education level, or psychological or social characteristics of the participants [36]. On the contrary, other authors show that CR mechanisms are closely associated with the tau pathology and tau deposition in the medial and inferior temporal lobes [37].

Some authors believe that CR is a property of the brain that allows for cognitive performance that is better than expected given the degree of brain damage associated with neurodegeneration, traumatic brain injury, or other diseases [38]. Meta-analyses of cohort studies on CR localization in healthy aging, AD, and mild cognitive disorders, such as mild cognitive impairment (MCI), using functional MRI and positron emission tomography (PET) of the brain, demonstrated that in healthy and pathological aging CR is mediated by different brain regions [39]. In healthy older adults, the same cognitive tasks are associated with the activation of a broad network of brain regions, including the medial and lateral frontal regions (anterior cingulate cortex, dorsolateral prefrontal cortex, precuneus). In patients with AD and amnestic MCI, successful completion of the same cognitive task is associated with isolated activation of the anterior cingulate cortex [40]. A positive correlation between the brain volume and CR has also been demonstrated [41]. In a systematic review, Harrison et al. defined CR as the ability to use more efficient and flexible cognitive strategies, and engaging alternative networks, which can be enhanced through continuous cognitive training [42].

**Table 3. Mechanisms of brain reserve**

| Author | Year of publication | Concept |
|---|---|---|
| Barnes, McNaughton [32]<br>Norris et al. [33] | 1980<br>1996 | Studies on animal models have shown that CR depends not on the number of neurons, but on their plasticity and the quality of connections between them. |
| Katzman et al. [7] | 1988 | The concept of CR includes such parameters as brain size, the proportion of healthy and abnormal neurons, and the structural integrity of neurons and synapses. This model defines brain reserve as an organ (physical) quality of the brain: some people have larger brains, with more neurons and synapses, which, according to researchers, maintains the brain's resilience to damage, preventing cognitive dysfunction. |
| Kunkle et al.[34] | 2019 | CR becomes evident in the settings of neuropil loss, manifested by axon shortening and dendrite thinning. This results in loss of pathways transmitting signals between neuronal bodies, while a more powerful signal than normal is transmitted through the remaining synapses. This results in neuronal hyperexcitability. |
| Soldan et al. [35] | 2020 | CR is a morphological concept reflecting the structural properties of the brain that ensure its ability to maintain cognitive functions despite the significant loss of their material substrate. |

*Note:* CR — cognitive reserve.

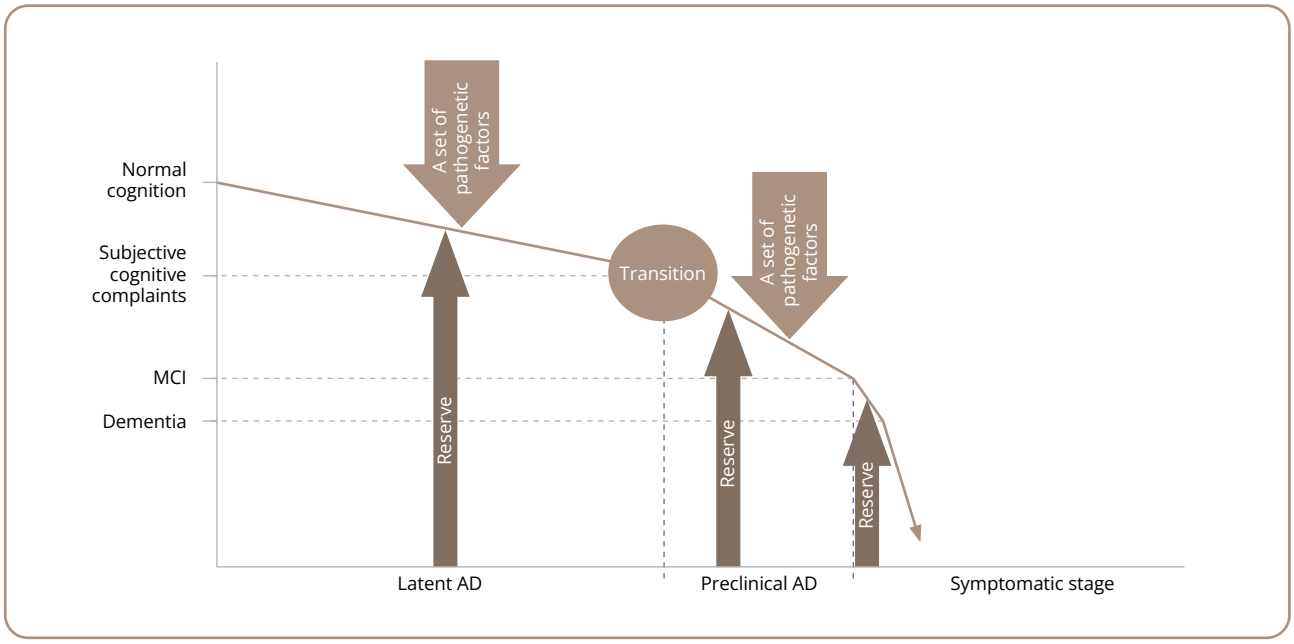


**Figure 2. Brain and cognitive reserve in Alzheimer's disease.**

*Note:* MCI — mild cognitive impairment; AD — Alzheimer's disease.
*Source*: Sidenkova et al., 2024.

Meta-analyses show that CR is influenced by numerous environmental factors and individual psychological features, such as gerotranscendence, psychological well-being, the coping strategies used, and lifelong self-regulation strategies [43].

The following combination of morphofunctional and psychosocial factors makes cognitive (active) reserve possible:

- The morphofunctional characteristics of brain cells include a relatively increased size of the neuron body, a large number of axons, synapses, intensive DNA and RNA synthesis, and active functioning of presynaptic receptors [28].
- The psychological and social factors developed during lifetime are intelligence indicators, the level of education, professional affiliation, the volume of leisure activities, as well as the cognitive, communicative, social, and motivational activity of an individual [44–46].

According to current knowledge, the brain and cognitive reserves are not mutually exclusive. The dynamic capacity and structural characteristics of the neural network determine the quality of brain functioning in the settings of age-related changes and cerebral disorders. A systematic review and meta-analysis by Nelson et al. convincingly demonstrate that a higher CR is associated with a lower relative risk of MCI or dementia progression, reducing the risk of symptomatic AD almost twofold (47%) [47]. These results suggest that CR delays the onset of MCI and dementia in AD, and, therefore, serves as a potential target for preventive interventions.

The models of brain and cognitive reserves reflect the substrate and level of brain functioning, and represent a BCR. BCR is dynamic and depends on environmental factors and an individual's life experiences throughout their lifespan.

## Functions of brain and cognitive reserve

The brain and cognitive reserve reduce the negative impact of degeneration on the brain function in several ways described below.

BCR reduces MCI or dementia risk through mechanisms independent of the degree of neurodegeneration [48].

BCR interacts with markers of brain pathology or health, influencing future cognitive decline or the risk of disease progression. The protective effects of BCR decrease as the number of damaged neurons increases [49].

The protective effect of BCR increases with later AD onset and a lower rate of damaged substrate accumulation [50].

In individuals with a high reserve, neurodegeneration is less likely to affect the brain structure and function compared to those with a low reserve [51].

Data from the studies included in our meta-analyses suggest that the roles of the reserve are different in aging and neurodegeneration (Figure 2).

BCR mechanisms prevent progressive depletion of the regulatory function of the cortex, support motivational and behavioral activity, ensure functional hemispheric asymmetry, and have a neuroprotective impact during normal aging [52, 53].

BCR mechanisms support the activity of the frontal lobes and the hippocampus, and they compensate for dysfunction of these regions, allowing for the preservation of cognitive regulatory functions at preclinical AD stages, presumably thanks to the relatively larger area of the Brodmann hippocampal subfields (CA1/CA2/CA3 and subiculum), as was demonstrated in the functional MRI study in AD patients [54].

BCR delays clinical manifestations of AD until the reserve is depleted. In individuals with a large BCR volume, AD onset is characterized by pronounced symptoms, a high rate of progression, and a high incidence of affective and behavioral disorders. This is due to the fact that neurodegeneration is restrained by the reserve, but when it is depleted, this process manifests itself as marked synaptic and cholinergic neuronal dysfunction [55]. At this stage of the disease, BCR acts as a compensation mechanism aimed at reorganizing brain resources [39].

### Cognitive continuum

Another meta-analysis demonstrated that in elderly patients with AD and MCI, previously active, coordinated and extensive neural networks stop functioning, and that task performance induces the activation of energy-consuming associative connections in the frontotemporal regions, compensating for the lost capabilities of the previously extensive healthy networks [56]. In their meta-analysis, de Las Fuentes et al. explained the faster cognitive decline in patients with high BCR by the older age of the participants, and, consequently, significant accumulation of amyloid and the tau protein at symptoms onset, as well as by a high incidence of age-related concomitant diseases; e.g., cerebrovascular disorders [57]. BCR appears to delay the onset of clinical symptoms associated with underlying AD.

Our understanding of the BCR concept is supported by the analysis of certain typical clinical situations: e.g. extremely fast progression of dementia in highly educated individuals engaged in active intellectual work. Some experts believe that the educational level is a type of protection against severe cognitive impairment [58]. According to this view, the above-mentioned example of the extremely fast AD progression into severe dementia represents an inexplicable exception. In his book "Problems of Causality in Medicine", Davydovsky stated that any disease results from an interaction between a combination of pathogenic processes and protective and adaptive mechanisms aimed at restoring the impaired body self-regulation [59]. The actual manifestation of the disease is due to the failure of protective elements, when the disease breaks out. The authors of the Rotterdam study of patients with cerebrovascular disorders also came to an interesting conclusion: The lower risk of dementia in highly educated study participants could be explained by a higher BCR [60]. From this point of view, symptoms of dementia develop when the BCR depletes below a certain threshold. A smaller initial BCR would mean that less change would be required to reach the dementia threshold at which impairment would be evident, whereas a larger BCR would presumably provide greater protection against dementia. According to this theory, BCR may reflect either innate differences in cognitive abilities determined by the characteristics of prenatal synaptogenesis or postnatal maturation of brain structures (myelination, synaptic sprouting, development of hierarchical connections within the brain, etc.), which underlies the quality of cognitive processes. In any case, the level of education is an indicator of a higher BCR [61].

## DISCUSSION

Investigation of the mechanisms of AD pathogenesis allowed modern researchers to come to the conclusion that disease manifestations are the result of an interplay of two countervailing processes: traditionally widely studied neurodegeneration and the brain repair mechanisms, represented by the BCR. The aim of this review was to summarize the results of meta-analyses and original studies on the mechanisms and functions of the BCR in patients with AD. The BCR concept helps us understand why not all individuals with preclinical AD transition to the symptomatic disease, despite the development of a pathological process confirmed by biomarkers. According to some authors, this transition occurs when the protective brain repair mechanisms fail and are no longer able to maintain the body's homeostasis in the settings of progressive brain damage caused by neurodegeneration [62, 63–66]. As the number of damaged neurons increases (as evidenced by amyloidosis and tauopathy), the protective role of

the BCR that passively maintains the brain resilience to damage recedes [67]. Acceleration of disease progression and worsening of cognitive impairment, confirmed by morphological biomarkers, change the protective function of BCR into a compensatory one, which manifests itself by irrational, energy-consuming, widespread involvement of intact brain structures during cognitive tasks [68, 69]. BCR involvement in the general AD scenario implies that it is a factor, or a group of factors, capable of altering the expected course of a neurodegenerative disease [70, 71].

We believe that the BCR is formed long before brain aging. Robitaille et al. showed that the level of intelligence before the disease onset and the quality and type of leisure activity are inversely correlated with the resting regional metabolic activity of the brain and cerebral blood flow in different cortical and subcortical regions [72]. This suggests that the differences in dementia onset may have to do with the individual features of environmental and social factors not only in adulthood and old age, but also in childhood and adolescence. Liberati et al. believe that CR is not a fixed factor but is constantly changing in response to environmental factors and life experiences throughout one's lifespan, even if the brain has already sustained damage [73]. Valenzuela and Sachdev agree with this contention and state that that is why education received in childhood and early adulthood can hypothetically increase the CR volume and, as a result, delay the clinical manifestations of neurodegeneration [74].

Some researchers believe that the mechanisms underlying the BCR are triggered in the selective strengthening and recruitment of neuronal connections. The results of a meta-analysis show that BCR preserves cognitive abilities and executive function despite the decrease in the volume of the hippocampus and the associative frontoparietal cortex due to progressive neurodegeneration [75].

Erratic functioning of brain regions (brain network) is one of the marked features of neurodegeneration. Compensatory BCR function allows one to reorganize brain network activity and preserve cognitive functions [76].

Therefore, the BCR functions differ between healthy individuals and patients with neurodegenerative disorders. In normal aging, an effectively functioning BCR ensures a balance of brain network activity and energy saving during intellectual tasks [77]. At the symptomatic disease stages, excessive interneuronal activity, reflecting the hypercompensatory function of the reserve, contributes to the accelerated depletion of brain structures, promoting the development of clinical and psychopathological manifestations of AD [20, 78].

## Prospects for further research on the brain and cognitive reserve

The concept of BRC as a dynamic system retaining the ability to change under the influence of environmental factors and life experiences throughout life even in the presence of neurodegeneration is consistent with the results of meta-analyses, which showed the efficacy of neurocognitive training for brain resilience augmentation even in patients with MCI and AD [79]. A review of neuroimaging studies showed that elderly patients with AD and amnestic MCI retain compensatory mechanisms of neural network activation during cognitive tasks [80]. The authors of other studies define BCR as the ability to form effective and flexible cognitive strategies, which can be augmented through neurocognitive interventions, implying a potential role in AD dementia prevention programs [81, 82].

Thus, promising research directions in the BCR concept development are as follows:

- determination of the reserve volume associated with the degree of brain resilience to neurodegeneration; that is, the transition of AD from the latent to the clinical stage and
- alignment of reserve parameters with different biomarkers (biomarkers of neurodegeneration and disease progression) to predict the probable relationship between pathological and protective factors. This is necessary for the development of individual programs aimed at preventing the transition of preclinical AD stages to clinical ones [77, 78].

## Limitations

The holistic nature of the scientific publication coverage achieved with the combination of selected keywords means that this review includes all existing scientific papers on the given topic from the PubMed database and the eLIBRARY electronic library. A limitation with the inclusion of some publications in this review was their descriptive nature. The search was also constrained by the above-mentioned search engines and keywords. In our opinion, a common drawback of the publications included in this review is the heterogeneity of the study materials (laboratory animals, humans) in the studies included in meta-analyses; the retrospective nature of the meta-analyses; and the

checkered nature of the studies that were initially included in the meta-analysis. Therefore, the authors of this review admit the limitations of the information presented herein.

This review may be of interest to specialists in the field of mental health and cognitive neuroscience.

## CONCLUSION

The authors of this study believe that the mechanisms of AD pathogenesis cannot be properly understood without taking into account the interactions between pathogenic factors and brain repair mechanisms, such as the BCR. BCR slows the rate of transition from preclinical to clinical disease, thereby changing the AD prognosis. The BCR concept allows one to shift the emphasis towards the prevention of preclinical AD and augment therapeutic efforts at the symptomatic stages of the disease by maintaining and enhancing compensatory mechanisms. In this work, we described the different positions held by researchers regarding the BCR mechanisms and functions at different stages of AD. According to some researchers, interventions aimed at mechanisms of AD pathogenesis and the possibility of their regulation would reduce age-related morbidity and promote healthy aging. The BCR concept actualizes the problem of searching for compensatory strategies for AD-associated cognitive deficit, assessing the structure and volume of the reserve, developing and implementing programs for its maintenance, and battling its depletion as early as in the preclinical stage of the disease.


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# Biological Methods for Diagnosing Depressive Symptoms in Patients with Schizophrenia: A Narrative Review

## Биологические методы диагностики депрессивных симптомов при шизофрении: нарративный обзор литературы

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**Review**

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**ABSTRACT**

**BACKGROUND:** Depressive symptoms in patients with schizophrenia lead to more frequent exacerbations of the underlying disease, worsen the prognosis, and increase the risk of suicide. Clinical practitioners continue to face challenges in diagnosing this disorder.

