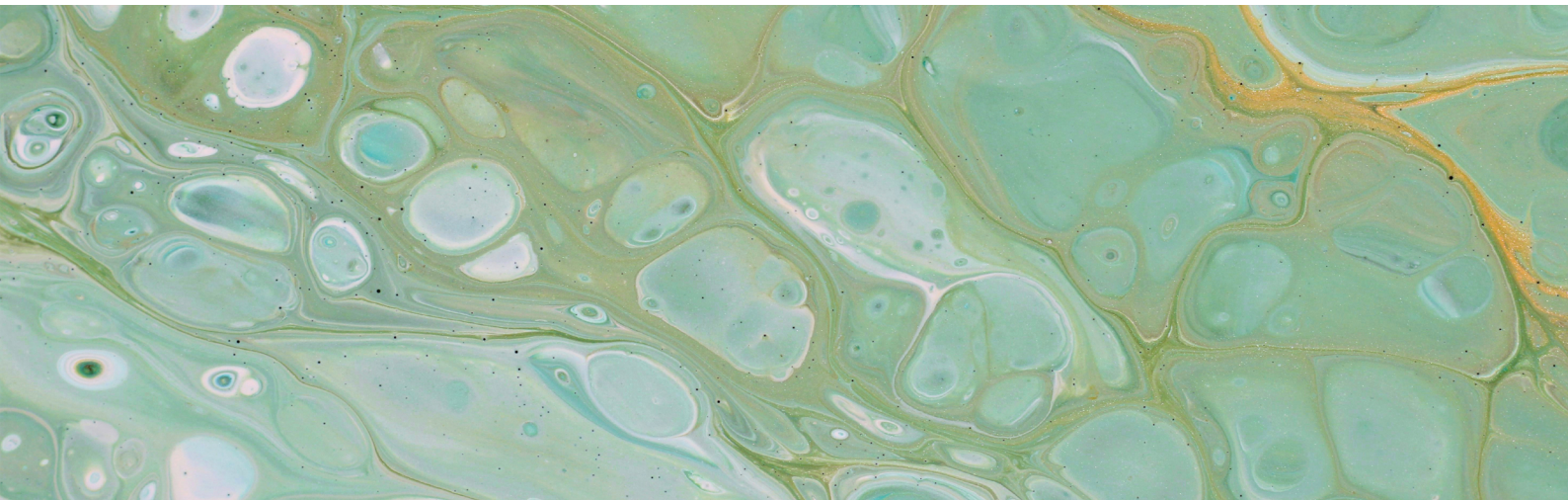
Consortium PSYCHIATRICUM

2025 | Volume 6 | Issue 1 | www.consortium-psy.com | ISSN 2712–7672 (Print) | ISSN 2713-2919 (Online)

Comparative Analysis of Corpus Callosum Lipidome and Transcriptome in Schizophrenia and Healthy Brain Page 5



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DOAJ Seal

Volume 6 Issue 1
ISSN 2712-7672 (Print)
ISSN 2713-2919 (Online)
Frequency: 4 times a year. Signed for printing: 24.03.2025. Printing House: Mediacolor LLC, 19, Signalny proesd, Moscow, Russia, 127273.

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Том 6 Выпуск 1
ISSN 2712-7672 (Print)
ISSN 2713-2919 (Online)
Журнал зарегистрирован Федеральной службой по надзору в сфере связи, информационных технологий и массовых коммуникаций. Свидетельство о регистрации ПИ № ФС 77-78122 от 13 марта 2020 г. Периодичность: 4 раза в год. Дата выхода в свет: 24.03.2025.
Типография: ООО «Медиаколор», 127273, г. Москва, Сигнальный проезд, д. 19. Тираж: 350 экз. Распространяется бесплатно.

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Comparative Analysis of Corpus Callosum Lipidome and Transcriptome in Schizophrenia and Healthy Brain

Сравнительный анализ липидома и транскриптома мозолистого тела головного мозга при шизофрении и в здоровом состоянии

doi: 10.17816/CP15491

Original research

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ABSTRACT

BACKGROUND: Functional and structural studies of the brain highlight the importance of white matter alterations in schizophrenia. However, molecular studies of the alterations associated with the disease remain insufficient.

AIM: To study the lipidome and transcriptome composition of the corpus callosum in schizophrenia, including analyzing a larger number of biochemical lipid compounds and their spatial distribution in brain sections, and corpus callosum transcriptome data. To integrate the results of molecular approaches to create a comprehensive molecular perspective of the disease.

METHODS: A total of 8 brain tissue samples (4 from healthy controls (HC) + 4 from schizophrenia patients (SZ)) were analyzed using high-performance liquid chromatography with mass spectrometry (HPLC-MS) and RNA sequencing for transcriptome profiling. Additionally, 6 brain tissue samples (3 HC + 3 SZ) were analyzed using matrix-assisted laser desorption/ionization mass spectrometric imaging (MALDI-MSI). This approach enabled the characterization of mRNA and lipids in brain tissue samples, and the spatial distribution of selected lipids within brain sections.

RESULTS: The analysis revealed a general trend of reduced lipid levels in the corpus callosum of schizophrenia patients for lipid classes measured by mass spectrometric methods. Specifically, nine lipid classes detected via HPLC-MS showed significant differences in schizophrenia samples, with seven of them having lower median intensity. The results between

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HPLC-MS and MALDI-MSI were highly concordant. Transcriptome analysis identified 1,202 differentially expressed genes, clustered into four functional modules, one of which was associated with lipid metabolism.

CONCLUSION: We identified a series of lipidome and transcriptome alterations in the corpus callosum of schizophrenia patients that were internally consistent and aligned well with previous findings on white matter lipidome changes in schizophrenia. These results add to the existing scope of molecular alterations associated with schizophrenia, shedding light on the biological processes potentially involved in its pathogenesis.

АННОТАЦИЯ

ВВЕДЕНИЕ: Функциональные и структурные исследования мозга свидетельствуют о важной роли изменений белого вещества при шизофрении. Однако исследований молекулярных изменений в белом веществе, связанных с заболеванием, недостаточно.

ЦЕЛЬ: Изучить липидомный и транскриптомный составы мозолистого тела головного мозга при шизофрении и в норме, включая анализ большего числа биохимических классов липидных соединений и их пространственного распределения в срезах мозга, с помощью данных транскриптома. Объединить результаты различных молекулярных подходов для создания комплексной молекулярной картины заболевания.

МЕТОДЫ: Исследовали 8 образцов мозговой ткани: 4 от здоровой контрольной группы (КГ) + 4 от больных шизофренией (Ш) с использованием высокоэффективной жидкостной хроматографии с масс-спектрометрией (ВЭЖХ-МС) и секвенирования транскриптома. Дополнительно 6 образцов мозговой ткани (3 КГ + 3 Ш) проанализировали с помощью масс-спектрометрической визуализации с использованием матрично-активированной лазерной десорбции/ионизации (МАЛДИ-МС). Это позволило выявить относительное количество мРНК и липидов в образцах мозговой ткани, а также определить пространственное распределение некоторых липидов в срезах мозга.

РЕЗУЛЬТАТЫ: Исследование на основании данных масс-спектрометрических методов выявило общую тенденцию к относительно более низкому количеству липидов в мозолистом теле при шизофрении. Измерение количества липидов в образцах мозговой ткани пациентов с шизофренией с помощью ВЭЖХ-МС показало различия в уровнях липидов всех 9 классов. Кроме того, 7 из них имели относительно более низкую медианную интенсивность. Результаты методов ВЭЖХ-МС и МАЛДИ-МС продемонстрировали высокую степень соответствия. Анализ транскриптома определил 1202 дифференциально экспрессируемых гена. Они составляют 4 функциональных модуля, один из которых связан с метаболизмом липидов.

ЗАКЛЮЧЕНИЕ: Мы обнаружили в мозолистом теле головного мозга пациентов с шизофренией ряд изменений липидома и транскриптома, которые внутренне консистентны, а также хорошо согласуются с предыдущими выводами о липидоме белого вещества при шизофрении и дополняют их. Полученные в исследовании данные указывают на биологические процессы, которые могут претерпевать изменения во время развития патологии, и расширяют знания о существующем спектре молекулярных изменений, связанных с шизофренией.

Keywords: *schizophrenia; lipidomics; transcriptomics; mass spectrometry; corpus callosum*
Ключевые слова: *шизофрения; липидом; транскриптом; масс-спектрометрия; мозолистое тело*

INTRODUCTION

Schizophrenia is a multifactorial, distributed, and prevalent mental disorder that affects millions of people worldwide. It is characterized by a range of symptoms, including delusions, hallucinations, incoherent speech and behavior, and cognitive impairment. Despite extensive research, the causes and molecular basis of schizophrenia remain poorly substantiated. Nonetheless, emerging evidence suggests that alterations in the lipid metabolism at the molecular level might be associated with the disorder [1, 2].

In addition, differences in the transcriptomic profile between a schizophrenia and healthy brain appear to be characteristic of this disease [3] and reflect system-level alterations in the molecular composition of the brain in a pathological state [4, 5].

Lipidome is a complete set of lipids present in a particular cell or tissue. Lipids are essential components of cell membranes and play a critical role in a wide range of physiological processes, including energy storage, signal transduction, and membrane traffick [6]. Recent studies have revealed that alterations occur in several classes of the lipids of the corpus callosum lipidome of a brain suffering from schizophrenia, including phospholipids and sphingolipids [7, 8]. What is more, it is known that abnormalities in the corpus callosum (smaller size, shape variation, and loss of connectivity) are common in people with schizophrenia [4, 5].

While the mechanisms underlying these alterations in lipid metabolism are not yet fully understood, several hypotheses have been proposed [9–11]. One hypothesis suggests that alterations in lipid metabolism may disrupt the integrity of cell membranes, leading to neuronal dysfunction and cognitive impairment [12]. Another hypothesis holds that with schizophrenia, the signaling pathways involved in neurotransmission might be disrupted, leading to abnormal neural activity and the development of schizophrenia [13]. Understanding the alterations in the lipidome that are associated with schizophrenia may provide new insights into the mechanisms underlying this disorder. This may also lead to the development of new diagnostic tools. For example, blood lipidome profiling can be used to identify biomarkers for the early detection and diagnosis of schizophrenia [14]. A widely used method in lipidome studies is high-performance liquid chromatography with mass spectrometry (HPLC-MS). This method allows one to identify a large number of compounds within a single analysis. But during sample preparation, the tissue is homogenized, which results in the loss of unique spatial information. The possibilities afforded by matrix-assisted laser desorption/ionization mass spectrometric imaging (MALDI-MSI) allow one to try to solve this problem. Thus, the HPLC-MS method, paired with MALDI imaging, provides information with reliable signal annotations and a high spatial resolution, making it possible to create a comprehensive picture of the structure of the brain lipidome.

Previous studies investigating the differences in brain transcriptome composition and the expression levels of selected gene groups observed previously in schizophrenia primarily focused on the cortical regions [3, 15, 16], while white matter tracts remain underexplored. Moreover, the number of studies that have simultaneously analyzed the lipidome and transcriptome on the same tissue samples in the context of schizophrenia white matter is very limited [7], with none incorporating spatial information. Taken together, this represents a gap in knowledge as regards the comprehensive study of the white matter lipidome of the brain, particularly with regard to a multi-omics approach.