**AIM:** This study aims to analyze published material on biological markers of depressive symptoms in patients with schizophrenia.

**METHODS:** The search of literature was conducted using the following electronic search engines (the total number of relevant papers found is also specified): ACCESSSS (*n*=150), Cochrane Library (*n*=48), PubMed (*n*=623), eLIBRARY (*n*=216), and Google Scholar (*n*=367). The final discussion included 67 papers consistent with the study aim and were published between January 1, 2018 and December 31, 2023.

**RESULTS:** Based on the available scaterred data, it appears that plasma biomarkers (e.g. C-reactive protein, metabolic parameters, hormones, enzymes, neurotrophic factors) are limited in specificity when it comes to diagnosing depressive symptoms in schizophrenia. Our analysis of the neuroimaging findings showed that depressive manifestations are associated with a decrease in the volume of the gray matter in the parietal, frontal, and temporal lobes (particularly in Broca's and Wernicke's areas) and in specific regions of the prefrontal cortex (including the medial right superior frontal, medial orbitofrontal, and superior and middle frontal gyri). It has been suggested that the *SIRT1*, *OXT*, *CDKAL1*, and *APOE* genes are involved in the development of depressive symptoms in patients with schizophrenia.

**CONCLUSION:** Understanding and identifying depressive symptoms in schizophrenia will improve the quality of care for patients with this disorder.

**АННОТАЦИЯ**

**ВВЕДЕНИЕ:** Депрессивная симптоматика при шизофрении приводит к более частым обострениям основного заболевания, ухудшению прогноза и повышению риска суицида. Перед клиницистами до сих пор стоит вопрос, связанный с трудностями диагностики этого расстройства.

**ЦЕЛЬ:** Произвести обзор литературы, направленный на поиск информации о биомаркерах депрессивных проявлений при шизофрении.

**МЕТОДЫ:** Поиск данных литературы осуществляли с применением следующих электронных сервисов для поиска публикаций (также указано общее число источников, обнаруженных по искомой теме): ACCESSSS (*n*=150), Cochrane Library (*n*=48), PubMed (*n*=623), eLIBRARY (*n*=216), Google Scholar (*n*=367). В итоговое обсуждение было включено 67 публикаций, соответствующих цели работы и опубликованных не ранее 01.01.2018 и не позднее 31.12.2023.

**РЕЗУЛЬТАТЫ:** При суммировании разрозненных данных предположено, что плазменные показатели (концентрация С-реактивного белка, метаболические, гормональные, ферментативные показатели, значения нейротрофических факторов) слабоспецифичны для диагностики депрессивных симптомов при шизофрении. С помощью методов нейровизуализации установлено, что уменьшение объема серого вещества в теменной, лобной и височной доле (особенно в зонах Брока и Вернике), а также в префронтальной коре — в медиальной части правой верхней лобной, медиальной орбитофронтальной, верхней и средней фронтальных извилины — связано с депрессивными проявлениями. Предполагается связь между генами *SIRT1*, *OXT*, *CDKAL1* и *APOE* в возникновении депрессивных симптомов у пациентов с шизофренией.

**ЗАКЛЮЧЕНИЕ:** Понимание и выявление депрессивных симптомов при шизофрении позволит улучшить качество помощи, получаемой пациентами с этим расстройством.

**Keywords:** *depressive symptoms; schizophrenia; neurobiology*
**Ключевые слова:** *симптомы депрессии; шизофрения; нейробиология*

## INTRODUCTION

Schizophrenia is a chronic mental disorder that affects approximately 1% of the global population [1]. In 1911, Bleuler identified affective disorders as one of the core symptoms in his "4A" framework (associations, affect, ambivalence, autism) for schizophrenia [2], a concept that continues to be recognized in modern diagnostic classifications. For instance, the International Classification of Diseases, 10th revision (ICD-10), includes both depressive and psychotic symptoms under the following categories [3]:

- F31.5 — Bipolar disorder, current episode depressed, severe, with psychotic features;
- F25.1 — Schizoaffective disorder, depressive type;
- F20.4 — Post-schizophrenic depression;
- F32.3 — Severe depressive episode with psychotic symptoms;
- F33.3 — Major depressive disorder, recurrent, severe without psychotic features.

When considering the overlap between affective and psychotic symptoms, most of the research focuses on schizoaffective disorder, which encompasses depressive episodes in the context of schizophrenia [4, 5]. However, depressive symptoms do not always meet the full diagnostic criteria for a depressive episode, which is why this review explores depressive manifestations of schizophrenia.

The transition from Liddle's two- (positive and negative symptoms) and three-factor model (positive symptoms, negative symptoms, and disorganization) of schizophrenia

[6] to the five-factor model underscores the distinct role and significance of depressive symptoms in the disease's structure. Reflecting on evolving diagnostic paradigms, Mosolov et al. [7] highlight the independence and value of the dimensional model in psychiatry. The 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1] outlines 8 clinical dimensions for schizophrenia spectrum and other psychotic disorders:

- hallucinations;
- delusional beliefs;
- disorganized speech;
- abnormal psychomotor behavior;
- negative symptoms;
- impaired cognition;
- depression;
- mania.

ICD-11 [8] identifies domains of schizophrenia and other primary psychotic disorders similar to dimensions (used as additional codes): positive, negative, depressive, manic, psychomotor, cognitive. Thus, the importance of identifying depressive symptoms is recognized in both classifications [9].

The relationship between schizophrenia and depressive symptoms is bidirectional: the presence of depressive symptoms worsens the course of schizophrenia, while a more severe progression of schizophrenia increases the likelihood of developing depressive symptoms [10]. The reported prevalence of depressive symptoms among individuals with schizophrenia varies widely, from 6% to 75% [11], depending on factors such as study design, disease stage, and diagnostic methods [12]. On average, depressive states occur in about 25% of patients with schizophrenia, a rate higher than that in the general population [13]. Additionally, depressive symptoms can manifest themselves at any stage of schizophrenia [14] and tend to be more severe in males [15]. These are often the most common and persistent symptoms of schizophrenia [16], contributing to reduced social functioning [10, 17], strained family relationships, and poorer treatment adherence [18]. Vauth et al. found that two-thirds of patients with schizophrenia are unable to fulfill basic social roles, and that only one-third are employed, often in positions requiring less qualifications than those they held before the onset of the illness [19]. As a result, depressive symptoms in schizophrenia contribute to dysfunction in the conduct of daily tasks [20]. Furthermore, the presence of depressive symptoms increases the risk of suicide in individuals with schizophrenia [21] and suicide is a leading factor in the reduced life expectancy of these patients [22], particularly in the early stages of the disease [23].

While the diagnosis of schizophrenia remained based on the presence of specific symptoms according to ICD-10 criteria [3], it also is a highly heterogeneous disorder. Although biomarkers are widely used in other areas of medicine, they remain absent for psychiatric conditions like schizophrenia [24]. Understanding the pathophysiology of depressive symptoms in schizophrenia could improve diagnosis and infrom more effective treatment choices [25].

The aim of this review is to analyze publications focused on identifying biological markers of depressive symptoms in schizophrenia.

## METHODS

### Eligibility criteria

Inclusion criteria:

- study participants had a confirmed diagnosis of "Schizophrenia" with depressive manifestations;
- studies aimed at identifying biological markers of depressive symptoms in schizophrenia;
- publication in English and/or in Russian;
- the period of publication is from January 01, 2018, to December 31, 2023.

Exclusion criteria:

- study participants had disorders comorbid with schizophrenia, including a depressive and/or manic episode.

### Information sources

The search for papers was conducted using the following keywords in both Russian and English (as well as their combinations): "depressive symptoms", "schizophrenia", "neurobiology", "biological markers", "blood plasma", "gene". Articles from January 01, 2018, to December 31, 2023, were selected. This time period was selected to encompass the most relevant studies based on their recency. The group of authors conducted the information search process in turn and collegially. Each of the authors took equal part in the development of inclusion and exclusion criteria, data selection, information processing, and the writing of the literature review.

### Search strategy

The search was conducted according to the principles of the clinical decision-making model "6S Hierarchy of

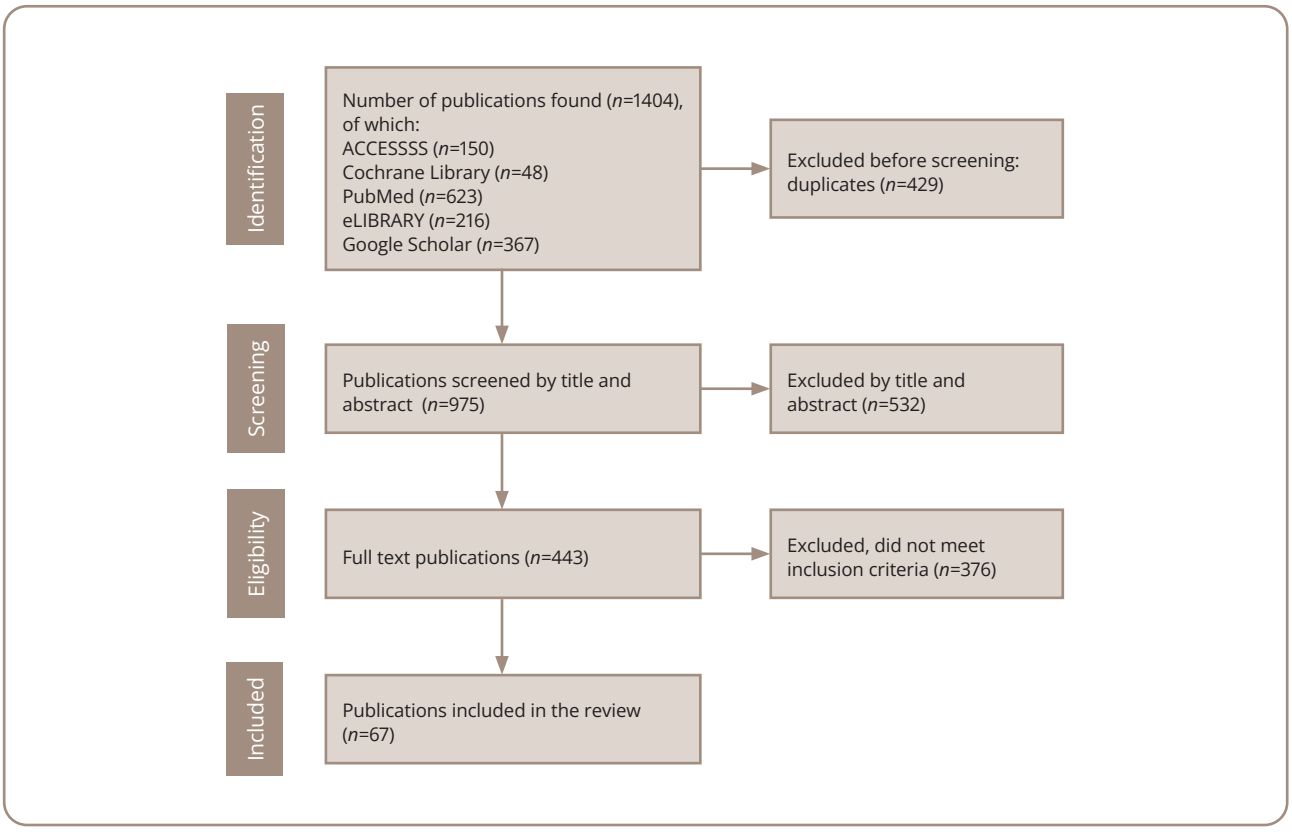


**Figure 1. PRISMA flow diagram of the literature search and the selection process.**

*Source:* Sultanova et al., 2024.

EBM Resources"[1] [26] using the service for the search for publications ACCESSSS from McMaster PLUS[2] (Figure 1).

The structure of the "6S Hierarchy of EBM Resources" model is presented in Figure 2.

The search resulted in the extraction of clinical guidelines from DynaMed (*n*=40), BMJ Best Practice (*n*=30), and EBM Guidelines (*n*=9), from which all papers were excluded by abstract and title (*n*=79), as none of them met the selection criteria. No systematic guidelines were identified, and the next stage of the search included systematic review-level studies (ACP Journal Club, *n*=2; McMaster PLUS, *n*=18). None of the studies met the inclusion criteria (*n*=20). Further screening was performed from unrated sources (*n*=51), including UpToDate, of which 4 articles met the criteria and were included in the current review.

One publication from the Cochrane Library (*n*=48) was included in the review[3]. Studies (*n*=839) were also extracted from the PubMed (*n*=623)[4] and eLIBRARY (*n*=216)[5] portals, of which 24 were included in the final version of the article (duplicates were excluded beforehand). The remaining sources were selected in Google Scholar (*n*=367), and 38 sources were included in the final version of the paper. The primary challenge in the search was ensuring the careful exclusion of studies where patients with schizophrenia had a comorbid depressive disorder, as this review focuses solely on publications addressing depressive manifestations at the symptomatic level.

[1] 6S Hierarchy of EBM Resources is a hierarchy of resources (information sources) based on evidence-based medicine and provides a model for guiding clinical decision-making.

[2] Available from: https://www.accessss.org/

[3] Cochrane [Internet]. London: Cochrane [cited 2024 Aug 26]. Available from: https://www.cochrane.org

[4] PubMed [Internet]. Bethesda: National Center for Biotechnology Information, U.S. National Library of Medicine [cited 2024 Aug 26]. Available from: https://pubmed.ncbi.nlm.nih.gov

[5] eLIBRARY.RU [Internet]. Moscow: Scientific Electronic Library [cited 2024 Aug 26]. Available from: https://elibrary.ru

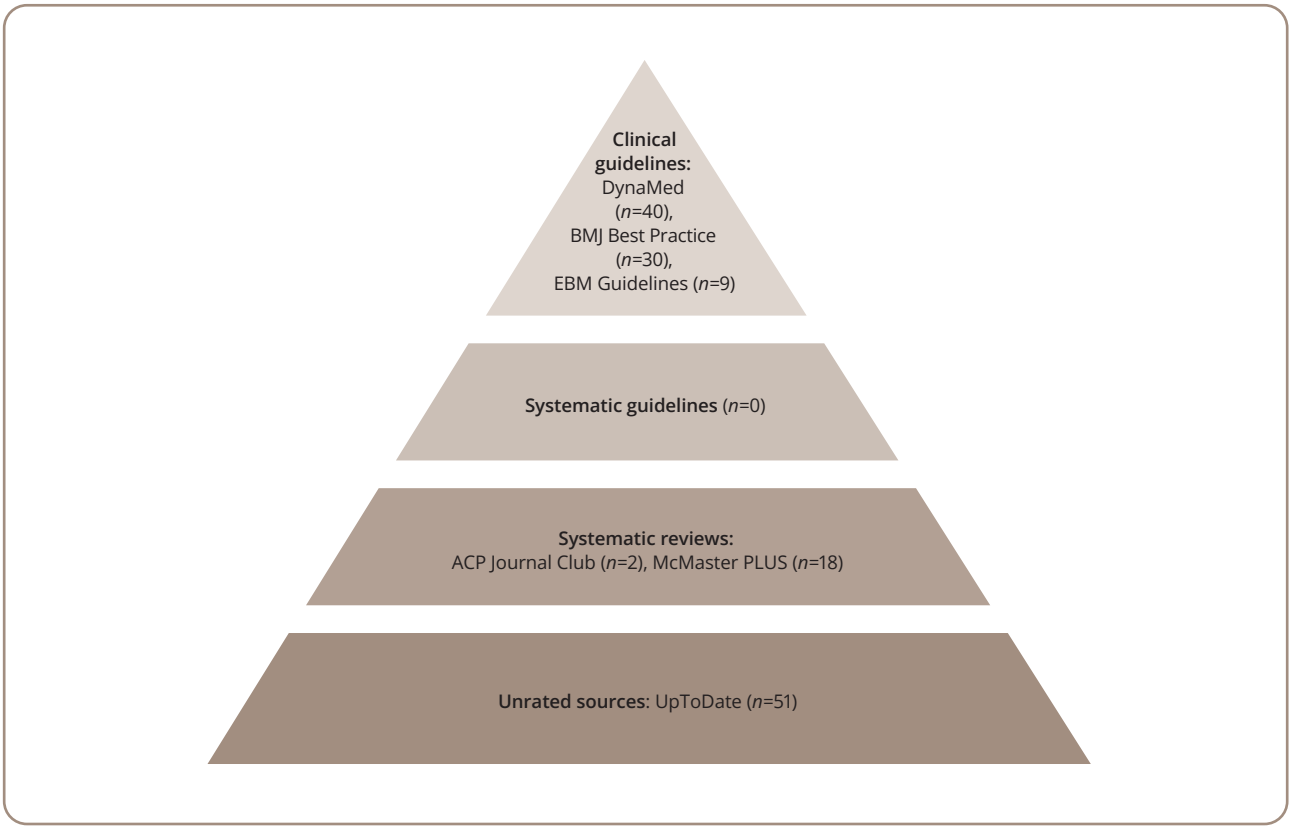


**Figure 2. The 6S Hierarchy of EBM Resources model using McMaster PLUS's ACCESSSS.**

*Note:* DynaMed[6] is a medical information Internet resource; Best Practice[7] is an information Internet resource that physicians can use to make clinical decisions; EBM Guidelines[8] are clinical guidelines based on the principles of evidence-based medicine; ACP Journal Club[9] is a medical publication that publishes current literature on internal medicine; Mcmaster PLUS[10] is a service of the research unit of the medical information of McMaster University (Canada); UpToDate[11] is a medical Internet resource providing medical information based on evidence-based information.
*Source:* Sultanova et al., 2024.

## Analysis of the results

Two reviewers independently reviewed all the verified documents. As a result, 67 papers were included in the current review. The publications found and selected for analysis were studied in full (full-text versions of the manuscripts). The data were analyzed from the perspective of utilizing biological methods to study depressive manifestations in schizophrenia. As a result, it was decided to divide the presented results into three blocks:

[6] DynaMed [Internet]. Ipswich (MA): EBSCO Information Services. 1995 [cited 2024 Aug 26]. Available from: https://www.dynamed.com

[7] BMJ Best Practice — a resource that physicians can use to make clinical decisions [Internet]. London: BMJ Publishing Group Limited [cited 2024 Aug 26]. Available from: https://bestpractice.bmj.com/info

[8] EBM — Evidence-Based Medicine Guidelines [Internet]. Helsinki: Duodecim Medical Publications Ltd [cited 2024 Aug 26]. Available from: https://www.ebm-guidelines.com/apps/dtk/ebmg

[9] ACP Journal Club — a medical publication that publishes current literature on internal medicine [Internet]. Philadelphia: American College of Physicians [cited 2024 Aug 26]. Available from: https://www.acponline.org/clinical-information/journals-publications/acp-journal-club

[10] McMaster PLUS — a service of the research unit of the medical information of McMaster University (Canada) [Internet]. Hamilton: McMaster University [cited 2024 Aug 26]. Available from: https://plus.mcmaster.ca/McMasterPLUSDB

[11] UpToDate provide medical information based on evidence-based information [Internet]. Waltham: UpToDate, Inc. [cited 2024 Aug 26]. Available from: https://www.uptodate.com/login

- biochemical factors of depressive symptoms in schizophrenia;
- neuroimaging methods of depressive symptoms in schizophrenia; and
- genetic predictors in patients with schizophrenia with depressive manifestations.

Statistical methods were not used for data analysis.

## RESULTS

### Biochemical factors of depressive symptoms in schizophrenia

The data collection process began with an examination of biochemical markers in blood plasma, as it is a widely accessible and commonly used research method. Faugere et al. found that elevated C-reactive protein levels were associated with the presence of depressive symptoms in patients with schizophrenia [27]. Another study revealed a link between depressive symptoms in schizophrenia and elevated metabolic parameters, particularly triglycerides and low-density lipoproteins [28]. It has been found that, the peptide hormone leptin may influence the appearance of depressive symptoms in schizophrenia, with significantly higher levels observed in patients with depressive manifestations compared to healthy individuals. Moreover, leptin levels were shown to negatively correlate with the depression factor on the PANSS (Positive and Negative Syndrome Scale), though not on other subscales [29]. Other researchers identified a correlation between a higher dietary intake of glutamic acid and increased depressive symptoms in non-obese adults with schizophrenia, while no such correlation was observed in obese participants [30]. Further study demonstrated a connection between adiponectin, a hormone involved in fatty acid breakdown and glucose regulation, and depressive symptoms in schizophrenia, with lower baseline adiponectin levels being significantly associated with higher baseline depressive symptoms [31].

Research on biomarkers related to the body's defense mechanisms revealed a correlation between depressive symptoms and the antioxidant enzymes manganese superoxide dismutase and total superoxide dismutase activity in the blood plasma of patients experiencing their first episode of untreated schizophrenia [32]. In a study by Bigseth et al., elevated levels of the soluble urokinase plasminogen activator receptor (suPAR) were linked to depressive symptoms in women with schizophrenia, suggesting abnormal immune activation within this subgroup [33].

Brain-derived neurotrophic factor (*BDNF*), a key modulator of neuroplasticity, is implicated in the pathogenesis of both schizophrenia and depression [34]. Although *BDNF* is not a specific synaptic molecule, research has shown that reduced serum *BDNF* levels in patients with schizophrenia are associated with more severe depressive symptoms [35], particularly in the early stages of the illness [36]. Han et al. study of patients with schizophrenia and depressive symptoms who were on monotherapy with olanzapine for 12 weeks demonstrated a significant increase in BDNF levels and a reduction in depressive symptoms following treatment [37]. Additionally, it was found that the concentration of another neurotrophic factor, neurotrophin-3 (NT-3), increased in the serum of patients with schizophrenia only in the presence of depressive symptoms, with no significant difference in NT-3 levels between schizophrenic patients and a control group in the absence of depression [38].

### Neuroimaging methods of depressive manifestations in schizophrenia

Neuroimaging is a key research tool in schizophrenia studies. In a meta-analysis of 4474 patients with schizophrenia and 5098 controls, brain imaging of cortical thickness and surface area abnormalities revealed a decreased gray matter volume in regions crucial to both schizophrenia [39] and depression [40]. Specifically, a reduced gray matter volume in the prefrontal cortex, including the medial part of the right superior frontal, medial orbitofrontal, and superior and middle frontal gyri, was linked to depressive symptoms in schizophrenia patients. Notably, depressive symptoms in schizophrenia had a more significant impact on gray matter reduction than negative symptoms [41]. According to magnetic resonance morphometry, a comparison between schizophrenia patients with/without depressive symptoms with a healthy control group indicated pronounced gray matter abnormalities concentrated in the cingulate gyrus in schizophrenia patients with depressive symptoms [42]. The reduction in gray matter was most significant in first-episode schizophrenia patients with depressive symptoms, especially in the parietal, frontal, and temporal lobes, including Broca's and Wernicke's areas, and the prefrontal cortex [43]. In comparisons of patients with depressive episodes and psychotic symptoms and those with schizophrenia and depressive symptoms, the latter group showed reduced gray matter in the left tegmental area and left frontal lobe [44].

Although electroencephalography (EEG) is not a neuroimaging method, a study by Shor et al. using EEG demonstrated that patients with both schizophrenia and depression exhibit lower hierarchical interconnectivity and reduced information segregation compared to healthy controls [45].

In animal studies, *in vivo* two-photon calcium imaging and electrophysiological recordings, combined with behavioral phenotyping, were used to investigate schizophrenia models. To create a mouse model of schizophrenia, the animals received dizocilpine (an N-methyl-D-aspartate, NMDA antagonist); depressogenic factors were created three days after the injection by tilting the cage, wet bedding, forced swimming, physical restraint, and sleep deprivation. The study found that schizophrenia with depression is expressed by a variety of symptoms, including helplessness, anhedonia and reduced filtering of sensory information, having worse indicators for these symptoms than depression or schizophrenia alone. These behavioral deficits were associated with disrupted neuronal calcium activity in the frontal cortex and thalamic nuclei [46, 47].

### Genetic predictors in schizophrenia patients with depressive symptoms

Research on candidate genes has identified a number of common genetic factors associated with depressive manifestations in schizophrenia. One such gene is the methylenetetrahydrofolate reductase (*MTHFR*) gene [48]. In our study, while we did not uncover an association with the *MTHFR C677* polymorphism, we found that elevated homocysteine levels may serve as a risk factor for the development of depressive symptoms in patients with schizophrenia [49].

Low levels of *BDNF* and *SIRT1* have also been implicated in the emergence of depressive symptoms in schizophrenia [50]. However, the *BDNF* gene contains multiple single nucleotide polymorphisms (SNPs) that exhibit strong linkage disequilibrium and interact in ways that may affect susceptibility to a mental illness. This complexity suggests the need for further detailed investigations of the gene [51]. The *SIRT1* gene encodes a protein belonging to the sirtuin family, whose functions are not yet fully understood. However, emerging evidence suggests that this gene may play a role in the pathogenesis of depression [52]. Preliminary findings from one study indicate that the *SIRT1* gene may increase the susceptibility of patients with schizophrenia to depressive symptoms [53].

Oxytocin, a regulator of social and emotional behavior, is a promising candidate for assessing susceptibility to schizophrenia. Research on schizophrenia patients suggests that oxytocin may play a role in the cognitive and social deficits development, possibly due to overactivation of the hypothalamic-pituitary-adrenal (HPA) axis, a known contributor to neurodegenerative changes in schizophrenia. Given its involvement in emotion and facial expression recognition, oxytocin has become a focal point for studying the pathophysiology of negative and depressive symptoms in schizophrenia, particularly reduced emotional expression. A study by Broniarczyk-Czarniak et al. demonstrated a correlation between the expression of the *OXT* gene, at both the mRNA and protein levels, and the severity of depressive symptoms in schizophrenia patients [54].

The impact of lipid metabolism disorders in schizophrenia patients has attracted particular attention from researchers. They have proposed a genetic link between depressive symptoms and lipid metabolism. Preliminary evidence indicates that the rs7754840 polymorphism of the *CDKAL1* gene, which is crucial for lipid metabolism, may contribute to the development of depressive symptoms in drug-naive schizophrenia patients [55]. Additionally, a study by Li revealed that the apolipoprotein E gene (*APOE E2*) is associated with the emergence of depressive symptoms in schizophrenia patients [56].

## DISCUSSION

### Brief interpretation of results

In this literature review, we consolidate the disparate data on biological markers of depressive symptoms in schizophrenia. Upon reviewing blood parameters, it becomes evident that this method cannot currently be considered specific for diagnosing depressive manifestations in schizophrenia. Changes in the concentration of proteins, such as C-reactive protein, soluble urokinase plasminogen activator receptor (suPAR), enzymes (superoxide dismutase), metabolic markers (triglycerides and low-density lipoproteins), and hormonal profile markers (leptin and adiponectin), are also observed in other conditions.

Analyzing the literature data on blood parameters, we obtained information on the influence of neurotrophic factors. For instance, NT–3 levels were significantly elevated, while *BDNF* levels were decreased in patients with schizophrenia experiencing depressive symptoms. However, these findings cannot be currently used as a diagnostic feature as they lack specificity, as reduced

*BDNF* levels are also associated with several other psychiatric disorders. Based on current evidence, it can be concluded that blood parameters cannot yet be used as specific markers for identifying depressive symptoms in schizophrenia, prompting an attempt to explore other research methods.

Clarifying the neural mechanisms by which depressive symptoms exacerbate the course of schizophrenia is essential for identifying new therapeutic targets and developing treatment strategies [57]. In a study of depression and psychosis, Lalousis et al. [58] suggested that a neurobiologically driven approach is more effective in predicting symptomatic and functional remission than traditional diagnostic categories in predicting the course of the disease. A reduction in the gray matter volume [41] has been observed in the parietal, frontal, and temporal lobes, particularly in Broca's and Wernicke's areas [43], as well as in the prefrontal cortex, including the medial part of the right superior frontal, medial orbitofrontal, and superior and middle frontal gyri [42, 44]. Several studies have confirmed gray matter reduction in cases of depressive symptoms in schizophrenia, though some findings require further confirmation through additional research [45–47].

The results of the analysis of candidate genes that contribute to the development of depressive symptoms in schizophrenia were also presented. The *SIRT1* [50, 53], *OXT* [54], *CDKAL1* [55], and *APOE* [56] genes may contribute to the development of depressive symptoms in a sample of patients with schizophrenia. However, findings on the *MTHFR* gene remain inconsistent and require further investigation [48, 49]. Although genetic studies have limitations, the search for genetic associations represents one of the most promising approaches for identifying biological markers, particularly in patients with depressive symptoms in schizophrenia. An equally important issue for clinicians is the differential diagnosis of depressive symptoms in schizophrenia, which can be complicated by adverse reactions to antipsychotic medication [59, 60], substance abuse [61], and psychosis-related manifestations that may induce depression [62, 63]. A key challenge in diagnosis is distinguishing between depressive and negative symptoms [64]. Some researchers posit that negative symptoms are not exclusive to schizophrenia but may also occur in depressive disorders [65]. Negative symptoms can be secondary to depression or overlap with depressive features [66]. Other researchers emphasize certain shared characteristics, such as anergia, poverty of speech, and anhedonia, while recommending a symptom-based approach for differentiation: depression is associated with hopelessness, pessimistic and suicidal thoughts, while negative symptoms are characterized by blunted affect, poverty of speech, objective depression, social withdrawal, and reduced attention span [57]. Nevertheless, network analysis has shown that depressive symptoms in schizophrenia are weakly correlated with negative symptoms, making them relatively distinguishable [67]. The complexities inherent in differentiating depressive manifestations in schizophrenia result in many patients receiving inadequate treatment, underscoring the need for further research into biological markers [29].

### Limitations

One limitation of this review is the six-year publication window for the analyzed studies. The studies included were notably heterogeneous, with varying methods used to diagnose depressive symptoms in schizophrenia. The sample comprised both treatment-experienced and naive patients, which adds to variability. While the data on biological markers show promise for research, these markers must undergo standardization, sensitivity and specificity testing, and validation before they can be introduced into clinical practice. The practical relevance of these findings lies in the potential for neurobiological methods to improve the diagnosis of depressive symptoms in schizophrenia, enhancing research practices and facilitating psychiatrists' clinical work. This is particularly relevant given the challenges in differentiating depressive symptoms from negative symptoms, which remain significant. Early detection of depressive symptoms is also crucial for preventing severe complications, such as completed suicide attempts. Overall, the review underscores the considerable potential of neurobiology in diagnosing depressive manifestations in schizophrenia. The adoption of these methods could lead to significant improvements in diagnosis, treatment, and, ultimately, the quality of life for these patients.

## CONCLUSION

In recent years, numerous studies have explored the neurobiological aspects of depressive symptoms in schizophrenia. However, it remains premature to implement these diagnostic methods in routine clinical practice. Continued research into biological markers will provide

greater clarity about the development of depressive symptoms in schizophrenia and will influence the choice of priority treatment methods.


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REVIEW

# The Modern Concept of Schizoaffective Disorder: A Narrative Review

## Современная концепция шизоаффективного расстройства: нарративный обзор литературы

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**Review**

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**ABSTRACT**

**BACKGROUND:** Schizoaffective disorder (SAD) is one of the most complex and controversial diagnoses in clinical psychiatry. Despite the significant changes that have occurred in the conceptualization of SAD in modern classifications and the publications of recent years, many unresolved issues remain regarding the disease, from the point of view of clinical psychiatry and basic neuroscience.

**AIM:** The purpose of this paper is to summarize published data on the concept of SAD, its clinical characteristics, cognitive profile, potential biomarkers, as well as the place of the disease in the following modern international classifications: the International Classification of Diseases (ICD) 9th, 10th and 11th revisions, and the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

**METHODS:** We undertook a review of the scientific studies in the relevant bibliographic systems and databases (eLIBRARY, PubMed) of the past 15 years. The descriptive analysis method was used to summarize the collected information. A total of 70 publications were selected for review, including different versions of international classifications of diseases (ICD and DSM-5).

**RESULTS:** There has been some improvement in the inter-rater reliability of SAD criteria in modern classifications, but this has not yet led to a clearer understanding among mental health specialists, while the various subtypes of SAD identified so far fail to account for the heterogeneity in the clinical presentation of the disorder. The dimensional approach to diagnosing SAD, according to which the intensity of psychotic and affective symptoms can fluctuate over time and they can influence one another, more accurately reflects the disease's ability to embody different forms. Basic research does not support the identification of a distinct cognitive, neuroimaging, or immunological SAD endophenotype that differs qualitatively from schizophrenia and affective psychoses.