In this paper, we aimed to study the composition of a schizophrenia-associated corpus callosum lipidome and transcriptome, as well as conduct an analysis of a larger number of biochemical classes of lipid compounds, a spatial analysis of the distribution of these compounds in brain sections supported by an analysis of corpus callosum transcriptome data, and, finally, to integrate the results yielded through different molecular approaches to the analysis in order to create a comprehensive molecular picture of the disease.

METHODS

Tissue samples

Samples were prepared from 14 frozen slices of the human corpus callosum: seven from healthy controls (HC) and seven from schizophrenia patients (SZ). Four samples (HC: two males aged 34 and 62, two females aged 34 and 61; SZ: two males aged 36 and 74, two females aged 57 and 62) from each group were used for the HPLC-MS measurements and RNAseq, and three samples (HC: two males aged 58 and 60, female aged 60; SZ: two males aged 69 and 57, female aged 62) from each group were used for the MALDI-MSI experiment. The demographic data of postmortem brain tissue donors and the ribonucleic acid (RNA) integrity number (RIN)[1] of the samples are presented in Table S1 in the Supplementary.

The postmortem human brain samples were provided by the biobank of the Contract Research Organization (CRO)

[1] Ribonucleic acid (RNA) integrity number (RIN) is a measure that evaluates the quality and integrity of RNA in samples; RIN values range from 1 to 10: 10 indicates high-quality, intact RNA; 7–9 suggests good quality with minor damage; 4–6 indicates moderate quality with noticeable degradation; and 1–3 signifies severely degraded RNA that is unsuitable for analysis. RIN allows researchers to ensure that RNA samples are suitable for further experimentation.

National BioService (Saint Petersburg, Russia). No subject in the HC 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 based on ICD-10 by psychiatrists during inpatient treatment at Mental-health clinic No. 1 named after N.A. Alexeev (Moscow, Russia). Each subject had 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. For mass spectrometric imaging, 300 mg samples were cut using sterile and chilled scalpels, forceps, and tubes. These samples were promptly frozen and stored in a low-temperature freezer at −80 °C until further analysis.

Tissue preparation

Brain samples were sectioned according to The Atlas of the Human Brain [17] by a neuroanatomist using the Leica CM1950 microtome cryostat (Leica Biosystems, China). Cutting was performed at a chamber temperature of −18 °C and sample temperature of −15 °C. The thickness of the sections was set at 20 µm. The sections were placed on an ITO (indium tin oxide) coated glass slide without any adhesive medium (Hudson Surface Technology, Bruker Glass Slides for MALDI imaging [pn 237001], Republic of Korea) and attached to the glass by thaw-mounting. The sections were next placed in a desiccator for 90 min. Air was removed from the chamber using a MEMVAK 2x1 membrane pump to a 30 mbar pressure level 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% trifluoroacetic acid (TFA, Sigma-Aldrich, USA) was diluted twice. The diluted solution was sprayed using an Iwata Micron CM-B2 airbrush (Anest Iwata, Japan) for 2 sec and allowed to dry for 2.5 min. This process was repeated 20 times.

RNA library and assessing sequencing data

RNA data acquisition, equipment, reagents and processing were done as described in [18]. Briefly, the libraries for sequencing were prepared following an RNA selection protocol utilizing polyadenylation (poly-A selection) and sequenced using the Illumina Hiseq 4000 platform. The raw data were filtered to discard low-quality reads and adapter sequences, then mapped and aligned to human reference genome GRCh38. Data provided in transcripts per million (TPM) was further log-transformed and normalized.

Modules combining functionally similar transcripts were identified using algorithms based on the HumanBase networks [19], which predict gene interactions based on large data sets specific to different types of tissue and regions of the brain covered by more than 14,000 publications. The list of differentially expressed genes in schizophrenia obtained in this work was assessed for the reliability of its correspondence to each of the 144 functions listed in the database. *Corpus callosum* was taken as a reference tissue for the functional analysis. Functional modules were determined by the software based on a community detection algorithm from a provided list of genes and the selected relevant tissue (brain). Genes within a cluster share local network neighborhoods and together form a cohesive, specific functional module.

Lipid extraction

Before lipid extraction, tissue pieces (10–15 mg) were transferred to pre-chilled reinforced 2 ml Precellys tubes (Bertin Technologies). The extraction buffer (MeOH:MTBE, 1:3, v/v) was spiked with the following lipid standards to reach a concentration of 0.5 µg/ml: TAG (15:0/18:1-d7/15:0, Avanti Lipids, 791648C), DAG (15:0/18:1-d7, Avanti Lipids, 791647C), Cer (d18:1-d7/15:0, Avanti Lipids, 860681), LPC (18:1-d7, Avanti Lipids, 791643C), PG (15:0/18:1-d7, Avanti Lipids, 791615C), PC (15:0/18:1-d7, Avanti Lipids, 791637C), PE (15:0/18:1-d7, Avanti Lipids, 791638C). The buffer was prepared once, stored at −20 °C, and was used for all the samples in the batch. Prior to preparation, samples were randomly mixed. "Blank" samples, representing empty tubes without brain tissue, were also processed after biological samples. For lipid extraction, 1 ml of buffer was added to each tube, followed by the homogenization of tissue pieces using the Precellys Evolution homogenizer (Bertin Technologies). Then the samples were shaken on an orbital shaker (30 min, 4 °C) and processed in an ultrasonic bath (10 min, 0 °C). The suspension was then transferred to a new tube (2 ml), and 700 µl of a H_2O:MeOH mixture (3:1, v/v) was added. The resulting mixture was shaken on an orbital shaker (5 min, 4 °C) and centrifuged (11,500 g, 10 min, 4 °C). After centrifugation, 540 µl of the upper phase containing hydrophobic compounds (lipids) was collected, transferred to a 1.5 ml new tube, and the organic solvent was removed using a rotary evaporator

(Thermo Scientific SpeedVac) in ambient temperature. The obtained dry lipid samples were stored at −80 °C.

HPLC-MS analysis

To reconstitute the dry lipid fraction, 200 µl of a pre-cooled (0 °C) mixture of acetonitrile:isopropanol (7:3, v/v) was added to each sample. The samples were shaken on an orbital shaker (10 min, 4 °C), followed by incubation in an ultrasonic bath (10 min, 0 °C), and centrifugation (11,500 g, 10 min, 4 °C). For the preparation of quality control (QC) samples, 5 µl of each sample was pooled. Prior to mass spectrometric analysis, 25 µl of each sample was transferred into 200 µl vials and diluted with an acetonitrile:isopropanol mixture (7:3, v/v) at a ratio of 1:15 for positive polarity and with no dilution for negative polarity measurements. QC samples were introduced at the beginning of the mass spectrometric analysis to condition the column and then after every 12th sample in the series.

The analysis was conducted on a Bruker Impact II Quadrupole Time-of-Flight (QTOF) mass spectrometer (Bruker Daltonics, Bremen, Germany), coupled with the Waters Acquity HPLC chromatographic system (Waters, Manchester, UK) using a method adapted from [20]. Chromatographic separation was performed using a reversed-phase ACQUITY HPLC BEH C8 column (2.1×100 mm, 1.7 µm, Waters Co., Milford, Massachusetts, USA) with a Vanguard pre-column of the same sorbent. The column temperature was maintained at 60 °C. The injection volume was 3 µl. Mobile phase A consisted of 10 mM ammonium acetate in water with 0.1% formic acid, and mobile phase B consisted of 10 mM ammonium acetate in a mixture of acetonitrile:isopropanol (7:3, v/v) with 0.1% formic acid. The flow rate was set to 0.4 ml/min in the following gradient of elution: 1 min — 55% B; 3 min — linear gradient from 55% to 80% B; 8 min — linear gradient from 80% B to 85% B; 3 min — linear gradient from 85% B to 100% B. The phase composition was held at 100% B for 4.5 min, after which the column was re-conditioned at 55% B for 4.5 min. Mass spectrometry detection was performed in full scan mode for positive and negative ions separately within the 50–1,200 m/z range. Source settings in positive polarity were as follows: capillary voltage 4,000 V, nebulizer 2 bar, dry gas 6.0 l/min, and dry temperature 180 °C. MS settings for negative polarity were as follows: capillary voltage 4,000 V, nebulizer 2 bar, dry gas 6.0 l/min, and dry temperature 200 °C. The calibration solution of ammonium formate was infused every injection run.

To assess the lipid molecular structure, we conducted a fragmentation of the pre-selected m/z values. While keeping the chromatographic separation conditions, mass spectra were acquired using a hybrid Q Exactive instrument in the data-dependent (DDA) mode, separately recording spectra in the positive and negative modes. In each mode, the resulting spectra were generated by averaging three fragmentation spectra at different collision energies. A Q Exactive mass spectrometer equipped with a heated electrospray ionization source from Thermo Fisher Scientific (USA) had the following tune parameters: capillary temperature: 320 °C; aux gas heater temperature: 350 °C; capillary voltage: 4.5 kV (−3.5 kV); S-lens RF level: 60; sheath gas flow rate (N2): 45 arbitrary units (a.u.); auxiliary gas flow rate (N2): 20 a.u., sweep gas flow rate (N2): 4 a.u. The operational parameters of the mass spectrometer for the full scan mode were configured as follows: resolution: 70,000 at m/z 200; automatic gain control (AGC target): 5e5; maximum injection time (IT): 50 ms; scan range: 200 to 2,000 Da. For DDA mode: resolution 17,500 at m/z 200; AGC: 2e4; IT: 100 ms; mass isolation window: 1.2 Da; retention time window width: expected time ± 1 min; stepped normalized collision energy: 15%, 25%, 30%; dynamic exclusion: 12 sec; inclusion: on; customize tolerances: 10 ppm. The spectra were recorded in profile mode.

HPLC-MS data processing

Following the acquisition process, the Bruker raw data files (.d files) underwent automatic internal and lock mass calibration before being transformed into the mzXML format using a customized DataAnalysis script from Bruker (Version 4.3). The mzXML files were then imported into the XCMS software using the xcms package within R version 3.8.2. Mass spectrometric peaks falsely duplicated during the XCMS peak merging procedure were identified using a 10 ppm mass threshold within one second retention time difference. Peaks detected during the first minute of the run (retention time <1 min) and after retention time = 18.3 min were excluded from further analysis. The 'fillpeaks' procedure implemented in the xcms package was used for missing value imputation. The lipid intensity values missing after the 'fillpeaks' procedure were filled by random sampling from a normal distribution with the mean equaling the median of minimal intensity values of detected lipid peaks and the standard deviation equaling the 16th percentile of this distribution.

The .raw files were converted to the .abf format using the ABF-converter. Thereafter, the files were processed using the MS-DIAL software (version 4.90) separately for the positive and negative modes. The processing parameters were set as follows: the maximum allowable range for MS1 — 0.05; minimum peak height — 10,000; and mass window width — 0.05. Other parameters were kept at default values and remained unchanged. An internal lipid database was employed for lipid annotation, encompassing 34 lipid classes based on previous brain studies (PC, PC-O, PE, PE-O, PE-P, PS, PA, PG, BMP, PI, LPC, LPE, LPC-O, LPE-O, LPS, LPA, LPG, AHexCer, Cer, HexCer, SHexCer, SM, ST, CE, TAG, DAG, MAG, MGDG, DGDG, MGDG-O, DGDG-O, FFA, CAR, NAE). The obtained databases of lipid compound areas were exported and processed in the R environment. Polarities were merged, and lipid duplicates between the two polarities were filtered based on retention time overlap and exact mass. Annotations obtained with the Q Exactive instrument were aligned with peaks in a QTOF analysis based on the retention time and m/z ratio.