**CONCLUSION:** The conceptualization of SAD remains incomplete, and new approaches rooted in neuroscience are needed to better understand the coexistence of affective and psychotic symptoms.

## АННОТАЦИЯ

**ВВЕДЕНИЕ:** Шизоаффективное расстройство (ШАР) — один из самых сложных и дискуссионных диагнозов в клинической психиатрии. Несмотря на значительные изменения в концептуализации ШАР в современных классификациях болезней и публикациях последних лет, в отношении этого заболевания остается множество нерешенных вопросов с точки зрения клинической психиатрии и фундаментальных нейронаук.

**ЦЕЛЬ:** Целью работы было обобщить опубликованные данные о концепции ШАР, его клинических характеристиках, когнитивном профиле, потенциальных биомаркерах, а также о месте этого заболевания в следующих современных международных классификациях: Международной классификации болезней (МКБ) 9-го, 10-го и 11-го пересмотра и Диагностическом и статистическом руководстве по психическим расстройствам (Diagnostic and Statistical Manual of mental disorders, 5th edition — DSM-5).

**МЕТОДЫ:** Выполнен обзор научных исследований в релевантных библиографических системах и базах данных (eLIBRARY, PubMed) за последние 15 лет. Для обобщения полученной информации был использован описательный анализ. Всего для обзора отобрано 70 публикаций, включая различные версии международных классификаций болезней (МКБ и DSM-5).

**РЕЗУЛЬТАТЫ:** Некоторое улучшение межрейтинговой надежности критериев ШАР в современных систематиках пока не привело к лучшему их пониманию специалистами, а различные выделенные подтипы ШАР не могут объяснить гетерогенность клинической картины этого расстройства. Дименсиональный подход к диагностике ШАР лучше соответствует изменчивой природе заболевания. Согласно ему интенсивность психотических и аффективных симптомов может меняться в разные периоды времени и они могут взаимно влиять друг на друга. Фундаментальные исследования не поддерживают выделение особого когнитивного, нейровизуализационного или иммунологического эндофенотипа ШАР, качественно отличного от шизофрении и аффективных расстройств.

**ЗАКЛЮЧЕНИЕ:** Концептуализация ШАР в настоящее время далека от завершения. Чтобы лучше понять природу одновременного существования аффективных и психотических симптомов, необходимы новые концептуальные подходы, основанные на достижениях нейронаук.



**Keywords:** *schizoaffective disorder; ICD-9; ICD-10; ICD-11; DSM-5; biomarkers; cognitive functioning*
**Ключевые слова:** *шизоаффективное расстройство; МКБ-9; МКБ-10; МКБ-11; DSM-5; биомаркеры; когнитивное функционирование*


## INTRODUCTION

Schizoaffective disorder (SAD) is undoubtedly one of the most significant challenges of modern clinical psychiatry, the importance of which is increasing due to the accumulation of a large body of new data and the development of updated classification systems. [1]. Despite the wide application of this diagnostic category, it remains characterized by low diagnostic stability and validity [2]. Debates is ongoing about whether SAD should be classified as a type of schizophrenia, a type of bipolar affective disorder (BAD), an independent diagnostic category, or whether it is better conceptualized along a continuum of varying combinations of psychotic and affective symptoms. A more precise definition of SAD could reduce diagnostic heterogeneity and improve the reliability of the "schizoaffective disorder" category [1].

A survey of 873 specialists from various countries found that the level of diagnostic agreement for the ICD-11 criteria for SAD was moderate (Cohen's kappa — a measure of inter-rater agreement — was $\kappa$=0.38), although this was significantly higher than the inter-rater agreement level for the ICD-10 criteria for SAD ($\kappa$=0.27) [3]. Field studies leading up to the DSM-5 revision have reported moderate inter-rater reliability for SAD ($\kappa$=0.5), lower than for bipolar disorder type I ($\kappa$=0.56) but higher than for schizophrenia ($\kappa$=0.46) [4]. A more recent study revealed that the inter-rater reliability of the DSM-5 SAD diagnosis ($\kappa$=0.57) is even lower than that for schizophrenia, bipolar disorder, and

major depressive disorder, by an average of 19–22%, in a sample of 7912 patients assessed by different raters. This highlights the importance of the re-diagnosis of patients with SAD [5]. Additionally, low diagnostic reliability was encountered in a study of children and adolescent populations ($\kappa$=0.27): much lower than that of schizophrenia ($\kappa$=0.56) and bipolar disorder ($\kappa$=0.64) [6]. A study involving 33 patients using the M.I.N.I. interview (a brief structured diagnostic interview for major psychiatric disorders in DSM-IV and ICD-10) in a psychiatric hospital in Moscow, where patients were initially diagnosed with SAD (F25 in ICD-10), found that in 23 (69.7%) cases the condition aligned with the diagnostic criteria of bipolar disorder, and that only in 10 (30.3%) patients was the diagnosis of SAD confirmed [7].

The aim of this paper is to summarize both the Russian and international literature on the concept of SAD, including its clinical characteristics, cognitive profile, potential biomarkers, and the evolution of the Schizoaffective Disorder category in international classifications, such as the International Classification of Diseases (ICD) 9th, 10th, and 11th revisions, as well as the Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5).

## METHODS

### Eligibility criteria

Inclusion criteria:

- original studies dedicated to the conceptualization, clinical characteristics, cognitive profile, differential diagnosis, comorbidity, and potential biomarkers of SAD, in which SAD or its types were separated into distinct clearly defined groups or subgroups;
- international classifications (ICD-9, ICD-10, ICD-11, DSM-5).

Exclusion criteria:

- case reports;
- case series;
- articles dedicated to the treatment of SAD.

### Information sources

The work was carried out from February to August 2023. The search for sources was conducted in the scientific electronic library eLIBRARY and the PubMed database (full-text articles) with a focus on publications in the past 15 years (2008–2023). Also, the three most significant papers on the topic for an earlier period were included, where the division of two main endogenous mental illnesses with the dominance of psychotic and affective disorders is substantiated and the term "schizoaffective disorder" is introduced [8–10].

### Search strategy

The number of publications in the initial search query by keywords in the PubMed was 1257; in the eLIBRARY — 46. In accordance with the inclusion criteria, 67 publications were selected (including the three works mentioned above [8–10]), of which 56 were in English, 11 were in Russian, including ICD-9, ICD-10, ICD-11 and DSM-5. The number of publications over the past 10 years amounted to 47 (70.1%).

The search strategy for sources is presented in Figure 1.

### Selection process

The following combinations of keywords in Russian and English were used to select the publications: "schizoaffective disorder", "concept", "diagnosis", "DSM-5", "ICD-11", "clinical features", "comorbidity", "neuroimaging", "cognitive impairment". Keyword searches were also used to find two related words (e.g., "schizoaffective disorder" and "comorbidity").

### Analysis of results

A descriptive approach was applied to summarize the information obtained, which consisted of analyzing and evaluating the data from the point of view of the purpose of the current study.

## RESULTS

### Schizoaffective disorder in modern disease classifications

In 1899, Emil Kraepelin had the idea to divide the so-called functional psychoses into "dementia praecox" and "manic-depressive insanity" ("manisch-depressives Irresein") [8]. In later work in 1920, he arrived at the conclusion that it was impossible to draw a satisfactory distinction between the two diseases, although he acknowledged the existence of patients with "irreversible mental decline" [9]. In 1933, the American psychiatrist Kasanin introduced the term "schizoaffective psychosis" based on his study of 9 patients with good premorbid functioning who happened to develop a combination of psychotic and affective symptoms, with full recovery within a few months [10].

The ICD-10 Clinical Descriptions and Diagnostic Guidelines allows for the diagnosis of SAD if the patient's mental state exhibits "one or, preferably, two typically schizophrenic

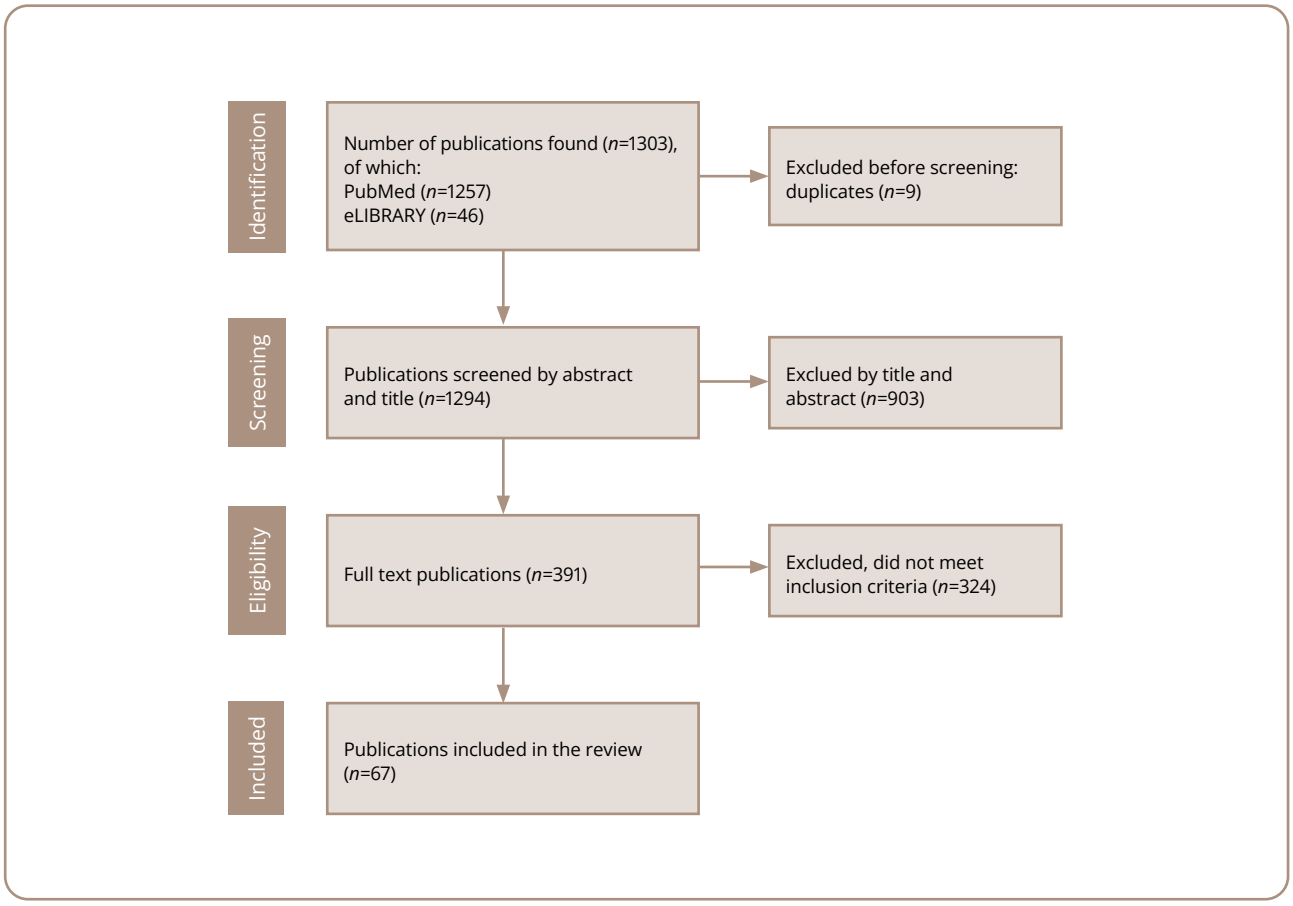


**Figure 1. PRISMA flow diagram of the literature search and the selection process.**

*Note:* Total number of references: 67 +3 most significant works on the designated topic for an earlier period [8–10].
*Source:* Pavlichenko et al., 2024.

symptoms (criteria A–D in ICD-10), and two characteristic depressive symptoms (depressive type), manic symptoms such as a prominent elevation of the mood, or a less obvious elevation of the mood combined with increased irritability" (manic type), or "a combination with mixed bipolar affective disorders" (mixed type) [11]. Notably, this version of ICD-10 does not provide a clear specification of episode duration, stating only that schizophrenic and affective symptoms must co-exist "for at least several days". Meanwhile, the ICD-10 Diagnostic Criteria for Research specifies that the "disorder meets the criteria for one of the moderate or severe affective disorders", meaning that the duration of depressive and mixed symptoms should be at least two weeks; and manic symptoms, at least one week [12]. Additionally, the state must include one of the typical symptoms of schizophrenia, which, in addition to psychotic symptoms consistent with the schizophrenia criteria in the ICD-10 Clinical Descriptions and Diagnostic Guidelines (criteria A–G), also includes disorganized thinking ("clearly incoherent or irrelevant speech, or frequent use of neologisms") and catatonia ("frequent occurrence of catatonic behavior, such as posturing, waxy flexibility, and negativism"). The duration of schizophrenia symptoms should be at least two weeks, and within a single episode, they must co-exist with affective symptoms "at least for some time simultaneously" [12].

A diagnosis of "Schizoaffective Disorder" does not apply when schizophrenic symptoms predominate in some episodes and affective symptoms in others, according to the ICD-10 guidelines. In such cases, the diagnosis of two separate disorders is possible when schizoaffective episodes alternate with affective episodes of bipolar or recurrent depressive disorder [11]. On the other hand, if schizophrenic and affective symptoms develop concurrently and are "relatively balanced in severity and duration" in relation to each other, a diagnosis of SAD is in order, even if the schizophrenic symptoms taken separately would justify a diagnosis of "Schizophrenia" [11]. Thus,

ICD-10 departs from the hierarchical diagnostic principle that has long prevailed in psychiatry, where psychotic symptoms were considered more significant than affective ones [13]. Notably, in ICD-9, SAD was classified within the schizophrenia group rather than as a separate category [14]. It is also stated therein that the presence of delusions or hallucinations incongruent with mood, including first-rank symptoms, is not sufficient for an SAD diagnosis if these symptoms had not preceded the development of affective syndromes and/or had not persisted after their remission [12].

According to ICD-11, a diagnosis of SAD is warranted when the current episode simultaneously meets the diagnostic criteria for both schizophrenia and a manic, mixed, or moderate-to-severe depressive episode [15]. It is also important to note that in ICD-11, Kurt Schneider's first-rank symptoms have lost their relevance for the diagnosis of schizophrenia [16]. For schizophrenia, at least one of the following four symptoms is required: "persistent" delusions, "persistent" hallucinations, disorganized thoughts, or passivity and delusions of control [15].

A schizoaffective episode should last at least one month, and there should be no relationship between the symptoms of SAD and other diseases and/or the use of psychoactive drugs [15]. In addition, the description of the patient's clinical condition can be supplemented with the following features: first episode of the disease, multiple episodes of the disease, or continuous course, and the severity (mild, moderate, moderate) of positive, negative, cognitive, manic, depressive, and psychomotor symptoms according to the proposed assessment scale should be indicated [15]. If the patient has no history of schizoaffective episodes and the symptoms persist for at least one month, the diagnosis of "Schizoaffective disorder, first episode" is appropriate. If subclinical symptoms persist for one month or more, including as a result of treatment, a diagnosis of "Schizoaffective disorder, first episode, in partial remission" is made. In a situation where the patient's current state presents "no clinically significant symptoms" and the condition previously "met the diagnostic criteria for SAD", the diagnosis of "Schizoaffective disorder, first episode, in full remission" is the right one. If the patient has a history of SAD or schizophrenia episodes and his current state meets the diagnostic criteria for SAD, the diagnosis should be "Schizoaffective disorder, multiple episodes, currently symptomatic". The qualification of partial and full remission in SAD with multiple episodes is reached in the same way as in SAD with the first episode. If the symptoms of SAD persist for at least one year with possible "short periods of subclinical symptoms", the diagnosis should be "Schizoaffective disorder, continuous, currently symptomatic". In this case, the qualification of partial and full remission is also possible [15].