To ensure a high quality of the annotated peaks, account for the extraction chemical noise and technical variability, filtering procedures were applied on the resulting target list. Firstly, a blank samples filter was applied: only those features with a mean intensity at least twice greater than in the blanks were selected for further analysis. Secondly, a variance filter was applied: the coefficient of variation was calculated across QC samples for each peak, and only those peaks with a median coefficient of variation (CV) below 0.25 were selected.

After that, all lipid intensities were log10-transformed and normalized on the median value of standards within a sample and wet weight of the sample. For normalization purposes, wet weights and standard intensities were log10-transformed, then the difference of sample values from the mean of a parameter was subtracted. Resulting lipid intensity values were further normalized using the mean intensity of the lipid calculated within each individual's brain to adjust for inter-individual variability.

MALDI experiment

MALDI-MSI data acquisition, equipment, reagents, peak annotation, and processing were done as described in [21]. Briefly, MALDI images were obtained using a modified Thermo Scientific Q Exactive Orbitrap mass spectrometer equipped with a 355 nm Nd:YAG laser. Imaging involved controlling the tissue region and raster step size with the Spectroglyph software and collecting spectra at 40-µm intervals in both dimensions. Ion images were generated from raw and coordinate files using the Image Insight software. The raw mass spectra were converted to the .ibd and .imzML formats with a zero background noise threshold, and further processing was conducted using Cardinal 2.8.0, an R package for mass spectrometry imaging data analysis. For image analysis, duplicate coordinates were removed and peak intensities were normalized by total ion current. Peak picking was performed using a signal-to-noise ratio threshold of three. Spectra were aligned to the average spectrum, and the peaks that were present in less than 7% of the spectra were excluded.

Peaks from the glass slide surface and uninformative spectrum parts were removed. The sample area was divided using a spatial k-means algorithm to distinguish between tissue and sample-free areas. Clusters were manually curated, and only peaks with 1.5 times greater mean intensities in the tissue cluster were retained. Finally, all the spectra were aligned to the one with the most detected peaks.

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 rules described in [21] were applied.

Statistical analysis

Lipid intensities were log10-transformed, and the average across all individuals in a group was used for further analysis. Next, differences between the peak averages of the two groups were calculated and the one-sample Student t-test was applied to test whether the resulting distribution of mean peak intensities differed significantly from zero. The Benjamini-Hochberg correction for multiple hypothesis testing was used. Data analysis and visualization were performed using R packages (Ggplot2, MixOmics, and other standard R packages).

To compare our dataset with previously published data on lipidomic alterations in the SZ-affected corpus callosum [7], log2 transformation was applied to downloaded original fold changes in lipid intensities. Lipid compounds were matched manually based on annotation (HPLC-MS data) or exact mass (MALDI) with respect to the common adducts. To compare with MALDI data, all detected m/z values were rounded to two decimal and only lipids that exactly matched by mass were used in the analysis. To compare HPLC-MS

data, mean fold changes were calculated for each class. Only lipid classes containing more than three lipids were used in the analysis. Pearson's correlation coefficient was then calculated based on the log2 fold changes of lipid compounds matched between datasets.

Differences in the distribution of lipids across the corpus callosum sections were assessed via the coefficient of variance (CoV). The coefficient for the control and schizophrenia groups was calculated for the masses annotated by HPLC-MS as the ratio of the standard deviation to the mean for each mass. The difference in the CoV for the two groups was tested using the Wilcoxon signed-rank test.

Ethical approval

The data for the brain samples obtained from National BioService contained no personal information or any other information that could allow donors identification. Informed consent for the use of the biomaterial for research purposes were secured from the individuals or from the next-of-kin at the respective clinical organizations that provided the samples to National BioService in accordance with international regulations[2].

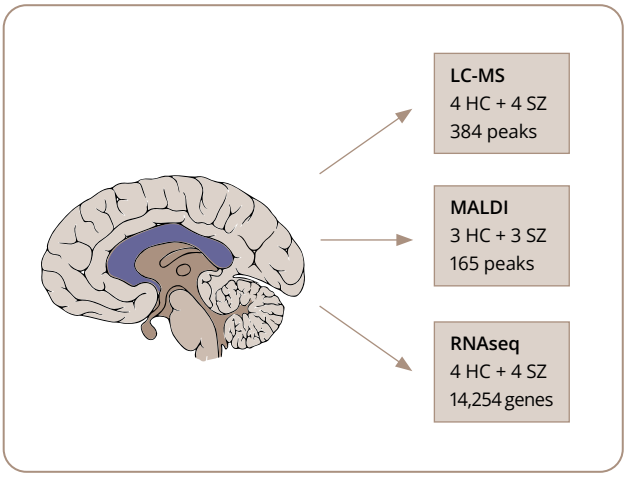


Figure 1. Experiment design.

Note: Samples of corpus callosum were dissected and used for three types of measurements: HPLC-MS; MALDI-MSI and RNAseq. Number of features detected in each type of analysis provided on the plot. HC — healthy controls; HPLC-MC — high-performance liquid chromatography with mass spectrometry; MALDI-MSI — matrix-assisted laser desorption/ionization mass spectrometric imaging; RNAseq — sequencing of ribonucleic acid; SZ — schizophrenia patients.

Source: Osetrova et al., 2025.

RESULTS

We examined the alterations in the white matter lipidome composition between SZ and HC individuals using HPLC-MS, as well as MALDI-MSI (Table S1 in the Supplementary).

The application of each technique resulted in the detection of 384 and 165 lipid features for HPLC-MS and MALDI, respectively (Figure 1; Tables S2 and S3 in the Supplementary). Additionally, we measured changes in the RNA expression in the brain region associated with schizophrenia, which resulted in the evaluation of 14,254 genes expressed in the corpus callosum (Figure 1).

For each of the 20 lipid classes detected with HPLC-MS, we calculated mean intensities for the SZ and HC groups and conducted the one-sample Student t-test of the differences between groups vs zero to evaluate the class-level differences characteristic of schizophrenia (Figure 2A). For two lipid classes, such as diacylglycerols (DG) and free fatty acids (FA), significant upregulation was detected in schizophrenia samples. In contrast, the majority of lipid classes (seven classes) demonstrated significantly lower levels in SZ samples compared to the HC. Among them are phosphatidylcholines (PC) and phosphatidylethanolamines (PE) — the major components of cell membranes; three classes previously shown to be components of the myelin sheath — sphingomyelins (SM), hexosylceramides (HexCer), and sulfohexosylceramides (SulfoHexCer); triacylglycerides (TG) used as lipid storage substrate; and phosphatidylglycerols (PG), which are synthesized in mitochondria (Figure 2A). The demonstrated differences in the level of lipid classes are in good agreement with previously reported lipidome alterations data in a corpus callosum associated with schizophrenia [7], with Pearson's R=0.74 (p=0.0142), calculated based on the same 10 lipid classes measured in two works (Figure 2B).

MALDI imaging yielded similar results with a statistically significant lower average peak intensity evaluated via one-sample Student t-test for the distribution of the differences between peaks averages between the two groups for all peaks (p=0.0013) (Figure 2C). Additionally, the coefficient of variance across all MALDI pixels calculated for each peak intensity differed significantly between the schizophrenia and control groups (Wilcoxon signed-rank test, p <4e-10, Figure 2D). For a subset of peaks matched with the HPLC-MS result, good agreement was demonstrated between the two mass spectrometric techniques with R=0.77 and p=0.0061

[2] National BioService, LLC.