ICD-11 experts have sought to resolve the ambiguities and inconsistencies of ICD-10, particularly the version for clinical use, by stipulating that the patient's condition must meet the full gamut of diagnostic criteria for schizophrenia — not merely "at least one symptom" — and a moderate-to-severe depressive episode, rather than just "some depressive features" [3]. Additionally, ICD-11 enables one to assess other clinical manifestations (beyond affective symptoms) of SAD using supplementary codes under "Symptomatic manifestations of primary psychotic disorders" [15]. Moreover, the diagnosis of affective disorder with psychotic symptoms may be changed to SAD if psychotic symptoms meet the threshold for schizophrenia.

ICD-11 also outlines key aspects of the differential diagnosis for SAD [15]. In particular, the occurrence of a SAD episode does not preclude a diagnosis of schizophrenia, and vice versa. In both schizophrenia and SAD, at least two characteristic symptoms of schizophrenia must be present during one month or more. However, only in SAD do schizophrenic symptoms coexist with affective symptoms that meet the criteria for an affective episode. On the other hand, in schizophrenia, affective symptoms may occur, but they last less than one month and do not reach the level of the moderate-to-severe depression, manic, or mixed episodes. If an episode initially meets the criteria for SAD, but only affective symptoms recede, and psychotic symptoms without affective symptoms persist longer than their combination does, the case may be diagnosed as an episode of schizophrenia. In a depressive, manic, or a mixed episode of affective disorders, psychotic symptoms may emerge alongside affective symptoms but not meet the diagnostic requirements for schizophrenia (e.g., hallucinations without other schizophrenia symptoms).

According to DSM-5 criteria A, for SAD it is necessary to have concurrently a depressive or manic episode and criteria A for schizophrenia, which includes the presence of at least two of five symptoms (delusions, catatonic behavior, hallucinations, disorganized speech, negative symptoms), wherein the presence of one of the first three is mandatory [17]. That is, in fact, the first criteria for SAD in ICD-11 and DSM-5 coincide, except for the fact that

there are no mixed affective episodes in DSM-5. There is also a significant difference between the classifications in the understanding of SAD. Thus, according to the DSM-5 classification, for a diagnosis of SAD it is necessary that the symptoms of mood disorders predominate over psychotic symptoms (criteria C) and that early hallucinations or delusions last for at least two weeks in the absence of depressive, manic, or mixed symptoms (criteria B). The patient description can be further detailed by the classification of SAD as a depressive or bipolar type, the presence of catatonic symptoms, as well as a description of the type of course (first episode, multiple episodes, continuous course) and full or partial remission. In addition, an additional assessment of SAD symptoms is possible according to the Psychosis symptom severity scale (0 to 4 points): hallucinations, delusions, jumbled speech, abnormal psychomotor behavior, negative symptoms, decreased cognition, depression, and mania [17]. Also, DSM-5 indicates that criteria C is intended to differentiate SAD from schizophrenia, and that criteria B is intended to differentiate SAD from depressive or bipolar disorder with psychotic features, in which psychotic symptoms occur only during an affective episode [17].

Table 1 lists the main principles of the SAD diagnosis in different international classifications.

## Conceptualization of schizoaffective disorder

The relationship and boundaries between affective disorders and schizophrenia spectrum disorders remain a central topic of debate in psychiatry [18]. The categorical model

**Table 1. Diagnosis of SAD in different international classifications of diseases**

| Classification version (year of publication) | Title | Diagnostic features | Additional features |
|---|---|---|---|
| ICD-9 (1979) | Header "Schizoaffective type", chapter "Schizophrenic psychoses" | Descriptive approach | Types are not distinguished. Includes: circular schizophrenia, schizoaffective psychosis, periodic schizophrenia. |
| ICD-10, Clinical Descriptions and Diagnostic Guidelines (1993) | Header "Schizoaffective disorder", chapter "Schizophrenia, schizotypal and delusional disorders" | Categorical approach. Schizophrenic symptoms occur simultaneously or sequentially over several days. At least one symptom of schizophrenia (criteria "A–G") and at least two symptoms of depression or elation, or mixed bipolar disorders are required. | Manic, depressive, mixed types are distinguished. The duration and severity of affective episodes are not specified. |
| ICD-10, Clinical Descriptions and Diagnostic Guidelines (1993) | Header "Schizoaffective disorder", chapter "Schizophrenia, schizotypal and delusional disorders" | Categorical approach. Schizophrenic and affective symptoms co-exist "at least for some time simultaneously" and in relative "equilibrium". At least one symptom of schizophrenia must be present (criteria "A–D", "E", "G"). The duration of depressive and mixed symptoms is at least two weeks, manic – at least one week. Moderate or severe affective symptoms. | Manic, depressive, mixed types are distinguished. |
| ICD-11 (2022) | Header "Schizoaffective disorder", chapter "Schizophrenia and other primary psychotic disorders" | Categorical-dimensional approach. Schizophrenic and affective symptoms are present either simultaneously or with an interval of several days. The criteria for schizophrenia and a moderate to severe depressive episode or a manic or mixed affective episode must be met. Episode duration is at least one month. Possibility of qualifying the first and multiple episodes, continuous course, full or partial remission. | No types distinguished. Additional symptoms may be assessed using additional codes with severity rating (mild, moderate, severe): positive, negative, depressive, manic, cognitive psychomotor symptoms. |
| DSM-5 (2013) | Header "Schizoaffective disorder", chapter" "Schizophrenia spectrum and other psychotic disorders" | Categorical-dimensional approach. Mandatory presence of criteria A for schizophrenia and criteria for a depressive or manic episode. History of delusions or hallucinations for at least two weeks in the absence of affective symptoms. Predominance of affective symptoms during the episode. Episode duration is at least one month. Possibility of qualifying the first and multiple episodes, continuous course, full or partial remission. | Bipolar and depressive types are distinguished, as well as a type with symptoms of catatonia. An additional assessment of the state is possible according to the Psychosis Symptom Severity Scale (0 to 4 points): hallucinations, delusions, disorganized speech, abnormal psychomotor behavior, negative symptoms, decreased cognition, depression, mania. |

suggests that clear distinctions can be made between schizophrenia and affective disorders, leading to the classification of SAD either as a form of schizophrenia, a form of affective disorder, or a distinct condition separate from both. It has been suggested that the classification of SAD as an independent disorder can be viewed as arbitrary and controversial [19]. On the other hand, some patients seem more prone to schizophrenia, while others are more prone to affective disorders [20]. In Russian psychiatry, schizoaffective psychosis has traditionally been regarded both as a favorable variant of shift-like schizophrenia and as a separate disorder. The clinical typology of the episodes was developed with a differentiation between affect-dominant and schizo-dominant forms, based on the duration of symptoms and the degree of progression [21, 22]. As a distinct disease, schizoaffective psychosis is considered a schizophrenic reaction in schizotypal personalities with signs of reactive lability in which schizophrenic psychotic symptoms, although they occur during affective phases, are not pathogenetically related to them [23].

In the review by Potuzak et al. [24], only 7 publications were found that examined how different categories of psychotic disorders differ from the current headers in modern classifications. All the studies have mentioned the need to distinguish one or more classes of psychotic disorders where affective symptoms play an important role. Depending on the prevalence of specific affective syndromes, it was proposed to distinguish the following conditions: SAD, schizomania, schizodepression, and schizobipolar disorder. A subtype with a moderately high level of positive, depressive and manic symptoms and a low level of negative symptoms (bipolar-schizomanic, schizobipolar disorder, affective psychosis, schizoaffective psychosis) was distinguished in five studies; a subtype with a high level of depressive and negative symptoms and a moderate or high level of positive symptoms (schizodepression), in four studies, and a subtype with a high level of manic and positive symptoms and a low level of negative symptoms (schizomania) in two studies. In a sample of 4956 patients with psychotic disorders, seven homogeneous classes of psychoses were identified. The second most common class (after "Kraepelinian schizophrenia") was the class of "affective psychoses", accounting for 15% of the patients diagnosed with schizophrenia, characterized by a combination of disorganized thinking, negative symptoms, normal IQ, and a favorable prognosis [25].

The spectrum model assumes that the severity of symptoms is in constant flux, and that individual symptoms fit on a scale, with "pure" affective disorder at one end, "pure" schizophrenia at the other, and SAD positioned in between [17]. It has been shown that diagnostic categories such as schizophrenia, SAD, and BAD do not represent distinct entities but rather reflect areas characterized by certain psychopathological dimensions and neurobiological processes, the boundaries of which are probably arbitrary and are in continuity or overlap with other mental health illnesses, extending even to the edges of "normal" human experience and functioning [26, 27].

An analysis of relevant studies using the dimensional (from "dimension", degree of severity) model of psychosis showed that the overwhelming majority of studies (31 out of 39) also distinguish an affective dimension, or mania, and depression separately; that is, affective symptoms should be considered not as an additional, but rather as the central component of the psychotic state, along with directly psychotic and negative symptoms [28]. In particular, an analysis of the structure of five groups of symptoms (disorganized thinking, negative symptoms, positive symptoms, depression, mania) in a cohort of 1056 inpatients with psychotic disorders revealed that affective symptoms — rather than negative symptoms or disorganized thinking — are the most distinguishing features of the six identified clusters of psychosis symptoms [27]. A study of associations between three categories of psychotic disorders (schizophrenia, SAD, delusional disorder) and Positive and Negative Syndrome Scale (PANSS) items showed no statistically significant differences between schizophrenia and SAD in terms of negative and positive symptoms, while manic and depressive symptoms were significantly more common in SAD, and there was a continuum of affective disorder severity, with delusional disorder at one pole and SAD at the other [28].

Instead of the concept of a single psychotic spectrum, a model of the so-called metaspectrum was proposed, which includes, in addition to schizophrenia and bipolar, the SAD spectrum [29]. Each spectrum contains various nosologically independent units: from personality traits to clinically complete psychotic syndromes. A three-dimensional model of the spectrum was proposed. The SAD spectrum consists of the following elements (axes):

- SAD in its traditional description, including its various subtypes;

- Leonhard's cycloid psychosis, confusion psychosis, including motility psychosis, and anxiety-happiness psychosis; other atypical psychoses outside of schizophrenia and affective disorders;
- a subtype of borderline personality disorder with a high proportion of psychotic symptoms in the clinical presentation, which are not sufficient for diagnosing a psychotic disorder.

## Clinical and dynamic characteristics of schizoaffective disorder

DSM-5 estimates the lifetime risk of SAD at 0.3%, which is 1/3 higher than in schizophrenia [17]. The incidence of SAD among adult Europeans is 1.1% [6], with "schizomanic" episodes being more common than "schizodepressive" episodes during the first hospitalization; however, depressive episodes are much more common during follow-up than manic ones [30].

Prodromal states in SAD have been more extensively researched in the context of depressive SAD, where a longer prodrome is observed, along with a high prevalence of perceptual disturbances, such as imperative hallucinations, suicidal behavior elements, and paranoid personality traits. A significant frequency of psychotic symptoms is associated with initial diagnoses of non-affective psychotic disorders in the majority (60.6%) of individuals with a final diagnosis of depressive SAD [31]. A follow-up study of individuals at ultra-high risk (UHR) of developing psychosis syndrome, which is characterized by the presence of individual short-term psychotic symptoms, showed that 29.9% of individuals with UHR develop signs of affective disorders within five years: accordingly, UHR can be considered a prodrome of not only psychotic, but also affective disorders [32]. Loss of a parent and divorce in the family are more often associated with an earlier onset of SAD for both sexes. Women with SAD have more often reported a history of sexual abuse in childhood or adulthood; and men, stress associated with work or academic exams [33].

The clinical characteristics of SAD have been studied mainly in comparison with schizophrenia and affective disorders. It has been shown that individuals with SAD experience an earlier disease onset and exhibit higher levels of psychotic symptoms and depression compared with control groups, while many characteristics — clinical, demographic, and psychometric — of SAD map those of schizophrenia more closely than those of affective disorders [34]. The Australian National Survey of Psychosis, which included 1825 patients, found that SAD is characterized by more delusional symptoms and thought disorders, as well as depressive and manic episodes, than schizophrenia [35]. In contrast to bipolar disorder, patients with SAD exhibited more pronounced current positive symptoms, delusions, and thought disorders, as well as a lifetime history of psychotic symptoms, including hallucinations and delusions, but that they experienced fewer manic episodes. Compared with patients with schizophrenia, patients with SAD diagnosed according to DSM-5 criteria show higher rates of suicidality and comorbid anxiety disorders, which is important in terms of differential diagnosis with schizophrenia [1].

The dynamic aspects of SAD have been examined in several studies. A ten-year follow-up of 2524 adolescents aged 14–24 years showed that the presence of psychotic symptoms is associated with a 51% increased risk of developing two or more manic symptoms and a 15% increased risk of experiencing depressive symptoms compared with those who did not present psychotic symptoms [36]. The opposite is also true: the presence of at least three depressive and two manic symptoms increases the likelihood of developing psychotic symptoms by 28% and 37%, respectively. In another study, during a 15-year follow-up of 43,495 individuals with unipolar depression, 2.5% of the cases showed a transition to schizophrenia; and another 1.3%, to SAD, with the diagnosis most often changing during the first years of observation [37]. Earlier long-term follow-up studies had shown that 70% of individuals with SAD may subsequently develop a wide variety of episodes (schizophrenic, schizodepressive, schizomanic, manic, depressive, mixed), and the prognosis is similar to that of affective disorders and is much more favorable than in individuals with schizophrenia [38].

A prospective observation with an average follow-up period of 4.47 years of individuals with the first episode of SAD showed that, 83% of the time, they were in a morbid state, including subsyndromal manifestations. This is significantly higher than the same indicator for individuals with manifest psychotic depression (57.8%) and psychosis in the context of bipolar disorder type I (45%) [39].

A one-year follow-up study of individuals with SAD showed that in 31.6% of cases there was at least one, and in 21.1% of cases — two or more anxiety disorders. The presence of obsessive-compulsive disorder at the beginning of observations was associated with a greater severity of the disease [40], and the comorbid panic disorder

with an earlier (by four years) onset of the disease [41]. In addition, complaints of anxiety by patients with SAD may indicate a lower level of global functioning in the future [42]. Comorbid posttraumatic stress disorder and SAD correlate with a worse outcome, a higher number of hospitalizations, and relapses in women [33].

Irritability in the structure of affective episodes in SAD occurs in 27.1% of cases and is associated with a greater severity of mania, depression, suicidality, and a decrease in the quality of life. It persists in more than 1/2 of patients for at least two years, is not associated just with the severity of the disease, and can result in a greater number of symptoms and a more significant decline in social functioning. This suggests it should be considered an independent factor contributing to a less favorable disease prognosis [43].

### Cognitive profile of schizoaffective disorder

Neurocognitive and social cognition impairment is common in psychoses; so, neuropsychological assessment is gradually being integrated into the assessment of such patients, which is reflected in the need to assess cognitive functioning in SAD in DSM-5 and ICD-11 [15, 17].

In schizophrenia and SAD, there are common impairments in the neural processing of repeated emotional scenes, measured using the evoked potential method, which is associated with cognitive deficit (emotional processing, response suppression/amplification), rather than with affective symptoms [44, 45].

It has been suggested that insufficient inhibitory behavioral control is associated with symptoms such as impulsivity, aggression, substance abuse, and reckless behavior, which is consistent with our current understanding of the relationship between affective and psychotic disorders through a general deficit in inhibitory control [46].

Patients with SAD have a lower degree of emotion recognition impairment than patients with schizophrenia and a lower overall recognition accuracy of all emotions compared to healthy individuals. Effect sizes indicate a more significant deficit in the recognition of negative emotions associated with threat (fear, anger, disgust) in SAD, which indicates a dysfunction of the limbic structures [47].

A study of neurocognitive parameters, social cognition, as well as the brain structures associated with the processing of social stimuli, using valid test batteries and structural magnetic resonance imaging, showed that schizophrenia and SAD are similar in terms of most of the studied parameters, with the exception of better emotion regulation in patients with SAD [45], which, according to the authors, renders the issue of separating these two disorders in classifications debatable.