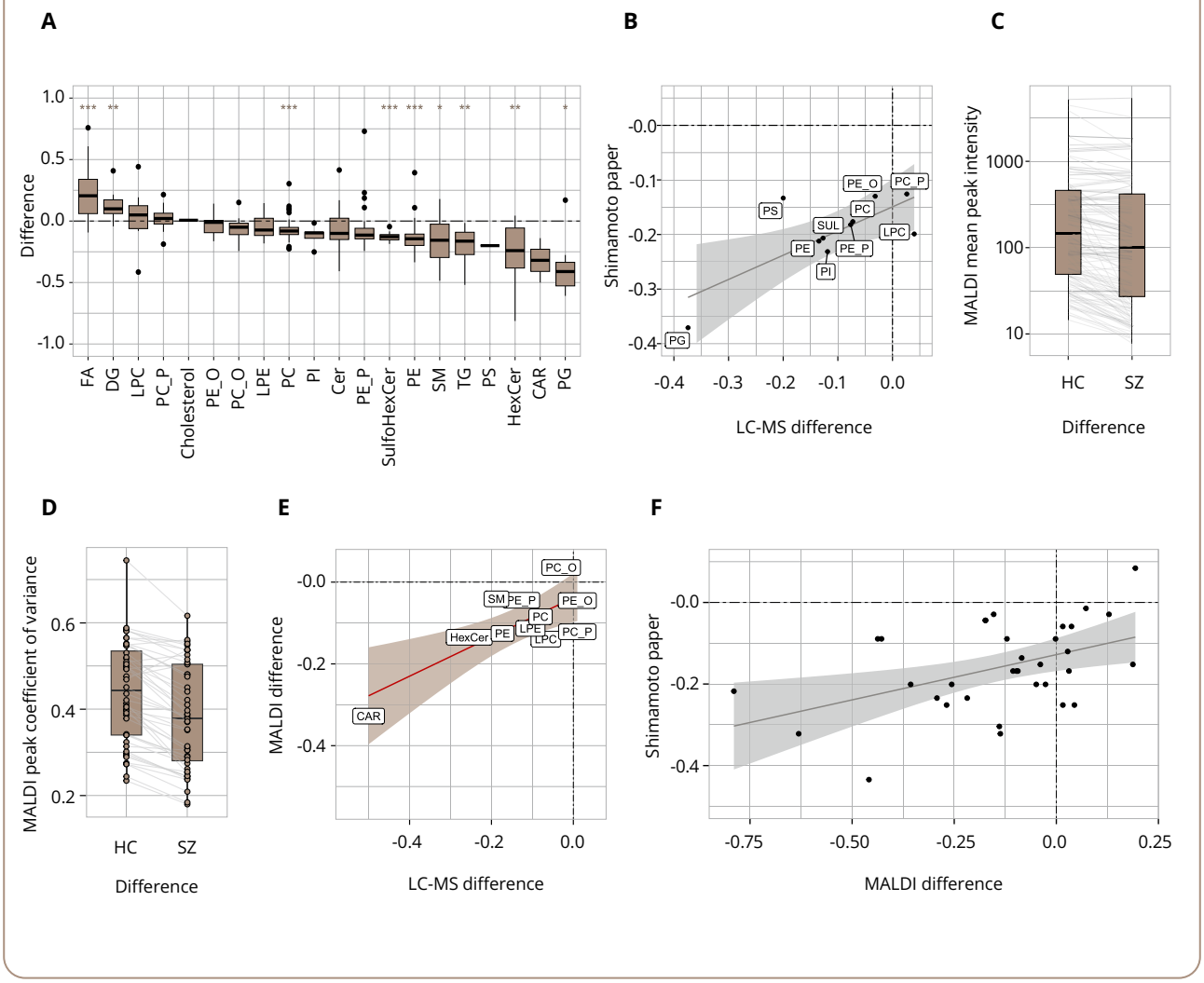


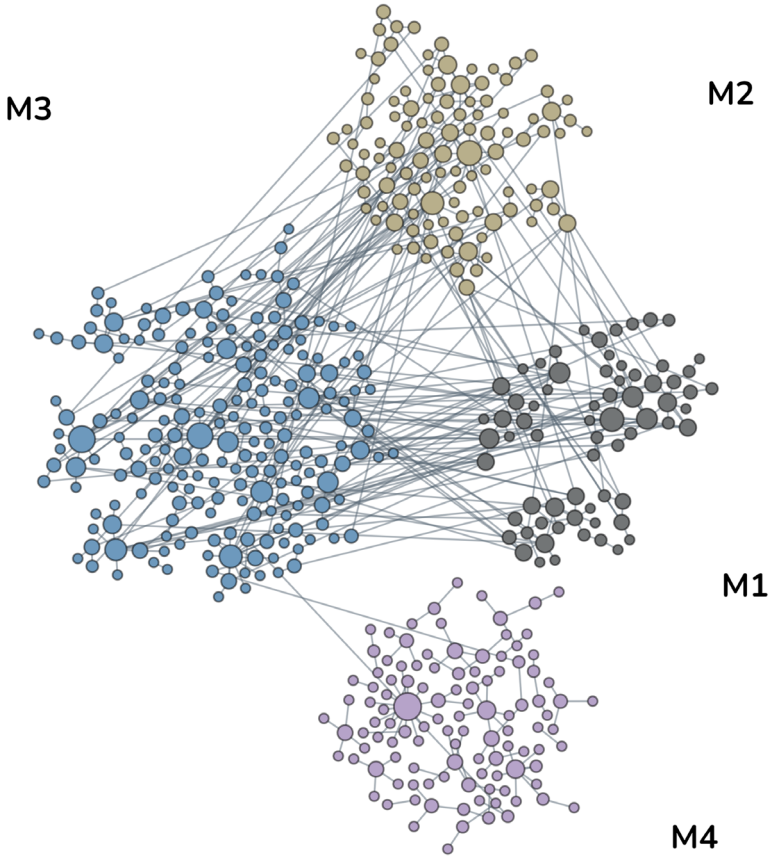
Figure 2. Schizophrenia-associated lipidome alterations in corpus callosum between the groups of patients with schizophrenia and the group of healthy controls.

Note: (A) Boxplots representing differences in lipid intensities between SZ patients and the HC for each lipid class, measured with HPLC-MS. Asterisks reflect the statistical significance of the difference evaluated via a one-sample Student t-test of the differences between groups vs zero for each class (*** — p <0.001; ** — p <0.01; * — p <0.05; p-values corrected for multiple hypothesis testing). Positive values represent higher levels in the schizophrenia group. (B) Correlation of average differences for each lipid class correlated to the published paper on the corpus callosum lipidome in schizophrenia by Shimamoto et al. [7]. The correlation is calculated based on the same 10 lipid classes measured in two works. (C) Boxplots of the peak intensity distribution for the MALDI imaging experiment. Each line connects the same peak in two sample groups. One-sample Student t-test was used to determine whether the distribution of the differences between peak averages between the two groups differed statistically significantly from zero (p=0.0013). (D) Boxplots of the coefficient of variance calculated for each MALDI peak within each group. Statistical significance of the differences between the coefficients of variance evaluated via the Wilcoxon signed-rank test (p <4e-10). Lines connect the same lipid intensity averaged within different groups. (E) Correlation of average differences for each lipid class between the two types of measurements (HPLC-MS and MALDI-MSI). (F) Correlation with [7] for the MALDI imaging experiment. Peaks-plotting was based on mass-matching, and one dot represents one matched peak.

Linear regression lines on the plots B, E, and F are drawn with CI=95% by shaded areas, demonstrating that all the represented correlations are statistically significant and positive. Full names for the lipid classes present in the Box 1 in the Supplementary. The box boundaries in the boxplots represent the 25% and 75% percentiles, the lines represent the spread, and statistical outliers are indicated by dots.

HC — healthy controls; HPLC-MC — high-performance liquid chromatography with mass spectrometry; MALDI-MSI — matrix-assisted laser desorption/ionization mass spectrometric imaging; SZ — schizophrenia patients.

Source: Osetrova et al., 2025.



Module	Top terms (Max 10)	Genes	Terms
M1	Cytoplasmic translation; translation; peptide biosynthetic process; amide biosynthetic process; peptide metabolic process; ribonucleoprotein complex biogenesis; ribosome biogenesis; regulation of translation; erythrocyte differentiation; regulation of cellular amide metabolic process.	69	54
M2	Negative regulation of extrinsic apoptotic signaling pathway via death domain receptors; regulation of extrinsic apoptotic signaling pathway via death domain receptors; regulation of extrinsic apoptotic signaling pathway; extrinsic apoptotic signaling pathway via death domain receptors; negative regulation of extrinsic apoptotic signaling pathway; histone acetylation; internal peptidyl-lysine acetylation; internal protein amino acid acetylation; peptidyl-lysine acetylation; spindle organization.	108	75
M3	Epithelial cell migration; tissue migration; epithelium migration; ameboidal-type cell migration; regulation of cell morphogenesis; regulation of cell shape; endothelial cell migration; cellular component morphogenesis; cell morphogenesis; regulation of epithelial cell migration.	203	120
M4	Fatty acid biosynthetic process; monocarboxylic acid biosynthetic process; chloride transmembrane transport; small molecule biosynthetic process; photoreceptor cell maintenance; chloride transport; response to fatty acid; inorganic anion transmembrane transport; unsaturated fatty acid biosynthetic process; retina homeostasis.	112	39

Figure 3. Modules of genes in the corpus callosum with differential expression between the group of patients with schizophrenia and the group of healthy controls.

Note: One dot represents one gene, colored according to module assignment, edges represent functional association between two genes, the size of the dots reflects the number of edges. The five most statistically significant functional terms for each module are presented in the Table S5 in the Supplementary.

Source: Osetrova et al., 2025.

(Figure 2E). If calculated without the most outstanding class, the carnitines, the correlation remained positive, but not statistically significant (R=0.29; p=0.42). Finally, MALDI peaks matched with Shimamoto et al. [7] demonstrated a statistically significant positive correlation between two datasets with R=0.46 and p=0.0066 (Figure 2F).

The analysis of 14,254 transcripts in specimens of the corpus callosum revealed 1,202 (8.4%) differentially expressed genes between the groups of patients with SZ and HC (Table S4 in the Supplementary). Twenty genes out of the 1,202 were excluded from the analysis due to the lack of information about them in the HumanBase. As a result, four functional modules were identified, which included 492 of the detected genes (Figure 3, Table S5 in the Supplementary). The main cellular functions of the M1 module are the following: cytoplasmic translation, translation, peptide biosynthetic process, amide biosynthetic process, and peptide metabolic process; module M2: negative regulation of extrinsic apoptotic signaling pathway via death domain receptors, regulation of extrinsic apoptotic signaling pathway via death domain receptors, regulation of extrinsic apoptotic signaling pathway, extrinsic apoptotic signaling pathway via death domain receptors, and negative regulation of the extrinsic apoptotic signaling pathway; module M3: epithelial cell migration, tissue migration, epithelium migration, ameboidal-type cell migration, and regulation of cell morphogenesis; module M4: fatty acid biosynthetic process, monocarboxylic acid biosynthetic process, chloride transmembrane transport, small molecule biosynthetic process, and photoreceptor cell maintenance.

DISCUSSION

Key results

The analysis of the alterations in the lipid composition of the corpus callosum of the brain of patients with schizophrenia using two mass spectrometric methods demonstrated a trend towards overall lower lipid levels for the most observed classes and consistency between techniques and studies. Among lipid classes with the most noticeable discrepancies are the ones previously associated with myelin sheath formation. Analysis of spatial-dispersion-of-lipids-across-the-corpus-callosum slides revealed a more homogeneous distribution for samples taken from schizophrenia patients. Functional gene analysis also identified a module associated with lipid metabolism.

Limitations

One of the major limitations of our study is the limited sample size, especially taking into account the high heterogeneity of the disease. Moreover, our study design did not exclude the potential influence of confounding variables, such as the use of antipsychotic medication, on the lipid composition of the white matter tracts of the brain. However, despite this, we observed a statistically significant correlation between two independent mass spectrometry experiments on different subsamples, as well as a correlation with previously published data obtained from a larger sample of individuals. Moreover, even with the possible "noise" of individual lipid measurements and annotation, the results at the lipid class level are consistent and reproducible. Another limitation of the article concerns the statistical analysis. Using unpaired comparison methods for the difference in the mean lipid levels and their CoV between groups, statistically significant differences were not observed (p >0.05 for the two-sample Student's t-test and the Mann-Whitney test, respectively). On the one hand, this may be due to the small effect size. On the other hand, the reason might be the fact that different lipids have a large spread of characteristic values due to methodological limitations, which makes the variance within sample groups comparable to the total variance for both groups.

Interpretation

Although previous studies had detected a few [7] or no [22] statistically significant differences between schizophrenia patients and control groups, we demonstrated class-level consistency in the direction of the differences, both for different techniques and in comparison of our results to previously published data on the subset of classes in intersection. Free fatty acids showed the greatest difference towards the higher level, which is also consistent in the direction of differences with the results of previous work from our group [23] and may be a general marker of lipid metabolism disorders characteristic of schizophrenia. Importantly, corpus callosum was the region with the most significant differences, as compared to the other five regions of white matter investigated, although differences at the level of individual classes could diverge, which may be a limitation in the use of a relatively small sample in our study. The decline in the level of lipids associated with myelin sheath formation, such as sulfohexosylceramides sphingomyelins, and hexosylceramides, aligns our results with previously shown disturbances in the myelin structure

detected in schizophrenia using various MRI techniques [24–27]. The decrease in the levels of phosphatidylglycerols might reflect mitochondrial dysfunction, which has also been linked to schizophrenia [23]. Interestingly, elevated levels of triacylglycerides have been designated as biomarkers of schizophrenia with elevated levels in the blood [28, 29]. Differences in the distribution of lipids across the corpus callosum sections assessed via the coefficient of variance for each peak demonstrated a more even intensity distribution for the schizophrenia samples, suggesting a less structured organization of lipids [30]. Such results might be a reflection of disturbances in cellular organization, such as less dense myelin packing and less compartmentalization [31].

The functional gene analysis results align well with recent studies on the disruption of ribosome action in schizophrenia [32, 33], the role of the extrinsic apoptotic pathway in the mechanisms of neuroprotection, the homeostasis of inflammatory reactions and neurodegeneration [34], the influence of alterations in histone acetylation on neuronal migration in schizophrenia [35], the direct connection between the expression of the factors that direct axon growth and the development of interhemispheric commissures [36], the regulation of the balance of excitation/inhibition in the brain by transmembrane transport of chlorides in schizophrenia [37, 38], and the key role of polyunsaturated fatty acids in the inflammatory response of different types of brain cells and dysfunction in neurotransmitter systems [39–42]. In the scope of the current paper, the latter is of special interest as further investigation of genes associated with M4 might help gain a deeper understanding of the discovered lipidome differences in the corpus callosum associated with schizophrenia.