Minor differences were found between different subtypes of SAD and schizophrenia. Thus, patients with the depressive type of SAD significantly outperformed the group of patients with schizophrenia in terms of information processing speed, according to the results of the Trail Making Test (TMT-A), which allows one to assess human cognitive abilities, while the group of patients with the bipolar subtype of SAD did not demonstrate significant differences from the schizophrenia group in any cognitive dimension. The obtained data confirm the hypothesis that both types of SAD are heterogeneous and include patients with different cognitive and clinical characteristics [48].

Conversely, a meta-analysis of 31 studies involving individuals with SAD, BAD, and schizophrenia found that patients with the depressive type of SAD exhibit neurocognitive impairments that are closer in severity to those with schizophrenia, while patients with the bipolar type of SAD show less severe impairments than those with schizophrenia, but more pronounced impairments than those with BAD. At the same time, there were no significant differences in the neurocognitive profile of patients with the depressive and bipolar subtypes of SAD. Cognitive impairment increased from BAD to SAD, to schizophrenia. It has been suggested that combining the SAD subtypes could complicate our understanding of the relationship between these three disorders [49].

Comparison of the cognitive status of patients with paranoid schizophrenia and SAD showed that at the remission stage, both disorders are characterized by a decrease in the rate of skill formation and the rate of mental performance and active attention, but compared to patients with schizophrenia, patients with SAD show less pronounced memory and executive function impairment; perseverative additions during immediate recall were also statistically significantly more often observed in SAD [50].

### Potential biomarkers of SAD

In patients with SAD and psychotic bipolar disorder, functional magnetic resonance imaging revealed increased randomness of brain signals in the ventromedial prefrontal cortex, while in SAD and schizophrenia, an increased chaotic nature of signals in the dorsomedial prefrontal cortex was noted [51]. Abnormal changes in the areas of

the prefrontal cortex are observed only in patients with psychosis, but not in their healthy relatives, which, according to us, allows one to consider this feature as a marker of the disease, rather than a familial trait, and the relevance of the biological approach to the classification of psychoses based on functional neuroimaging data.

Another potential marker is the dynamic functional connectivity of brain regions. Analysis of indicators in psychotic BAD, SAD, and schizophrenia allowed us to establish shared signs of dysfunction compared to healthy controls, including a decrease in the strength of the connection between the thalamus and cerebellum and an increase in the strength binding the postcentral gyrus and the thalamus. On the other hand, only in the case of SAD were differences found between the right, middle, and left inferior frontal gyrus, between the left central sulcus (the sulcus of Rolando) and the left Heschl's gyrus, between the left cuneus and the right middle temporal area, and between the left gyrus rectus and the left cerebellum [52].

In patients with SAD, structural brain abnormalities are found in various brain regions. Affected gray matter areas include the midline, the inferior and orbitofrontal structures, temporal lobes, left parahippocampal, right gyrus rectus, left fusiform gyrus, and bilateral thalamic nuclei. In the white matter, abnormalities in patients are primarily observed in the corpus callosum and corona radiata. Abnormalities are found predominantly in those brain regions where they have previously been observed in schizophrenia and, to some extent, in bipolar disorder [53]. Another study examined the differences in the shape of the basal ganglia in SAD and schizophrenia [54]. In particular, internal deformation on the anterior ventral surface was observed only in SAD, which may indicate a substrate for affective disorders, but not schizophrenia. Significant anteroventral abnormalities in the putamen observed only in SAD suggest that changes in this region contribute to affective disorders. These findings are consistent with ventral putamen shape changes in individuals with untreated major depressive disorder and BAD and, according to us, may be useful in improving diagnostic accuracy in SAD. Decreased amygdala and hippocampus volumes are characteristic of individuals with schizophrenia, SAD, and bipolar disorder compared with the healthy population. When comparing diagnoses and biotypes in the psychosis spectrum in terms of the volume and shape of the amygdala and hippocampus, a significant decrease in volume compared with healthy controls was found in the left amygdala in SAD, while shape abnormalities in the left and right hippocampus were observed in both SAD and schizophrenia [55].

Finally, the immune system may play an important role in the predisposition, occurrence, and progression of mental disorders. The neutrophil-to-lymphocyte ratio (NLR), monocyte-to-lymphocyte ratio (MLR), and platelet-to-lymphocyte ratio (PLR) are innovative, stable, reproducible routine markers of the systemic immune response [56, 57]. An increase in these parameters was noted in individuals with mood disorders and schizophrenia compared to healthy controls. NLR and MLR were higher in the schizophrenia group compared to SAD and can serve to differentiate these disorders. It has been suggested that in schizophrenia, in contrast to SAD, there is an innate immune response as a cause or consequence of microglial activation [58].

In the available literature, only a few publications are devoted to genetic predisposition to SAD. In particular, a study of individuals from the Ashkenazi population with bipolar I disorder, schizophrenia, and SAD showed that only 6 of 64 candidate genes (*DPYSL2, DTNBP1, G30/G72, GRID1, GRM4*, and *NOS1*) are common to schizophrenia and SAD [61]. On the other hand, in patients with bipolar disorder with psychotic disorders and schizophrenia, gene overlap was detected in only two chromosomal regions (13q31 and 22q12) [59].

Perhaps, in the future, when screening large samples of individuals with SAD in international genetic projects, rare copy number variations predisposing to specific psychotic disorders will be uncovered [60]. However, with our current knowledge, it is not possible to separate patients with schizophrenia, BAD, and SAD based solely on genetic research data.

## DISCUSSION

### Brief interpretation of results

Despite important changes in the ICD-11 and DSM-5 criteria for SAD, revision of these classifications has not resolved many of the issues important for clinical practice, and the concept of SAD remains inadequately defined [61, 62]. During an episode of illness, affective and psychotic symptoms may fluctuate, and, accordingly, the diagnosis of SAD may change. For example, the threshold for SAD may be crossed at some points in time, but not at others. Achieving greater clarity regarding the relationship between affective and psychotic symptoms throughout the illness may require additional information from medical records and from the persons interacting with the patient, and this

information cannot always be trusted. In addition, in real life, it may be difficult to determine the onset of an episode of illness, and the period between its manifestation and the seeking of help may be lengthy [63]. Often, it is difficult to identify the moment when affective symptoms play a significant role in the clinical presentation due to massive psychotic symptoms, or medical history information may be unavailable for various reasons, including information regarding a psychotic episode in the past [64]. According to the DSM-5 criteria, a diagnosis of schizophrenia may be erroneously established in the first case and an affective episode with psychotic symptoms in the second case. Also, in the literature on unipolar depression, difficulties in assessing the severity of a depressive episode are noted [65]; therefore, the requirement of both classifications for the presence of moderate to severe depression in SAD may be difficult to meet in practice. An additional source of confusion for clinicians is that both ICD-11 and DSM-5 additionally allow for the description of depressive symptoms in schizophrenia. In DSM-5, the task is simplified by the fact that in order to diagnose SAD, it is necessary to find a history of a psychotic episode without affective symptoms [17]. In ICD-11, only purely affective symptoms (low mood and suicidal thoughts) are included in the classification of depression in schizophrenia, and the assessment of its severity does not coincide with the assessment of the severity of a depressive episode in mood disorders [15].

The views of specialists on SAD often differ from the criteria outlined in classifications. A survey of 113 clinical psychologists showed that, in their opinion, SAD is a "less psychotic" disorder than schizophrenia and "less affective" than bipolar disorder and unipolar depression, which is inconsistent with the understanding of SAD as a disease of lesser severity compared to other psychiatric diseases [30].

Even in international classifications, there is no consensus on the specific subtypes of SAD. The ICD-11 recognizes three subtypes (manic, depressive, and mixed), while the DSM-IV identifies two (depressive and manic), and the DSM-5 distinguishes between bipolar and depressive subtypes. In addition, empirically identified classes of psychoses within the categorical approach also show poor correspondence with the diagnostic categories of DSM-5 and ICD-10. On the other hand, the empirical nature of the identified dimensions of psychoses, including SAD, explain the heterogeneity of clinical symptoms much better than the categories of psychoses [66], and an understanding of psychotic disorder as a "multidimensional syndromic variation with an unpredictable course and outcome" with the introduction of a single concept of "psychotic spectrum" would be generally useful for psychiatry [67], especially given the fact that combination of schizophrenia and affective disorders occurs much more frequently than might be expected on the basis of a random coincidence or common genetic factors [68]. As we criticize the modern concept of SAD for its reductionism and the subjectivity of the preferences of individual clinicians, it is our suggestion that each patient be evaluated holistically, taking into account follow-up data, disease course and pathophysiology, and to identify several discrete forms of these diseases [69].

The study of the cognitive functioning of individuals with SAD is of significant importance for diagnosis and prognosis, and its effective management can reduce the cost of care to such patients both in the short and long term [48, 70]. Neuroimaging changes explain the similarity of clinical manifestations of SAD and BAD with psychotic manifestations on the one hand, and cognitive deficit in schizophrenia and BAD, on the other. It is noteworthy that functional and morphological changes in SAD overlap with both schizophrenia and BAD, the combination of which, together with its unique features and clinical characteristics, allows one to situate SAD in the context of the BAD–SAD–schizophrenia metaspectrum.

### Limitations

The possible limitations of our work are related to the lack of a unified concept of SAD, the small number of studies identifying SAD (and particularly its subtypes) in distinct groups or subgroups, and the small sample sizes of patients with SAD included in the studies. In some studies, the differences between the groups resided at a subclinical level.

## CONCLUSION

Despite important changes in the diagnosis of SAD in ICD-11 and DSM-5, many unresolved issues persist as regards this disorder from the point of view of clinical psychiatry and neurobiology. There has been some improvement in the inter-rater reliability of SAD criteria in modern classifications, but this has not yet led to a clearer understanding among specialists, while the various subtypes of SAD identified so far fail to account for the heterogeneity in the clinical presentation. Apparently, the dimensional approach to the conceptualization of SAD, according to which the intensity

of psychotic and affective symptoms can fluctuate over time and they can influence one another, more accurately reflects the disease's variability. Basic research also does not support the identification of a distinct cognitive, neuroimaging, or immunological SAD endophenotype that differs qualitatively from schizophrenia and affective psychoses, which, according to some authors, justifies the use of the SAD category, despite the clinical uncertainty surrounding this diagnostic header. The conceptualization of SAD remains incomplete, and new approaches rooted in neuroscience appear to be needed to better understand the coexistence of affective and psychotic symptoms.


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# The Rising Cases of Suicide among Nigerians: What Are the Risk Factors, Prevention, and Remedies?

## Увеличение числа суицидов среди жителей Нигерии: факторы риска, профилактика, средства помощи

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**Opinion**

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**ABSTRACT**

The escalating suicide rate in Nigeria, exacerbated by economic, political, health, and social crises, represents a pressing concern. The aftermath of the global COVID-19 pandemic and subsequent lockdowns has exacerbated this issue, particularly in African nations with bare-bones governmental support systems. This paper examines the underlying causes of the alarming number of suicides in Nigeria, utilizing interviews to explore the risk factors, preventative measures adopted, and crisis interventions. Our findings reveal that spousal conflicts, job loss, and bereavement are significant triggers of suicidal ideation. Recommendations include fostering supportive environments, crisis interventions, and psychological rehabilitation services. Urgent attention is warranted to address this growing trend and mitigate its socioeconomic repercussions in Nigeria.

**АННОТАЦИЯ**

Повышение частоты суицидов в Нигерии является актуальной проблемой и усугубляется экономическим, политическим, медицинским и социальным кризисами. Последствия пандемии COVID-19 и вызванного ей локдауна обострили эту проблему, в особенности в африканских странах с минимальным уровнем государственной поддержки населения. Настоящая работа посвящена изучению причин, лежащих в основе угрожающего роста числа суицидов в Нигерии. Для решения этой задачи используются интервью для оценки факторов риска, анализ принятых в стране профилактических мероприятий и кризисных вмешательств. Полученные результаты показывают, что значимыми факторами, провоцирующими суицидальные мысли, являются супружеские конфликты, потеря работы и переживание тяжелых утрат. Рекомендации по противодействию сложившейся ситуации включают создание благоприятной поддерживающей среды, кризисные вмешательства и оказание услуг по психологической реабилитации. Обсуждаемая проблема требует незамедлительного привлечения внимания для уменьшения ее отдаленных социально-экономических последствий в Нигерии.

**Keywords:** *suicide; Nigeria; suicide prevention*

**Ключевые слова:** *суицид; Нигерия; профилактика суицида*

## INTRODUCTION

Suicide, the deliberate act of ending one's life, often serves as a desperate escape from unbearable suffering. Each year, nearly 800,000 individuals globally succumb to suicide, with many more attempting it, as reported by the World Health Organization[1]. Contrary to the perception that suicide is predominant in high-income nations, it is a widespread problem affecting various regions worldwide, particularly in low-income countries like those in Africa and Asia[1].

Nigeria is one of Africa's largest economies. In recent years, its Gross Domestic Product (GDP) growth has fluctuated, influenced by factors such as oil prices, which significantly affects its economy due to its strong reliance on oil exports. Before the pandemic, Nigeria's unemployment rate stood at 23%. During the pandemic, Nigeria, not unlike many other countries, experienced economic disruption that draw its unemployment rate to 46%, even as specific post-pandemic figures vary due to the unstable economic situation in that country. Nigeria also has to grapple with challenges related to hunger and food security. Factors such as internal displacement due to conflicts, climate instability affecting agriculture, and economic conditions also have bearing on food availability and access for many Nigerians. The current situation in the country has exacerbated the already high rate of preventable deaths witnessed in that country.

The economic downturn triggered by the global COVID-19 pandemic has plunged Nigeria into a severe recession, leading to a sharp rise in an already high unemployment rate. The COVID-19 pandemic had a significant impact on various economic and social indicators in Nigeria, including GDP, unemployment rate, hunger rates, and the number of killings and kidnapping. Nigeria's GDP growth rate stood at about 2.2% in 2019. Then economy was gradually recovering from a recession in 2016, driven by improvements in oil production and prices, as well as some economic reforms, before the advent of the COVID-19 pandemic that severely derailed the country's economy[2].

In 2020, Nigeria's economy contracted by 1.8% due to the pandemic, with a significant impact from lockdown measures and a drop in global oil prices. In 2021, the economy began to recover, growing by approximately 3.4%, supported by higher oil prices and a rebound in the non-oil sector. By 2022, GDP had continued to grow, albeit at a slower pace, constrained by ongoing challenges such as inflation and insecurity[3].

The unemployment rate in Nigeria was around 23.1% in the third quarter of 2018 (the latest data available before the pandemic). By the second quarter of 2020, it had jumped to 27.1%. By the fourth quarter of 2020, the unemployment rate had surged to 33.3%, reflecting the economic disruptions caused by the pandemic. Unemployment remained high in 2021 and 2022, with limited job creation and persistent economic challenges. According to the Global Hunger Index, Nigeria faced a serious hunger situation, with a score of around 27.9, in 2019[4].

The pandemic worsened food insecurity because of the lockdowns, disrupted supply chains, and loss of income. By 2021, the situation had worsened, with millions of Nigerians experiencing heightened food insecurity. Efforts to address hunger were launched, but challenges such as inflation and conflict continued to adversely affect food availability and access. Nigeria had been facing significant security challenges, with incidents of killing and kidnapping due to a long-running insurgency in the Northeast of the country, farmer-herder conflicts, as well as criminal gang activity in the middle belt region[5].

The fragile security situation worsened during the pandemic, with increased incidents of kidnapping, wanton violence and banditry. Kidnapping for ransom surged, particularly in the Northwest and North central regions, as well as in the Southeast. Killings related to the insurgency, banditry, and communal conflicts continued to escalate, straining the country's security apparatus. The COVID-19 pandemic had a profound impact on Nigeria's economy and social conditions. The country experienced economic contraction, increased unemployment, heightened food

[1] World Health Organization [Internet]. Suicides in the world: global health estimates. Geneva; 2023 [cited 2024 May 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide

[2] National Bureau of Statistics [Internet]. Economic situation in Nigeria in pre and post COVID-19 era. 2019 [cited 2024 May 15]. Available from: https://nigerianstat.gov.ng/elibrary/read/937

[3] International Monetary Fund [Internet]. 2020 [cited 2024 May 15]. Available from: https://www.imf.org/en

[4] National Bureau of Statistics [Internet]. Three years quarterly estimation. 2022 [cited 2024 May 15]. Available from: https://nigerianstat.gov.ng

[5] African Development Bank Group [Internet]. 2021 [cited 2024 May 15]. Available from: https://www.afdb.org/en

insecurity, and a deteriorating security environment. While there have been efforts to recover and stabilize the existing status-quo, the political and economic challenges remain significant[6].