CONCLUSION

We suggest that investigation of the molecular alterations in the composition of the white matter in schizophrenia and the combination of various measuring techniques might help us achieve a deeper understanding of the disease. The application of mass spectrometric neuroimaging methods to the analysis of the white matter composition showed to be a promising technique, with further potential to help peer deeper into the spatial nuances of lipidome alterations.

Article history

Submitted: 13 Dec 2023
Accepted: 27 Feb 2025
Published Online: 17 Mar 2025

Authors' contribution: Conceptualization — Maria Osetrova and Philipp Khaitovich; methodology — Olga Efimova, Gleb Vladimirov and Elena Stekolschikova; software — Maria Osetrova; validation — Maria Osetrova; formal analysis — Maria Osetrova; investigation — Maria Osetrova, Dmitry Senko; resources — Olga Efimova, Tatiana Zhuravleva, Gleb Vladimirov, George Kostyuk and Evgeniy Nikolaev; data curation — Maria Osetrova and Elena Stekolschikova; writing original draft preparation — Maria Osetrova and Marina Zavolskova; writing review and editing — Denis Andreyuk, Yana Zorkina, Anna Morozova and Philipp Khaitovich; visualization — Maria Osetrova; supervision — Philipp Khaitovich; project administration — Philipp Khaitovich. All authors checked and approved final version of the manuscript prior to publication.

Funding: The work of Maria Osetrova was funded by the Russian Science Foundation under grant No. 20-15-00299. The work of Dmitry Senko, Marina Zavolskova, and Olga Efimova was funded by the Russian Science Foundation under grant No. 22-15-00474.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data

Supplementary material to this article can be found in the online version:
Box 1: https://doi.org/10.17816/CP15491-145517
Table S1: https://doi.org/10.17816/CP15491-145515
Table S2: https://doi.org/10.17816/CP15491-145518
Table S3: https://doi.org/10.17816/CP15491-145519
Table S4: https://doi.org/10.17816/CP15491-145520
Table S5: https://doi.org/10.17816/CP15491-145516

For citation:

Osetrova MS, Efimova OI, Zavolskova MD, Stekolschikova EA, Vladimirov GN, Senko DA, Zhuravleva TA, Morozova AYu, Zorkina YA, Andreyuk DS, Kostyuk GP, Nikolaev EN, Khaitovich PhE. Comparative Analysis of Corpus Callosum Lipidome and Transcriptome in Schizophrenia and Healthy Brain. *Consortium PSYCHIATRICUM.* 2025;6(1):CP15491 doi: 10.17816/CP15491

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Psychometric Properties and Factor Structure Analysis of the Inventory of Statements about Self-injury (ISAS) in a Russian Non-clinical Sample

Психометрические свойства и анализ факторной структуры опросника утверждений о самоповреждениях (ISAS) на российской неклинической выборке

doi: 10.17816/CP15537

Original research

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ABSTRACT

BACKGROUND: The "Inventory of Statements About Self-Injury" (ISAS) is one of the most widely used and reliable psychometric tools for assessing non-suicidal self-injury (NSSI) and its motivations. The Russian adaptation of the ISAS, involving patients with nonpsychotic psychiatric disorders, demonstrated high internal consistency and a two-factor structure similar to the original. However, the reliability and suitability of ISAS in a non-clinical population remain unclear.

AIM: To adapt the ISAS in Russian, evaluate its psychometric properties, and analyze its factor structure in a sample of Russian university students.

METHODS: The psychometric properties and factor structure of the adapted ISAS version were evaluated through an anonymous online survey of Russian university students. Respondents had reported lifetime NSSI and scored above 4 on the ISAS-Functions subscale. Exploratory and confirmatory factor analysis (EFA/CFA) were performed on two randomly formed subgroups to evaluate the factor structure of ISAS. Additionally, the associations between the identified ISAS factors and the presence of suicidal thoughts and attempts over a lifetime and in the week before their participation in the study, as well as seeking psychiatric and/or psychotherapeutic care over a lifetime, were analyzed.

RESULTS: The survey included 3,919 participants, of whom 1,149 (29.3%; 88.0% female) reported NSSI, with a median age of 20 (18; 22) years. The Russian ISAS demonstrated high internal consistency (Cronbach's alpha = 0.851). EFA

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results supported the original two-factor structure. CFA results suggested an alternative three-factor structure of the ISAS, including “Signal”, “Regulation”, and “Influence” factors. Suicidal attempts were associated with the factors “Regulation” and “Influence”, suicidal thoughts with “Regulation” and female gender, and the seeking of psychiatric and/or psychotherapeutic care with “Regulation” and age.

CONCLUSION: The adapted ISAS in Russian is a reliable tool with high internal consistency. The study proposed a three-factor structure, indicating a greater heterogeneity of the NSSI phenomenon compared to earlier understandings. The study demonstrated the association between two of the three identified factors with suicidal behavior and thoughts, and the seeking of psychiatric care.

АННОТАЦИЯ

ВВЕДЕНИЕ: Одним из наиболее широко используемых и надежных психометрических инструментов для оценки несуицидального самоповреждающего поведения (НССП) и его мотивов является «Опросник утверждений о самоповреждениях» (Inventory of Statements About Self-Injury, ISAS). Опросник адаптирован на русский язык с участием пациентов с непсихотическими психическими расстройствами. Он продемонстрировал высокую внутреннюю согласованность и двухфакторную структуру, аналогичную оригиналу. Однако надежность и валидность ISAS в неклинической выборке остаются неизученными.

ЦЕЛЬ: Провести независимую русскоязычную адаптацию ISAS, оценку его психометрических свойств и факторной структуры на выборке студентов российских вузов.

МЕТОДЫ: Психометрические свойства и факторную структуру адаптированного ISAS изучили с помощью анонимного онлайн-опроса студентов российских вузов, сообщивших о НССП в течение жизни и набравших более 4 баллов по подшкале ISAS-Functions. Факторную структуру ISAS исследовали с помощью эксплораторного и конфирматорного факторного анализа в двух подгруппах, сформированных случайным образом. Дополнительно проанализировали ассоциации выделенных факторов ISAS с наличием суицидальных мыслей и попыток в течение жизни и за неделю до участия в исследовании, а также с обращением за психиатрической и/или психотерапевтической помощью в течение жизни.

РЕЗУЛЬТАТЫ: В опросе приняли участие 3919 человек. Из них 1149 респондентов (29,3%; 88,0% женщины) сообщили о НССП. Медианный возраст составил 20 (18; 22) лет. Русскоязычная версия ISAS показала высокую внутреннюю согласованность (альфа Кронбаха = 0,851). Данные эксплораторного факторного анализа подтвердили соответствие двухфакторной структуры русскоязычной версии ISAS оригинальной версии. По результатам конфирматорного факторного анализа предложена альтернативная трехфакторная структура ISAS с выделением факторов «Сигнал», «Регуляция» и «Влияние». С суицидальными попытками были ассоциированы факторы «Регуляция» и «Влияние», с суицидальными мыслями — фактор «Регуляция» и женский пол, с обращением за психиатрической и/или психотерапевтической помощью — фактор «Регуляция» и возраст.

ЗАКЛЮЧЕНИЕ: Русскоязычная версия ISAS характеризуется высокой внутренней согласованностью и валидностью. Обоснована трехфакторная структура опросника, указывающая на большую гетерогенность феномена НССП, чем предполагалось ранее. Показана ассоциация двух из трех выделенных факторов с суицидальными мыслями и поведением и обращением за психиатрической помощью.

Keywords: *non-suicidal self-injury; self-harm; questionnaire; ISAS; adaptation; factor analysis*
Ключевые слова: *несуицидальное самоповреждающее поведение; селфхарм; опросник; ISAS; адаптация; факторный анализ*

INTRODUCTION

Non-suicidal self-injury (NSSI) is intentional destruction of one's own body tissue without suicidal intent and for purposes not socially sanctioned [1]. According to a meta-analysis of epidemiological studies published between 1966 and 2012, 17.2% of adolescents, 13.4% of young adults (aged 18–24), and 5.5% of individuals aged ≥25 years have self-injured at least once in their life [2]. More recent data obtained in epidemiological studies during the COVID-19 pandemic (2019–2022) showed that the prevalence of self-harm stood at 22.9% in adolescents and 11.7% in other age groups [3]. NSSI is also known to be associated with a high risk of suicidal attempts [4–6].

NSSI is a heterogeneous clinical phenomenon. It is known that NSSI can vary significantly across different patients in terms of frequency, intensity, types, age of onset, and as well as in the range of subjective psychological motivations (reasons and goals, as defined by the patient) for self-injury [7].

To date, more than two dozen psychometric tools have been proposed for the quantitative assessment of various characteristics of NSSI, including psychological motivations for self-injury [8]. One of the widely used and reliable psychometric tools for the quantitative assessment of psychological motivations for NSSI is the Inventory of Statements About Self-Injury (ISAS) [8] developed by Klonsky et al. and freely available for use and adaptation [9]. Until recently, none of the existing psychometric tools for the quantitative assessment of NSSI was validated in the Russian language. However, in 2023, the ISAS was adapted in Russian by Zinchuk et al. on a sample of 614 patients with non-psychotic mental disorders [10]. The adapted inventory demonstrated high internal consistency and a two-factor structure similar to that of the original questionnaire [10]. Yet the factor structure of the Russian-language version of the questionnaire was not validated by the results of a confirmatory factor analysis (CFA) and the psychometric properties of the tool were not evaluated on a clinical sample.

The aim of this study is to conduct an independent evaluation of the psychometric properties of the Russian-language adaptation of the ISAS and conduct a factor structure analysis on a sample of Russian university students.

METHODS

Structure of the ISAS

The ISAS is a self-reporting tool consisting of two sections (see Appendix 1 in the Supplementary) [9].

The first section of the ISAS, the ISAS-Behavior (ISAS-B), is designed to capture non-suicidal self-harm behavior. In that first part, respondents are asked to indicate whether they have ever engaged in such actions over the course of their life and, if so, how many times. Respondents who report at least one instance of self-harm are asked to indicate the types of self-harm, the age at which the first incident occurred, their attitude towards pain, the social context, the time elapsed between the urge to self-harm and acting on it, as well as their desire to stop self-injuring. Responses to the ISAS-B section are analyzed as is, without summation or scoring, which means they are not subjected to a psychometric analysis.

The second section of the ISAS questionnaire, the ISAS-Functions (ISAS-F), is designed to allow respondents to describe their perceptions of self-injury. This section contains 39 statements about the reasons behind and purposes of self-harm, each must be assessed according to three categories with corresponding scores from 0 to 2 (0 — does not apply to me; 1 — partially applies to me; 2 — fully applies to me). According to the original methodology [9], the answers to these questions were combined into 13 groups of motivations ("functions") for self-injurious actions: 1) "Affect regulation" (items 1, 14, 27); 2) "Self-punishment" (items 3, 16, 29); 3) "Anti-dissociation/feeling generation" (items 5, 18, 31); 4) "Marking distress" (items 11, 24, 37); 5) "Anti-suicide" (items 6, 19, 32); 6) "Self-care" (items 4, 17, 30); 7) "Interpersonal boundaries" (items 2, 15, 28); 8) "Sensation-seeking" (items 7, 20, 33); 9) "Peer-bonding" (items 8, 21, 34); 10) "Interpersonal influence" (items 9, 22, 35); 11) "Toughness" (items 10, 23, 36); 12) "Revenge" (items 12, 25, 38); 13) "Autonomy" (items 13, 26, 39). These groups of motivations are considered under two subscales: "intrapersonal" (groups 1–5) and "interpersonal" motivations (groups 6–13). The item scores are summed up for each of the 13 groups of motivations, as well as for the two subscales of "intrapersonal" and "interpersonal" motivations.

Adaptation of the ISAS

The ISAS was translated into Russian by mental health professionals who are proficient in English. The draft translation was then reviewed by four psychiatrists and unanimously submitted for further testing to a focus group. The latter consisted of 28 patients from the V.M. Bekhterev National Medical Research Center for Psychiatry and Neurology, Saint Petersburg (25 women, median age — 23 [21; 25] years). The focus group also included five

mentally healthy participants, clinical residents of the same research center, among whom four were women with a median age of 25 (24.5; 25.5) years. The draft version of the inventory was tested in person with the researcher present. After completion of the questionnaire by the focus group participants, unstructured interviews were conducted to identify difficult-to-understand questions and wording. Based on the results of the survey and interviews, the Russian-language version of the inventory was fine-tuned (see Table S1 in the Supplementary). The final version of the inventory was achieved through consensus by the above-mentioned psychiatrists and is presented in Appendix 1 in the Supplementary.

Study design

To assess the psychometric properties and factor structure of the adapted version of the ISAS questionnaire, a cross-sectional online survey was conducted among students from Russian universities across all eight federal districts of the Russian Federation.

Eligibility criteria

The inclusion criteria for the study were as follows: age ≥18 years, a report of having a history of lifetime NSSI, and a total score on the ISAS-F >4 (the value of the first quartile for the range of scores on this scale). The last criterion was used to bolster the specificity of the test (to reduce the number of participants without a history of NSSI who incorrectly reported self-injury-related behavior because of uninformed response bias [11, 12]), which refers to errors in responses that stem from a lack of understanding or information. The threshold value (>4) was chosen arbitrarily to achieve a balance between high test specificity and maintaining a large sample size. Non-inclusion or exclusion criteria were not envisaged.

Conducting the survey

In January 2023, invitations to participate in a survey, including a link to the questionnaire, were sent to 70 partner universities of the not-for-profit organization "Union for Mental Health"[1]. The invitations were sent via email to the contact persons in the administrations of the partner universities. Survey period: from January 13, 2023 (date of questionnaire completion by the first participant) to February 13, 2023, inclusive. Methods for ensuring the uniqueness of survey participants, due to the confidential nature of the survey, were not planned.

The survey was conducted online using Google Forms[2] (Google LLC, USA). In addition to the adapted ISAS version (see Appendix 1 in the Supplementary), the questionnaire included questions about each respondent's sociodemographic characteristics (gender, age, marital status, place of residence), lifetime and weekly suicidal thoughts, lifetime suicide attempts, and if they had ever sought psychiatric or psychotherapeutic care at any point in their life. All the questions were mandatory. In case one missed questions, the survey was considered incomplete and the data not saved for further analysis. The approximate time for completing the questionnaire was 10–15 min.

Statistical analysis

The required sample size was not calculated in the study.

The data analysis included Exploratory Factor Analysis (EFA) and Confirmatory Factor Analysis (CFA). EFA was performed using the IBM SPSS Statistics software package, version 23.0 (IBM Corp., USA), while CFA was conducted using the IBM SPSS Amos software package, version 23.0 (IBM Corp., USA), utilizing the following plugins: Pattern Matrix Model Builder, Master Validity, and Model Fit Measures.

The analysis of the distribution of quantitative variables was performed using the Shapiro-Wilk test. In all cases, the hypothesis of a normal distribution was rejected (p <0.05). Consequently, the quantitative variables were described using the values of the median and the first and third quartiles (Q1; Q3).

To assess the internal consistency of the questionnaire, Cronbach's alpha was calculated and values ≥0.64 were considered acceptable [13]. The internal consistency was also evaluated using mean corrected item-total Spearman correlation. Corrected item-total correlation was defined as the correlation of the item score and total ISAS-F score minus the score for the item. The consistency was considered acceptable if the mean correlation coefficient was ≥0.30 [14].

The factor analysis was conducted only for the questions of the ISAS-F, the second section of the questionnaire. To assess the feasibility of conducting a factor analysis on the obtained sample, the Kaiser-Meyer-Olkin test for sampling adequacy and Bartlett's test of sphericity were

[1] Full list available from: https://mental-health-russia.ru/partnery/

[2] Available from: https://www.google.com/forms

used. The sample was considered adequate when the Kaiser-Meyer-Olkin test result was >0.6 and Bartlett's test of sphericity result was statistically significant (p <0.05) [15]. To conduct the EFA and the CFA, the sample was randomly divided into two equal parts using the "Random Sample" tool in the IBM SPSS Statistics software. The comparability of the subgroups was analyzed using the Mann-Whitney test (U-test) (for quantitative variables), Pearson's chi-squared test (for categorical variables with ≥3 categories), and Fisher's exact test (for binary categorical variables).

The EFA was conducted by the promax rotation method (k=4) with Kaiser normalization. At the first stage of the EFA, the number of factors was limited to 2 in order to test the fit to the factor structure proposed by the authors of the original questionnaire [10]. At the second stage, the number of evaluated factors was not limited. The scree plot method was used to determine the number of factors, and the model included factors having an eigenvalue >1, with at least 50% total variance explained [16]. Variables with a factor loading >0.3 on at least one factor were not excluded from the factor structure analysis [17]. Variables were distributed to factors based on the highest factor loading. The CFA was conducted to examine the one-factor and two-factor (original) structure of the questionnaire, as well as the factor structure identified by us at the second stage of the EFA. The quality of the factor model was considered acceptable if at least one of the following conditions was met: Root Mean Square Error of Approximation (RMSEA) <0.1 [18], Comparative Fit Index (CFI), or Tucker-Lewis Index (TLI) ≥0.9 [19].

To analyze the associations between the total scores on the identified factors (the sum of scores for all questions that comprise each factor) and the binary characteristics (dependent variables) of "lifetime suicidal thoughts", "lifetime suicide attempts", and "lifetime history of seeking psychiatric and/or psychotherapeutic help", binary logistic regression was employed while controlling for the variables of "sex", "age", "duration of NSSI", and "severity of NSSI". Results were considered statistically significant at p <0.05.

Ethical expert evaluation

The study was approved by the Ethics Committee of the Mental Health Research Center, Moscow (minutes No. 914 dated November 21, 2022). All potential study participants gave their informed consent to participate by clicking the "Agree" button under the following statement: "I confirm that I am 18 years old or older and give my consent to the use of my answers to these questions in an anonymous format for research purposes". The survey was anonymous. At the same time, respondents were asked to provide their email addresses to be informed about the recruitment of participants for future research. Completing this item was not mandatory.

RESULTS

Participants

A total of 3,919 individuals participated in the survey (neither the total number of students studying at the time when the invitation was sent, nor the number of students informed about the survey was known exactly). Of these, 1,673 (42.7%) reported lifetime NSSI. A total score of more than 4 points on the ISAS-F was recorded in 1,149 respondents (68.7% of those who reported NSSI).

Sample characteristics

The median age of respondents with NSSI and ISAS-F >4 points was 20 (18; 22) years. Most respondents were female, more than a quarter combined studying with work, and about half had a partner (in most cases, the relationships were not officially registered), see Table 1. Three-quarters of the respondents reported having had thoughts of not wanting to live or of committing suicide. About one-third of participants reported having had such thoughts during the week preceding their inclusion in the study. Almost a fourth of participants reported lifetime suicidal attempts. However, only about 30% of participants reported having ever sought assistance from a psychiatrist and/or psychotherapist (Table 1).

Characteristics of non-suicidal self-harm

The most common type of self-harm encountered was self-cutting (23.7%; n=272). Less common types included interfering with wound healing (14.3%; n=164), hitting one's head or other parts of the body (14.0%; n=161), biting (13.1%; n=151), severe scratching (12.3%; n=141), and even less frequent were pinching (7.0%; n=80), other ways of self-harm (7.0%; n=80), pulling hair (4.5%; n=52), burning (1.4%; n=16). Extremely rare types of self-harm were rubbing the skin against a rough surface (0.9%; n=10) and swallowing dangerous substances (0.9%; n=10), carving (0.7%; n=8), sticking needles in oneself (0.3%; n=4).

The vast majority of respondents (96.2%; n=1,105) reported several (≥2) types of self-harm methods; the median number of self-harm types was 5 (4; 7).

Table 1. Characteristics of the study sample (*n*=11,149)

Parameter	Value, abs. (%)
Sex (female)	1,011 (88.0)
Employment (combining study with work)	306 (26.6)
Marital status: • Single • Have a partner • Married • Divorced	 575 (50.0) 528 (46.0) 43 (3.7) 3 (0.3)
Federal district: • Central • Volga • Northwestern • Southern • North Caucasus • Siberian • Far Eastern • Ural	 101 (8.8) 265 (23.0) 142 (12.4) 63 (5.5) 160 (13.9) 170 (14.8) 246 (21.4) 2 (0.2)
Suicidal thoughts throughout lifetime: • No, never • Previous thoughts of not wanting to live • Previous thoughts about committing suicide without any specific ideas about the ways or specific plans • Previous thoughts of a specific way to commit suicide without a specific plan • Previous thoughts about a specific plan to commit suicide	 266 (23.1) 381 (33.2) 138 (12.0) 191 (16.6) 173 (15.1)
Suicidal thoughts over the past week: • No • Current thoughts of not wanting to live • Current thoughts about committing suicide without any specific ideas about the ways or specific plans • Current thoughts of a specific way to commit suicide without a specific plan • Current thoughts about a specific plan to commit suicide	 800 (69.6) 249 (21.7) 52 (4.5) 30 (2.6) 18 (1.6)
Lifetime suicide attempts	270 (23.5)
History of seeking assistance from a psychiatrist or a psychotherapist	338 (29.4)

The majority of participants reported first engaging in self-injury during their adolescence: the median age of the first NSSI episode was 14 (12; 15) years, and the duration of NSSI (the period between the first and last episode of self-injury) was 5 (2; 8) years. Some 117 (9; 875) days separated the last case of self-harm and the inclusion in the survey. The median severity of NSSI (the number of self-injury episodes per month during the period between the first and last NSSI episode) was 2 (1; 7) episodes per month.