Studies in Nigeria often highlight the indirect effects of corruption, such as economic instability, poverty, and social inequality, and a direct effect such as the mismanagement of public funds by corrupt officeholders in various governmental offices, which are known risk factors of mental health issues, including suicide [1]. Nigeria has a high corruption index, and there is evidence of poor-quality public services, economic disparities and lower levels of trust in institutions; all these factors collectively contribute to the stress and mental health challenges that are behind the high rate of suicide in Nigeria[7]. As a consequence, the specter of hunger looms over the nation, posing a threat to countless vulnerable individuals. If immediate measures are not taken by the Nigerian government to address the unprecedented economic crisis, an alarming number of Nigerians may succumb to hunger and suicide[7].

In Nigeria, suicide attempts often involve the ingestion of toxic substances such as rat poison, drugs, or pesticides. Some individuals resort to hanging or drowning in rivers or a pool water, because firearms are rarely used. Understanbly, women tend to opt for drug overdoses, a method with higher chances of intervention and survival. However, recent trends suggest an increase in the lethality of the suicide methods used among women, potentially placing them at equal risk of fatal outcomes as men. Unfortunately, suicide in Nigeria remains significantly underreported and under-documented due to the lack of a comprehensive system for collecting statistics and the societal stigma associated with suicide[8]. Cultural and religious beliefs often lead families to conceal suicides, portraying them as accidents or homicides to avoid social opprobrium. The criminalization of suicide in many African nations further reinforces the reluctance to acknowledge and address this issue [1].

Research on suicidal behavior in Nigeria identifies various methods, including chemical ingestion, self-cutting, burning, hanging, and the ingestion of lethal doses of rat poison or pesticides. These methods are often chosen impulsively by individuals experiencing emotional instability or psychosocial stressors [1].

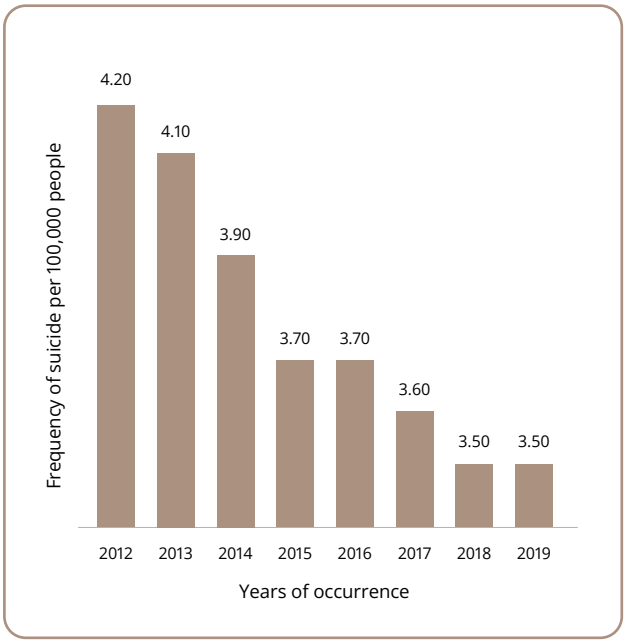


**Figure 1. Graphic representation of the frequency of suicide in Nigeria from 2012 to 2019.**

*Source:* Nigerian Bureau of Statistics (2012–2019).

Figure 1 illustrates Nigeria's suicide rates from 2012 to 2019, ranging from 4,200 to 3,500 cases annually. Data for the years 2020 onwards is currently being compiled and will be released soon.

## RISK FACTORS OF SUICIDAL BEHAVIOR IN NIGERIA

Age has long been recognized as a significant risk factor for suicide, with rates typically rising during adolescence and peaking in young adulthood (ages 20–24), before gradually increasing until around age 84 [2]. Individuals over 45 years of age account for the majority of suicides. Between 2012 and 2019 there was a notable increase in suicides among Nigerian adolescents and young adults, including those in secondary education and University, to the tune of 40,000 people per 100,000 population, compared to 15,000 per 100,000 between 2000 and 2009. This trend has solidified as a result of poverty and the current economic

[6] Council of Foreign Relation [Internet]. 2022 [cited 2024 May 15]. Available from: https://www.cfr.org

[7] National Bureau of Statistics [Internet]. Economic situation in Nigeria in pre and post COVID-19 era. 2019 [cited 2024 May 15]. Available from: https://nigerianstat.gov.ng/elibrary/read/937

[8] World Health Organization [Internet]. Suicides in the world: global health estimates. Geneva; 2023 [cited 2024 May 15]. Available from: https://www.who.int/news-room/fact-sheets/detail/suicide

realities in Nigeria. Particularly noteworthy are the critical periods of student suicides, often occurring within the first seven weeks of the academic term or semester in their first year and during their final year. These suicides are often linked to the immense pressure students face from high expectations, typically imposed by parents and guardians. Additional contributing factors include chronic health issues, interpersonal difficulties such as rejection from a love partner, and social isolation.

Psychologists have expressed alarm at the sharp rise in adolescent suicides, with recent opinion polls indicating that approximately 500,000 adolescents attempt suicide annually in Nigeria, resulting in 302,000 deaths [2]. Moreover, there has been an unsettling trend among Nigerian youths employing highly lethal methods such as shooting or injecting themselves with deadly substances to end their lives. Certain professions or vocations, such as medicine, psychology, nursing, engineering, priesthood, and trading, have also been found to have higher-than-average suicide rates. Thus, suicide affects individuals across various strata of society, irrespective of their social status.

Marital status is another significant risk factor of suicide, with divorce and separation rates being notable at the rate of 25% among Nigerians [3]. A reported 35% prevalence rate of single parenthood in contemporary Nigerian communities has further exacerbated psychological distress, especially concerning the challenges of raising children and managing family dynamics amidst the deplorable economic situation. Poverty, which has risen to 70% in many Nigerian communities, accounts for the 40% rise in stress level experienced by single parents, potentially leading to suicidal ideation or contemplation.

Drug and alcohol abuse also play a significant role in triggering suicide among Nigerian youths. About 50% of young individuals are enticed into substance abuse, including marijuana, cannabis, and methamphetamine, as well as locally brewed alcoholic beverages made from millets, often as a means of coping with the economic and social hardships prevalent in their communities as a result of joblessness [1].

Suicide often comes on the tail of profound emotions such as despair, guilt, and anger, driving individuals to seek an escape, punishment, or harm. These emotions may originate from romantic relationships, interpersonal conflicts within families, or other social dynamics. The impacts of economic and social challenges on suicidal contemplation in Nigeria are evidenced in alcohol-related issues, sexual adjustment difficulties, or unemployment [1]. Suicidal behavior represents a complex interplay of cultural, social, economic, and psychological factors, yielding varying manifestations across nations. Nigeria, with its rich cultural diversity, holds particular attitudes and beliefs concerning mental health and suicide. In several Nigerian cultures, mental health issues and suicidal ideation come with stigma and taboo are considered subjects, fostering underreporting and hindering access to essential mental health services [4].

Religion carries profound weight in Nigerian society, predominantly Christianity and Islam. Religious doctrines often denounce suicide as a sin, adversely impacting help-seeking behavior and creating internal conflicts for individuals contemplating suicide, who may feel torn between seeking support from their religious community or professional psychiatrists and community mental health centers [4]. The socio-economic landscape in Nigeria, marked by inequalities and challenges like poverty, unemployment, and inadequate access to basic services, amplifies psychological distress and susceptibility to suicidal behavior [4]. Economic hardship can exacerbate feelings of hopelessness that may contribute to a suicide attempt, particularly among marginalized groups in various Nigerian communities.

Gender dynamics also shape suicidal behavior in Nigeria, with studies indicating a higher rate of suicide among males compared to females, contrary to the patterns observed in certain Western countries [5]. Cultural norms of masculinity may discourage men from seeking help for mental health issues, aligning with societal expectations of strength and resilience. In Nigeria, the availability and accessibility of means for suicide differ from those in Western countries. Firearms, prevalent in some Western nations, are less common in Nigeria, where methods such as pesticide ingestion or hanging may be more prevalent due to their accessibility [4]. Limited access to mental health services and professionals further favors reliance on non-medical means for suicide attempts. This could include methods such as hanging from a rope, drowning in a river, sea or ocean, firearms, or other forms of self-harm that do not involve ingesting medication or substances typically used for medical purposes. This is a serious issue and often a sign of a person experiencing severe distress or crisis.

Due to cultural, religious, and legal factors, official statistics on suicides in Nigeria may be underestimated discouraging open discussion and reporting. Moreover,

inadequate resources and infrastructure for data collection and mental health research pose challenges in accurately assessing the prevalence and characteristics of suicidal behavior in the country [4].

Economic hardship, coupled with the inability to provide for one's family, can significantly impact mental health, potentially leading to suicide, in the absence of adequate psychological support. Sometimes communication breakdown among members of families may further exacerbate feelings of isolation and worthlessness, which may lead to suicide [6]. The role of severe hopelessness, exacerbated by adverse economic conditions resulting from the COVID-19 pandemic and job loss, is greatly implicated as an accelerants in the rising number of suicides in Nigeria. Individuals contemplating suicide are not always mentally ill; severe depression arising from stressful life events such as business failure, academic failure, spousal or partner infidelity and others can push anyone to consider suicide, especially during periods of significant life stressors such as job loss, divorce, or bereavement [7, 8].

It is our opinion that addressing suicidal behavior in Nigeria necessitates a nuanced understanding of its important cultural, religious, socio-economic, and gender dynamics. Tailored interventions must consider the influence of cultural and societal norms on help-seeking behavior and access to mental health services, ensuring comprehensive support for those at risk.

## REMEDIES/CRISIS INTERVENTIONS

To effectively reduce instances of suicide in our society, the following measures are crucial:

1. Establishment of Suicide Prevention Centers: It is imperative for every state or local government in Nigeria to establish centers dedicated to suicide prevention. These centers should be staffed with a mental health intervention team comprising psychologists, psychiatrists, occupational health therapists, and social workers. Psychologists trained to handle suicide situations should also be equipped to provide counseling over the phone. Individuals deemed at risk of committing suicide should be provided with the contact information of experts at these centers, encouraging them to seek help when they need it. Additionally, assistance should be offered to help individuals schedule appointments for psychological examination with a clinician. Nigeria is a country blessed with abundant human and natural resources, but the mismanagement of the country's resources by its political leaders has seemingly condemned it to a low-income status. Therefore, Nigeria cannot afford suicide prevention centers irrespective of its current economic status.

2. Involvement of Law Enforcement: In cases of attempted suicide within our neighborhoods, it is essential to promptly involve law enforcement agencies such as the Nigerian Police or the Nigerian Civil Defense Corps, particularly the Suicide Response Squad or Suicide/Crisis Intervention Centers. Law enforcement agencies like the Police and Civil Defense Corps can play a critical role in suicide prevention in Nigeria through several strategic actions. Police officers and Civil Defense Corps personnel are trained to recognize signs of suicidal behavior and respond appropriately. This training can equip them to intervene effectively in crisis situations. According to a study by Chan and Yip (2014) [9], training law enforcement officers in suicide prevention significantly enhances their ability to identify and interact with suicidal individuals. Research has shown that community-based suicide prevention initiatives involving law enforcement agencies can lead to increased awareness and improved access to support services (WHO, 2018)[9]. Law enforcement officers can play a key role in referring individuals in crisis to these facilities, ensuring that they receive timely assistance (WHO, 2018)[9]. Their intervention can be vital in preventing further harm and providing the necessary assistance to individuals in crisis. By implementing the above-mentioned strategies, law enforcement agencies in Nigeria can effectively contribute to suicide prevention efforts and support the mental health needs of their various communities.

## CONCLUSION

The prevention of suicide ideation and actual suicide can be achieved through active listening and provision of essential support to vulnerable individuals, thereby mitigating the triggers of suicide. To address the escalating rate of suicide in Nigerian society, it is crucial for community members to report any observable signs of suicidal behavior in individuals within their neighborhoods to designated suicide centers. These centers should be adequately staffed with qualified clinical psychologists and other mental health

[9] World Health Organization [Internet]. Preventing suicide: A community engagement toolkit. Geneva; 2018 [cited 2024 May 15]. Available from: https://www.who.int/publications/i/item/9789241513791

professionals, facilitating a multidisciplinary approach to effectively rehabilitate individuals rescued from the brink of suicide.


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# How NGO Staff Understand Maslow's Hierarchy of Needs and MHPSS Pyramid in Iraq: A Pilot Descriptive Study

## Как сотрудники НПО в Ираке понимают пирамиду потребностей по Маслоу и пирамиду Психического здоровья и психосоциальной поддержки: пилотное описательное исследование

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**Short communication**

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**ABSTRACT**

**BACKGROUND:** The Maslow's hierarchy of needs (Maslow's pyramid) and the Mental Health and Psychosocial Support (MHPSS) pyramid are integral frameworks in humanitarian settings whose aim is to address individual and community needs. However, confusion often arises among non-governmental organization (NGO) workers about the application and differentiation of these models.

**AIM:** This study aims to investigate the extent of confusion among NGO workers in Iraq as regards the Maslow's and MHPSS pyramids, identify the causes of this confusion, and explore its implications in the context of humanitarian mental health support.

**METHODS:** A pilot descriptive study was conducted in December 2023 through an online survey involving 61 local NGO workers from MHPSS components in Iraq. We created a measure to assess the participants' familiarity with both models, their perceived differences, and their views on the models' applicability in humanitarian contexts.

**RESULTS:** Male participants represented 55.7% (*n*=34) of the sample, while females accounted for 44.3% (*n*=27). Most participants were aged 25–34 (57%, *n*=35) and 35–44 (34%, *n*=21). A majority held bachelor's degrees (67.2%, *n*=41), with 21.3% (*n*=13) holding master's degrees. In terms of occupation, 49.2% (*n*=30) were engaged in the protection sector (gender-based violence and child protection), followed by health (19.7%, *n*=12), education (4.9%, *n*=3), and MHPSS staff roles in other sectors (26.2%, *n*=16). The study revealed that 54.1% (*n*=33) of the participants struggled to understand or differentiate between Maslow's and MHPSS pyramids. The causes of this confusion were related to perceived structural similarities (18.03%, *n*=11), lack of awareness and knowledge about the MHPSS pyramid (63.93%, *n*=39), and a combination of both (18.03%, *n*=11).

**CONCLUSION:** The study underscores the importance of better training and education for NGO workers to improve their understanding of the Maslow's and MHPSS pyramids. Addressing this knowledge gap can increase efficacy in humanitarian aid provision, ensuring that individual and community needs are adequately met in crisis situations.

**АННОТАЦИЯ**

**ВВЕДЕНИЕ:** Пирамида Маслоу и пирамида Психического здоровья и психосоциальной поддержки (ПЗПСП) — базовые инструменты оценки степени удовлетворенности потребностей индивида или группы людей. Сотрудники неправительственных организаций (НПО) часто испытывают затруднения в применении этих методик и плохо понимают отличия между моделями, лежащими в их основе.

**ЦЕЛЬ:** Определить уровень проблем и их причины при использовании пирамиды Маслоу и пирамиды ПЗПСП работниками НПО Ирака и исследовать применение этих инструментов при оказании психологической поддержки со стороны гуманитарных организаций.

**МЕТОДЫ:** В декабре 2023 г. было проведено пилотное описательное исследование в формате онлайн-опроса. В нем принял участие 61 работник служб ПЗПСП местных НПО в Ираке. Разработанная методика позволила оценить, насколько хорошо участники опроса знакомы с обеими моделями и знают об их различиях. Также исследование отражало мнение участников о применимости вышеуказанных моделей в гуманитарном контексте.

**РЕЗУЛЬТАТЫ:** Участники мужского пола составляли 55,7% (*n*=34) выборки, в то время как женщины — 44,3% (*n*=27). Подавляющая доля участников относились к возрастным группам 25–34 лет 57% (*n*=35) и 35–44 лет 34% (*n*=21). Большинство респондентов имели степень бакалавра 67,2% (*n*=41), а 21,3% (*n*=13) — степень магистра. При оценке распределения по роду деятельности установлено, что 49,2% (*n*=30) участников были заняты в сфере защиты (защита жертв гендерного насилия и защита детей), а остальные – в проектах по охране здоровья 19,7% (*n*=12), в образовательных проектах 4,9% (*n*=3) и работники ПЗПСП из других секторов 26,2% (*n*=16). Исследование показало, что 54,1% (*n*=33) участников испытывали затруднения в понимании правил применения пирамиды Маслоу и ПЗПСП и в определении принципиальных различий между ними. Причины подобных проблем были связаны с восприятием участниками пирамид как структурно сходных 18,03% (*n*=11), с недостатком осведомленности о пирамиде ПЗПСП 63,93% (*n*=39), а также с сочетанием обоих факторов 18,03% (*n*=11).

**ЗАКЛЮЧЕНИЕ:** Исследование подчеркивает важность обучения и повышения квалификации работников НПО для лучшего понимания сути пирамиды Маслоу и ПЗПСП. Устранение пробела в знаниях в этой области может повысить эффективность оказания гуманитарной помощи и гарантировать адекватное удовлетворение потребностей индивида и сообщества в кризисных ситуациях.

**Keywords:** *Maslow's pyramid; MHPSS pyramid; human needs; humanitarian context; crisis*
**Ключевые слова:** *пирамида Маслоу; пирамида ПЗПСП; человеческие потребности; гуманитарный контекст; кризис*

## INTRODUCTION

Two widely used models for understanding human needs and psychosocial needs are the Maslow's hierarchy of needs (Maslow's pyramid) and the Mental Health and Psychosocial Support (MHPSS) pyramid of intervention. The concept of pyramid diagrams is often used to represent the hierarchy of needs or levels of importance in various fields. In humanistic psychology and psychosocial support in humanitarian settings, two of these pyramid diagrams are the Maslow's pyramid of needs and the MHPSS pyramid.

The Maslow's pyramid is a hierarchical model of human needs proposed by the American psychologist Abraham Maslow in 1943 [1, 2]. According to Maslow's theory, human needs are arranged in a pyramid-like structure, with the most basic needs at the bottom and the most complex at the top. The five levels of the Maslow's pyramid are physiological needs, safety needs, love and belongingness needs, esteem needs, and self-actualization needs [3]. Maslow argued that once one level of need is met, individuals are motivated to move up the pyramid to the next level until they reach self-actualization, the highest level of human needs.

The Inter-Agency Standing Committee (IASC) in 2007 developed the MHPSS guideline for emergency situations

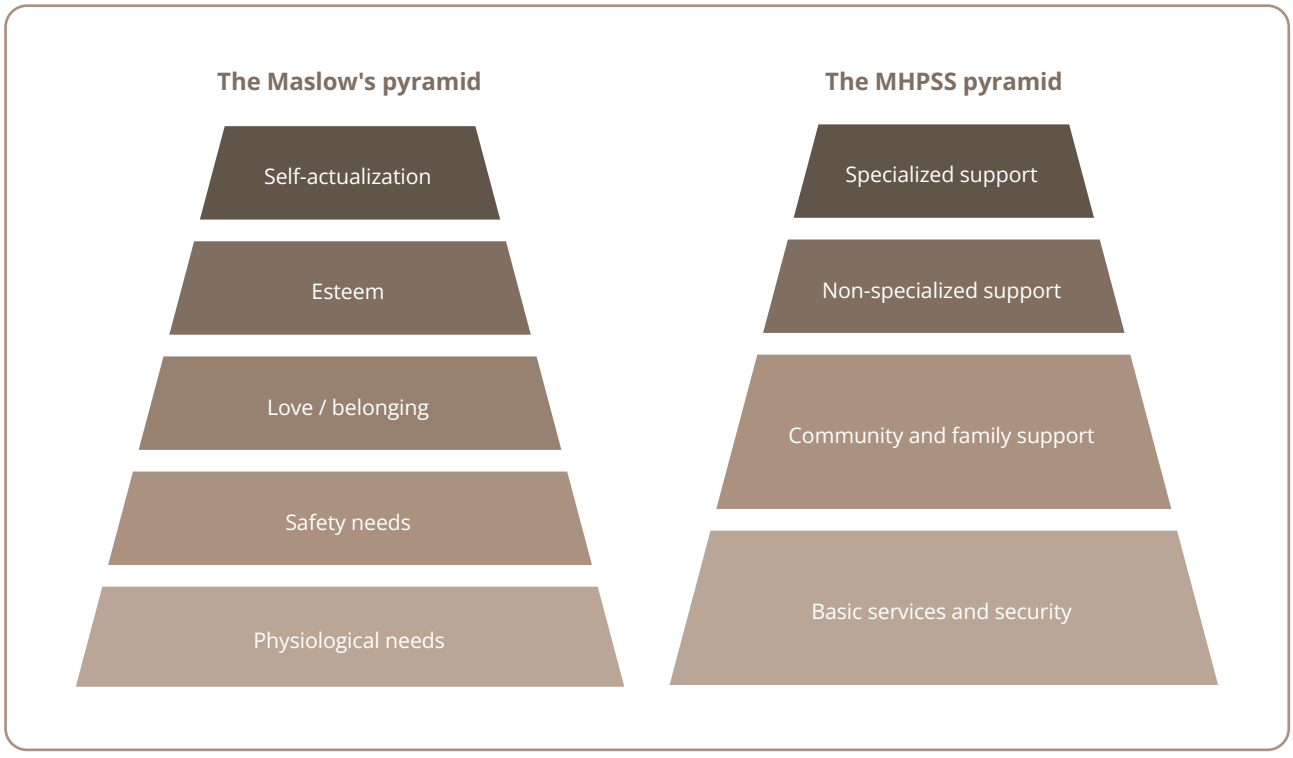


**Figure 1. Illustration of the The Maslow's pyramid and the Mental Health and Psychosocial Support (MHPSS) pyramid.**

to provide a framework to address the mental health and psychosocial needs of people affected by crisis[1]. Unlike Maslow's pyramid, which focusses on individual needs, the MHPSS pyramid is designed to address the needs of entire communities affected by a crisis [4]. The pyramid consists of four levels, starting with basic needs and safety at the base, followed by social and community support, non-specialized psychological support, and finally specialized mental health services at the top [5]. The model suggests that people must meet their basic needs before receiving more targeted support for their mental health and well-being. Figure 1 indicates the pyramids of both models.

## Rationality of the study and the hypothesis

We have noticed considerable confusion among non-governmental organization (NGO) workers about Maslow's pyramid and the MHPSS pyramid. This observation spurred us into investigating their understanding of these models in depth, with the aim of pinpointing the factors causing this confusion and understanding the nuances of their comprehension and its potential implications for mental health support in a humanitarian context. We hypothesize that NGO workers indeed struggle to understand and differentiate between Maslow's pyramid and the MHPSS pyramid in the context of humanitarian mental health assistance. No comprehensive studies have previously been conducted that exclusively focused on this topic, which underscores the originality and necessity of our survey. Understanding these challenges is crucial as it can significantly enhance the capacity of aid workers, allowing them to offer more effective assistance. This research is essential as it will provide insights that could potentially reshape training programs and improve the overall efficacy of humanitarian interventions.

## The objectives of the study

The study aims to examine NGO aid workers' grasp of human needs according to the Maslow's pyramid and the MHPSS pyramid. It seeks to identify the differences between the two models and clarify the reasons behind the difficulty in distinguishing between them.

[1] Inter-Agency Standing Committee [Internet]. IASC Guidelines on Mental Health and Psychosocial Support in Emergency Settings, 2007. Geneva; 2007 [cited 2024 Mar 27]. Available from: https://interagencystandingcommittee.org/iasc-task-force-mental-health-and-psychosocial-support-emergency-settings/iasc-guidelines-mental-health-and-psychosocial-support-emergency-settings-2007

## METHODS

### Study design

This research is a pilot study with a descriptive design. This type of study design allows one to collect and analyze data about a specific population at a given point in time. To add depth to the data collection process, we employed the snowball sampling method, which involves participants referring other potential respondents, thereby broadening the reach and diversity of the sample. This method is particularly effective in accessing a wider network of participants, especially when direct contacts are limited.

### Measurements

We designed a scale to evaluate the participants' viewpoints and comprehension regarding the Maslow's pyramid and the MHPSS pyramid (see Box S1 in the Supplementary). The scale comprised six sections, with the initial section focusing on demographic details and the subsequent sections featuring 10 questions concerning the participants' familiarity with both models, their perceived distinctions, and their perspectives on the applicability of each model in a humanitarian setting. The survey was conducted online using Google Form. Two MHPSS specialists with at least 9 years of experience in the field, coming from the public health and clinical psychology backgrounds, collaborated to develop the survey questionnaire, aligning it with the purpose and context of Iraqi NGO workers.

### Setting

Participants were randomly chosen from NGO workers in Iraq, from refugees and internally displaced persons (IDP) camps in Ninawa, Erbil, and Duhok provinces. Participation in the survey was voluntary, anonymous, and no personal data were collected. Informed consent was obtained from participants during data collection.

### Sample

A total of 61 participants from various educational levels participated in the survey, most being healthcare workers such as doctors, nurses, and psychologists who worked in the MHPSS unit.

Inclusion criteria: 1) being a local staff member; 2) actively participating in MHPSS-related humanitarian efforts within both local and international NGOs; and 3) participating in projects centered on protection, health, education and other units.

International staff and individuals from disciplines not related to MHPSS were excluded from the study.

### Data sources

The survey was anonymous, and for confidentiality we did not ask for names or personal information. The survey was distributed electronically to potential participants in December 2023, using a snowball approach to broaden participant engagement and capture diverse perspectives. Responses were collected over a two-week period between December 10th and December 24th.

### Statistical analysis

Descriptive statistics was used to analyze the rates and percentages of the responses, using the Statistical Package for the Social Sciences (SPSS) version 27.

## RESULTS

### Sample characteristics

Table 1 provides indicators about the demographics of the participants. The largest age groups were within the age ranges of 25–34 (57%) and 35–44 (34%), while smaller

**Table 1. Demographics of participants**

| Parameter | Value | N | % |
|---|---|---|---|
| Age (years) | 18–24 | 2 | 3.3% |
| | 25–34 | 35 | 57.4% |
| | 35–44 | 21 | 34.4% |
| | 45–54 | 3 | 4.9% |
| Gender | Male | 34 | 55.7% |
| | Female | 27 | 44.3% |
| Level of Education | High School or equivalent | 2 | 3.3% |
| | Bachelor's degree | 41 | 67.2% |
| | Master's degree | 13 | 21.3% |
| | Doctoral degree | 1 | 1.6% |
| | Other | 4 | 6.6% |
| Field or component in humanitarian/NGO | Protection (GBV and child protection) | 30 | 49.2% |
| | Health | 12 | 19.7% |
| | Education | 3 | 4.9% |
| | Other | 16 | 26.2% |

*Note:* NGO — non-governmental organization; GBV — gender-based violence.

representations were evident in the age ranges of 18–24 (3.3%) and 45–54 (4.9%). The gender distribution showed a slight male predominance, comprising 55.7% of males and 44.3% of females. Educational backgrounds varied, with a significant majority possessing Bachelor's degrees (67.2%), followed by those with Master's degrees (21.3%). Participants were involved in various sectors of humanitarian work, with substantial presence in Protection (gender-based violence (GBV), and child protection) roles (49.2%), complemented by contributions in Health (19.7%), Education sector (4.9%), and various roles categorized as 'Other' (26.2%).

### Distinguishing between Maslow's pyramid and the MHPSS pyramid

Our hypothesis contended that there is prevalent confusion between the Maslow's pyramid and the MHPSS pyramid among NGO workers active in Iraq. This was confirmed by the study results.

Table 2 represents the responses to a survey question regarding understating of and confusion between Maslow's pyramid and the MHPSS pyramid among NGO workers in Iraq (*Is it common for you to confuse Maslow's pyramid with the MHPSS pyramid?)* in which "Yes" means the participants cannot understand clearly and confuse between Maslow's pyramid and the MHPSS pyramid. "No" means they are not confused and understand the difference. Notably, 54.1% (33 participants) said they were confused, while 45.9% (28 participants) said they understood both models clearly.

### Causes of the confusion between Maslow's pyramid and the MHPSS pyramid

Table 3 shows the main causes behind the confusion between the Maslow's and MHPSS pyramids.

**Table 2. Confusion between Maslow's and MHPSS pyramids**

| Question | | N | % |
|---|---|---|---|
| Is it common for you to confuse Maslow's pyramid with the MHPSS pyramid? | Yes | 33 | 54.1% |
| | No | 28 | 45.9% |

**Table 3. Reasons for confusion**

| Question | | N | % |
|---|---|---|---|
| What is the primary cause of confusion between the Maslow's pyramid and the MHPSS pyramid? | Similar pyramid structure | 11 | 18% |
| | Lack of awareness about MHPSS pyramid | 39 | 63.9% |
| | Both | 11 | 18% |

Within this analysis (*What do you think is the primary cause of potential confusion between Maslow's pyramid and the MHPSS pyramid, considering their differences?*) in which 11 out of 61 participants (18%) attributed their confusion to a perceived similarity in the pyramids' structure, while an additional majority 39 out of 61 participants (63.9%) mentioned a lack of awareness about the MHPSS guidelines and its tools. Finally, 11 out of the 61 participants (18%) highlighted both factors as primary contributors to the general state of confusion between Maslow's and the MHPSS pyramid.

## DISCUSSION

### Comprehension and confusion among NGO workers

The study initially hypothesized that NGO workers struggle to understand and differentiate between Maslow's pyramid and the MHPSS pyramid in the context of humanitarian mental health assistance. The findings confirm this hypothesis, as more than half of the participants admitted to confusing the two models, underscoring a significant comprehension problem within the NGO workforce in Iraq. This confusion is concerning given the distinct and critical role each framework is supposed to play in humanitarian aid work. Maslow's pyramid, which is primarily focused on individual development and needs, contrasts sharply with the MHPSS pyramid, which is tailored for community-based psychosocial support in crisis situations.

### The causes of the confusion

The primary reasons for this confusion were identified as a lack of awareness and knowledge about the MHPSS pyramid and perceived structural similarities between the two pyramids. In particular, almost two-thirds of the respondents attributed their confusion to inadequate knowledge about the MHPSS pyramid. This indicates a critical gap in training and information dissemination among NGO workers. Addressing this gap is essential not only for the effectiveness of humanitarian aid work, but also for the mental health and well-being of communities in crisis. The identified facts are influenced by insufficient experience in the humanitarian field of MHPSS, which may be due to psychologists and social workers not having studied these specific models in university programs, further compounded by the shortcomings or lack of additional specialized training provided by specialists to improve aid workers' knowledge.

### Implications for capacity building

The study findings highlight a clear need for improved capacity building programs for NGO workers, as they are insufficient in Iraq [6]. Training should focus on clearly delineating these models, emphasizing their applications, and clarifying their distinct roles in humanitarian aid work. Furthermore, incorporating more comprehensive mental health and psychosocial support training into the regular training schedule of NGO workers could help mitigate this confusion. By improving their understanding of these frameworks, NGO workers can be better equipped to apply them appropriately in their respective roles.

### Limitations

This study has several limitations, such as a small sample size and potential biases from snowball sampling. The questionnaire was specifically developed for this pilot study, lacking detailed information collection protocol and relying solely on self-reported data, which may have introduced a response bias. Additionally, the descriptive nature of the study limited the ability to establish causality, monitor changes over time, and avoid overgeneralization. Future research could expand on this study by incorporating a larger and more diverse sample and employing a longitudinal design to examine changes in understanding over time after targeted educational interventions.

## CONCLUSION

The study's insights into the confusion between Maslow's pyramid and the MHPSS pyramid among Iraqi non-governmental organization workers highlight a crucial area for intervention. By improving training and clarity with respect to these models, we can improve the efficacy of humanitarian aid and ensure that individual and community needs are addressed effectively in crisis situations. This empowers NGO workers with the knowledge and skills necessary to make informed decisions in their critical roles.


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### Supplementary data

Supplementary material to this article can be found in the online version:
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