About half of the respondents reported having always experienced pain during attempts to self-harm (47.7%; *n*=548), 38.9% (*n*=447) of respondents reported experiencing pain sometimes, and 13.4% (*n*=154) reported not experiencing pain at all. More than two-thirds of the respondents (68.3%; *n*=785) reported being always alone when engaging in self-harm activity; 26.9% (*n*=309) reported having sometimes been alone, and 4.8% (*n*=55) reported never being alone. More than half of the respondents (57.4%; *n*=659) reported less than one hour passing between the urge to self-harm and its concretization, while this gap was larger in 7.7% (*n*=89) — 1 to 3 hours, 3.0% (*n*=35) — 3 to 6 hours, 2.1% (*n*=24) — 6 to 12 hours, 2.7% (*n*=31) — 12 to 24 hours, and was over 24 hours in 27.1% of study participants (*n*=311). Most respondents (79.7%; *n*=916) reported experiencing a desire to stop self-injuring.

The most potent motivations for self-injury according to the ISAS-F subscale were: "Affect regulation" — 4 (3; 5) points, "Self-punishment" — 3 (1; 5) points, and "Marking distress" — 2 (0; 3) points. The Cronbach's alpha value for the entire ISAS-F scale was 0.851. The mean corrected item-total Spearman correlation coefficient was 0.36.

ISAS factor structure

To perform the factor analysis, the sample was randomly divided into two groups: one for the EFA (*n*=605; 52.7%) and the other one for the CFA (*n*=544; 47.3%). No statistically significant differences were found between the groups on any of the study variables (sex, age, marital status,

Table 2. The results of the exploratory factor analysis (*n*=605), two-factor model structure

Variable	Factor loading	
	Factor 1 Interpersonal motivations	**Factor 2 Interpersonal motivations**
Autonomy	**0.757**	-0.129
Peer-bonding	**0.701**	-0.289
Revenge	**0.496**	0.029
Toughness	**0.494**	0.168
Interpersonal influence	**0.477**	0.248
Interpersonal boundaries	**0.473**	0.069
Sensation-seeking	**0.449**	0.100
Self-care	**0.347**	0.065
Marking distress	0.126	**0.704**
Self-punishment	-0.077	**0.576**
Affect regulation	-0.165	**0.541**
Anti-suicide	0.147	**0.413**
Anti-dissociation/feeling generation	0.117	**0.384**

Note: Bold font indicates the highest factor loadings for each variable.

Table 3. The results of the exploratory factor analysis (*n*=605), three-factor model structure

Variable	Factor loading		
	Factor 1 "Signal"	**Factor 2 "Regulation"**	**Factor 3 "Influence"**
Autonomy	**0.747**	0.113	0.454
Peer-bonding	**0.654**	-0.035	0.377
Toughness	**0.578**	0.330	0.349
Interpersonal boundaries	**0.479**	0.215	0.365
Self-care	**0.442**	0.224	0.174
Sensation-seeking	**0.434**	0.214	0.263
Marking distress	0.340	**0.720**	0.515
Self-punishment	0.097	**0.544**	0.161
Affect regulation	0.032	**0.503**	0.118
Anti-dissociation/feeling generation	0.337	**0.491**	0.086
Anti-suicide	0.313	**0.449**	0.213
Interpersonal influence	0.481	0.360	**0.811**
Revenge	0.384	0.158	**0.667**

Note: Bold font indicates the highest factor loadings for each variable.

employment status, region of residence, history of suicidal thoughts and attempts, history of psychiatric and psychotherapeutic care, age of NSSI onset, duration and severity of NSSI, type of self-injury, and scores on the ISAS-F subscales).

Exploratory factor analysis

The value of the Kaiser–Meyer–Olkin test for sampling adequacy was >0.6 (0.837), and the significant Bartlett's test of sphericity (p <0.001) indicated that the conditions for a factor analysis of the questionnaire were met. The EFA included 13 variables — the groups of psychological motivations for NSSI from the ISAS-F. When limiting the number of factors to two (according to the original data [9]), the resulting factor structure explained 41.5% of the total variance (Table 2). During the second stage of the EFA, an alternative 3-factor structure of the questionnaire was assumed based on the eigenvalues, which explained 51.2% of the total variance of the model (Table 3). Factor 1 included motivations related to self-harm as a way of "informing" others about an altered internal state (the "Signal" factor). All variables that the authors of the questionnaire attributed to intrapersonal motives [9] had high loadings on factor 2 ("Regulation").

Factor 3 ("Influence") comprised two motivations: "Interpersonal influence" and "Revenge". The internal consistency (Cronbach's alpha) for the "Signal" factor was 0.693; for the "Regulation" factor, it was 0.665; and for the "Influence" factor, it was 0.681.

Confirmatory factor analysis

During the CFA, the one-factor, two-factor (original), and three-factor structures of the questionnaire, identified as a result of the EFA, were investigated. The three-factor structure of the ISAS-F (RMSEA <0.1) was found to be the best model. The values of the CFI and TLI did not exceed 0.9 in any case; however, they were closest to this threshold value in the three-factor model (Table 4).

Association between the perception of self-harm and suicidal thoughts and behavior

According to the binary logistic regression analysis, lifetime suicidal thoughts were associated with the female sex and a higher total score on the questions that make up

Table 4. Results of the confirmatory factor analysis (*n*=544)

Model quality parameters	Factor structure		
	One-factor	Two-factor	Three-factor
RMSEA	0.132	0.106	0.094
CFI	0.632	0.765	0.822
TLI	0.558	0.558	0.713

Note: CFI — Comparative Fit Index; RMSEA — Root Mean Square Error of Approximation; TLI — Tucker-Lewis Index.

Table 5. Predictors of suicidal thoughts, behavior, and solicitation of psychiatric and/or psychotherapeutic care: results of the binary logistic regression

Parameters	Dependent variables (Exp(B), 95% CI)		
	Lifetime suicide thoughts	Lifetime suicide attempts	Seeking medical assistance*
"Signal" factor (+1 point)	0.992 (0.931–1.058)	0.950 (0.901–1.002)	0.962 (0.915–1.012)
"Regulation" factor (+1 point)	**1.147 (1.106–1.189)**	**1.143 (1.108–1.178)**	**1.094 (1.064–1.125)**
"Influence" factor (+1 point)	1.150 (0.995–1.328)	**1.174 (1.060–1.301)**	1.074 (0.973–1.185)
Female (0/1)	**1.888 (1.193–2.990)**	1.369 (0.764–2.456)	1.297 (0.776–2.169)
Age (+1 year)	1.058 (0.979–1.144)	1.028 (0.953–1.109)	**1.206 (1.126–1.293)**
Duration of NSSI (+1 year)	0.980 (0.942–1.019)	0.998 (0.958–1.039)	0.977 (0.941–1.013)
Severity of NSSI (+1 episode/month)	1.001 (0.995–1.007)	**1.005 (1.000–1.011)**	1.000 (0.997–1.004)
R2	0.162	0.176	0.119

Note: The statistically significant associations are highlighted in bold. CI — confidence interval; NSSI — non-suicidal self-harm; R2 — Nagelkerke R squared value. *Psychiatric or psychotherapeutic care.

the "Regulation" factor. Lifetime suicidal attempts were associated with higher total scores on the questions that make up the factors of "Regulation" and "Influence", as well as a higher severity of NSSI. A history of psychiatric and psychotherapeutic care throughout lifetime was associated with older age and a higher total score on the questions that make up the "Regulation" factor.

DISCUSSION

Interpretation of the study results

Two-factor structure of the ISAS-F

We conducted the first study on the reliability of the Russian-language version of the ISAS on a large non-clinical sample, as well as the first CFA of the Russian-language version of the questionnaire. The psychometric analysis demonstrated good internal consistency of the Russian-language version of the ISAS-F. Moreover, the EFA showed that when the number of factors is limited to two, the factor structure (the distribution of observed variables across factors) of the adapted ISAS-F version is fully identical to that of the original version of the inventory [10].

It is noteworthy that the obtained values of factor loading for the "self-care" motivation (by the "interpersonal motivations") and "anti-dissociation/feeling generation" motivation (by the "interpersonal motivations") were relatively low, at 0.347 and 0.384, respectively (0.41 and 0.50 in the original inventory [9]). The authors of the original version of the ISAS do not offer hypotheses regarding the high factor loading of the motivation "self-care" on the "interpersonal motivations".

The same factor structure was obtained in studies on the adaptation and validation of ISAS conducted in South Korea [20], Turkey [21], and Pakistan [22]. It is safe to assume that switching to caring for the wound resulting from self-harm can also be considered a kind of "signaling" behavior. However, in a number of other validation studies conducted, in particular, in Australia [23], Norway [24], and Russia [10], this motivation had a higher factor loading on the "intrapersonal motivations".

It is noteworthy that in a study conducted by Zinchuk et al., the EFA of certain questions revealed that two questions (No. 4 and 30) describing the motivation of

"self-care" had higher factor loadings on the interpersonal motivations (0.4 and 0.35, respectively), while the third question (No. 17) from this group had a higher factor loading on the "interpersonal motivations" (0.44) [10]. This apparent "divergence" in the questions grouped under "self-care" likely explains the differences in validation study results for this variable [20–24]. Furthermore, "marking distress" motivation in our study had a higher loading on the "intrapersonal motivations", similar to the findings of the studies of original [9] and adapted versions [23, 24]; however, in the study by Zinchuk et al. [10], this motivation had a higher loading on the "interpersonal motivations".

Three-factor structure of the ISAS-F

The EFA without limitations on the number of evaluated factors revealed the three-factor structure of the questionnaire. The CFA demonstrated the greater quality of this model compared to the one-factor and original two-factor structures. The groups of motives (factors) were identified as "Signals" (NSSI as a way to "inform" others about one's own state), "Regulation" (NSSI as a way to regulate and correct one's own mental state), and "Influence" (NSSI as a way to influence the behavior of others). The factors we identified logically align with the authors' original division of self-harm motives into "intrapersonal" and "interpersonal" as proposed in the original inventory [9]. The former ones determine the type of self-regulation, without any involvement of others in the formation of NSSI. The latter ones are related to interpersonal relationships and the social environment. This division also correlates with the earlier concept of "social" and "automatic" motivations for self-harm [25]. At the same time, the three-factor structure of NSSI that we identified suggests the need for further differentiation of "interpersonal" factors into "signal" and "influence" factors. The main difference between these groups of motivations, as we assume, is the expectation of change in the behavior of the surrounding people in response to one's self-harming actions. We have not been able to find any studies that evaluate the differences between the "signal" and "influence" types of NSSI. However, in some studies of the psychological motives behind suicide attempts, the factors of "appealing to others" and "revenge" were separated, where the latter implies a direct influence on the behavior of others as a result of the suicide attempt [26–28]. In some publications, "demonstrative suicide attempts" or "suicidal gestures" have been described; however, these concepts and their use remain controversial due to the lack of a clear, universally accepted definition. This ambiguity can potentially lead to a downplaying of the seriousness and danger of the situation, which may lead to a worsening of the quality of care provided [29].

The three-factor structure of the ISAS-F was also confirmed during the validation of the Japanese version of the questionnaire [30]. The authors of that study identified three groups of motives: "Coping with stress" ("Marking distress", "Anti-suicide", "Self-punishment", "Affect regulation"), "Interpersonal influence" ("Interpersonal influence", "Revenge", "Self-care"), and "Maintaining identity" ("Anti-dissociation/feeling generation", "Toughness", "Autonomy", "Peer-bonding", "Interpersonal boundaries", "Sensation-seeking"). It can be noted that this factor structure is similar to the one we obtained: the factor "Coping with stress" corresponds to the factor "Regulation" (with the exception of the motivation "Anti-dissociation/feeling generation"), the factor "Interpersonal influence" corresponds to the factor "Influence" (in our study, it also includes the motivation "Self-care"), and the factor "Maintaining identity" corresponds to the factor "Signal" (with the addition of the motivation "Anti-dissociation/feeling generation" and the exclusion of the motive "Self-care"). Nevertheless, further research on the three-factor structure of the questionnaire is needed on other samples.

Association of NSSI motives with suicidal thoughts and behavior

Our study showed that the suicidal thoughts and behaviors of the survey participants were associated with the factors "Regulation" and "Influence", but not the factor "Signal". The aforementioned study of the Japanese-language version of the questionnaire [30] showed that suicidal thoughts or attempts were associated with all three identified "Interpersonal influence" factors. We have not found any other studies that evaluates the association between "signal" and "influence" motivations for NSSI and suicidal thoughts and behavior. However, it can be noted that similar directions of association between internal factors of "Regulation" and external "influence" motivations are partially consistent with a concept proposed by Orri et al., according to which "the desire for revenge" as one of the "influence" motivations for engaging in a suicide attempt is an externalization and a direct expression of internal emotional distress, thus demonstrating the connection between the motivations of "Regulation" and "Influence" [27].

Given the phenomenological similarity between NSSI and suicidal behavior, this concept may also be applied to non-suicidal self-harm.

Limitations

This study has a number of limitations.

First, the study sample was limited to a specific social and age group (students). Therefore, the extrapolation of its results to the general population or to other social and age groups can be done only with reservations [31]. However, the percentages of gender- and age-based subgroups in the sample are consistent with the results of epidemiological studies which show that the prevalence of NSSI is higher among female and young people [2; 3]. Thus, the sample on which we conducted the adaptation, validation, and factor structure analysis of the ISAS questionnaire is close to the target audience of this questionnaire (individuals with NSSI) in the general population. Nevertheless, the gender-age characteristics of the sample do not allow for a broad attribution and identification of the associations between the factors "Regulation" and "Influence" to/with suicidal thoughts and attempts. It is known, e.g., that gender and age affect both the risk of suicidal thoughts and attempts, as well as the motivations for NSSI [28, 32]. However, the results we obtained were derived from regression models that took into account the factors of gender and age, thus demonstrating associations that are independent of these factors. Nevertheless, further research is needed to confirm these findings on samples with a different gender and age composition.

Secondly, during the development of the Russian version of the questionnaire, we did not follow all the recommendations for adapting psychometric tools [33]. In particular, we did not conduct a back-translation process, which could have negatively affected the semantic equivalence of the Russian-language and original versions (more details about the specifics of the translation can be found in Table S1 in the Supplementary).

Thirdly, the test-retest reliability of the questionnaire was not assessed owing to the cross-sectional study design. Nevertheless, the authors of the original inventory demonstrated sufficient test-retest reliability of the questionnaire when assessed after one year [34].

Fourthly, since the survey was distributed not only among individuals with NSSI, but also in an online format that did not allow for control over the completion of the questionnaire, some participants may have completed the ISAS-F questionnaire without having had any history of NSSI. To neuter such data, we did not include in the study individuals with a score of 4 points or less on the ISAS-F scale, which, as we expected, increased the specificity of the questionnaire (it minimized the proportion of individuals without a history of NSSI).

The strengths of this study include its wide geographical scope: participants from all federal districts of the Russian Federation; the large sample size, which allowed for conducting both EFA and CFA on different subsamples without a loss of statistical power; and the anonymous online format and the absence of a need to provide potentially identifying information, which potentially allowed for avoiding data distortion associated with the stigmatization that comes with mental disorders and the tendency to dissimulate suicidal experiences in the absence of anonymity and confidentiality [35].

CONCLUSION

We conducted an independent adaptation and validation of the Russian-language version of the ISAS in a large non-clinical sample, and also conducted the first confirmatory factor analysis of the Russian-language version of the questionnaire. The psychometric analysis demonstrated good internal consistency and reliability of the ISAS-F. During the factor analysis, an alternative three-factor structure of the questionnaire was proposed, which reflects the greater heterogeneity of the NSSI phenomenon and the mechanisms involved in its development. The proposed Russian-language version of the ISAS questionnaire is a reliable tool for describing NSSI and its psychological motivations.

Article history

Submitted: 21 Apr 2024
Accepted: 25 Dec 2024
Published Online: 05 Mar 2025

Acknowledgements: The authors would like to thank Mazo G.E., the staff and residents of the Department of Translational Psychiatry of the V.M. Bekhterev National Research Medical Centre for Psychiatry and Neurology (Saint Petersburg) for their assistance in the adaptation of the questionnaire.

Authors' contribution: All the authors made a significant contribution to the article, checked and approved its final version prior to publication.

Funding: The research was carried out without additional funding.

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data

Supplementary material to this article can be found in the online version:
Appendix 1: https://doi.org/10.17816/CP15537-145484
Table S1: https://doi.org/10.17816/CP15537-145485

For citation:
Kibitov AA, Potanin SS, Yagina OM, Borodin VI, Morozova MA. Psychometric Properties and Factor Structure Analysis of the Inventory of Statements about Self-injury (ISAS) in a Russian Non-clinical Sample. *Consortium PSYCHIATRICUM.* 2025;6(1):CP15537. doi: 10.17816/CP15537

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Generalized Bullous Fixed Drug Eruption Induced by Chlordiazepoxide: A Case Report of a Potentially Lethal Adverse Effect

Генерализованная буллезная фиксированная лекарственная эритема после применения хлордиазепоксида: клинический случай потенциально летального нежелательного явления

doi: 10.17816/CP15563

Case report

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ABSTRACT

BACKGROUND: Fixed drug eruption is a type of adverse drug reaction affecting the skin, marked by recurrent rashes that appear at the same site each time a particular drug is taken. Generalized bullous fixed drug eruption (GBFDE) is a severe form of FDE characterized by vesicles or bullae and involvement of a significant portion of the body surface area. To date, no association between GBFDE and chlordiazepoxide has been reported in the literature.

CASE REPORT: The authors present the case of a 40-year-old male inpatient in the psychiatry department of a tertiary care hospital in Assam, India. The patient was admitted in an alcohol withdrawal state and was initially prescribed chlordiazepoxide at a dose of 60 mg/day. He developed GBFDE within a day of chlordiazepoxide administration. The drug was discontinued, and he was treated with oral and topical corticosteroids instead, resulting in a significant improvement.

CONCLUSION: Chlordiazepoxide is a rare but potential trigger of GBFDE. Clinicians should closely monitor patients on chlordiazepoxide for possible signs of GBFDE.

АННОТАЦИЯ

ВВЕДЕНИЕ: Фиксированная лекарственная эритема — это тип нежелательной лекарственной реакции, поражающей кожу и характеризующейся рецидивирующей сыпью, возникающей на одном и том же участке кожи при каждом применении определенного препарата. В случаях, когда фиксированная лекарственная эритема сопровождается везикулами или буллами и затрагивает значительную часть поверхности тела, она классифицируется как генерализованная буллезная фиксированная лекарственная эритема (ГБФЛЭ). На сегодняшний день в научной литературе отсутствуют сведения о связи между ГБФЛЭ и хлордиазепоксидом.

КЛИНИЧЕСКИЙ СЛУЧАЙ: Пациент, мужчина 40 лет, госпитализирован в психиатрическое отделение высокоспециализированной больницы в Ассаме, Индия. Пациент поступил в состоянии алкогольной абстиненции,

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для лечения которой ему назначили хлордиазепоксид в таблетированной форме в дозе 60 мг/сут. В течение суток после начала приема хлордиазепоксида у пациента развилась ГБФЛЭ. Препарат отменили, а пациенту прописали пероральные и местные кортикостероиды, которые улучшили его самочувствие.

ЗАКЛЮЧЕНИЕ: Хлордиазепоксид является редким, но возможным триггером ГБФЛЭ. Важно сохранять высокий уровень клинической настороженности в отношении ГБФЛЭ у пациентов, принимающих хлордиазепоксид.

Keywords: *generalized bullous fixed drug eruption; chlordiazepoxide; alcohol withdrawal; benzodiazepines; adverse effect; case report*
Ключевые слова: *генерализованная буллезная фиксированная лекарственная эритема; хлордиазепоксид; алкогольная абстиненция; бензодиазепины; нежелательное явление; клинический случай*

INTRODUCTION

Fixed drug eruption (FDE) is a "distinct cutaneous drug eruption characterized by well-demarcated dusky-red or heavily pigmented patches involving the skin and mucosa. In recurrent episodes patients tend to develop lesions on the same location" [1]. The lesions commonly resolve with residual hyperpigmentation [1]. FDEs can be solitary, scattered, or generalized [2]. The generalized cases are sometimes associated with the eruption of bullae or erosions at multiple sites, a condition referred to as generalized bullous fixed drug eruption (GBFDE) [2]. GBFDE is the most severe form of FDE and can be misdiagnosed as epidermal necrolysis [3]. It has a high mortality rate of 22% [4]. Diagnosis of GBFDE requires "involvement of at least 10% of the body surface area (BSA) and at least three of six different anatomic sites (specifically, upper extremities, lower extremities, genitalia, the head and neck, anterior trunk, and back)" [5].

GBFDE secondary to chlordiazepoxide has never been reported in the literature, to the best of our knowledge. We present a case report of GBFDE following chlordiazepoxide administration in a 40-year-old male.

CASE REPORT

Patient information

General information

A 40-year-old married male, resident of Karnataka (India), educated up to 12th standard, employed in government service, of middle socio-economic status, with a history of alcohol consumption for the past 15 years, in a dependent pattern for the past 10 years, voluntarily admitted himself in the psychiatry ward on 8 Jul 2024 in an effort to quit alcohol.

The patient had no past history of allergy to drugs, or any medical, surgical, or psychiatric disorders.

Medical, family, and psycho-social history

The patient was born to a non-consanguineous couple. The father was a farmer with a history of regular consumption of alcohol and tobacco (however, a dependent pattern could not be established due to the lack of a detailed history). He passed away at the age of 59 years in 2019 following a road traffic accident. There is no history of any major medical/surgical illnesses in the family. No history of drug allergies in the family.

Clinical findings

A detailed history revealed features of alcohol dependence in the form of tolerance, craving, salience, and withdrawal discomfort upon abrupt cessation of alcohol consumption. Evaluation at the time of admission revealed moderate alcohol withdrawal state.

Diagnostic assessment

Diagnostic testing

The following scales were used to assess/grade the severity of alcohol use disorder:

1. Alcohol Use Disorders Identification Test [6]: patient scored 22, suggesting alcohol dependence.
2. Severity of Alcohol Dependence Questionnaire (SADQ-C) [7]: patient scored 34, suggesting severe alcohol dependence.
3. Alcohol withdrawal was assessed via Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) [8]: patient scored 12, suggesting moderate withdrawal.

The patient's relevant hematological and biochemical investigations, including the blood counts, liver/renal functions, blood glucose, lipid/thyroid profiles, were within normal boundaries (it is worth noting that while abnormal

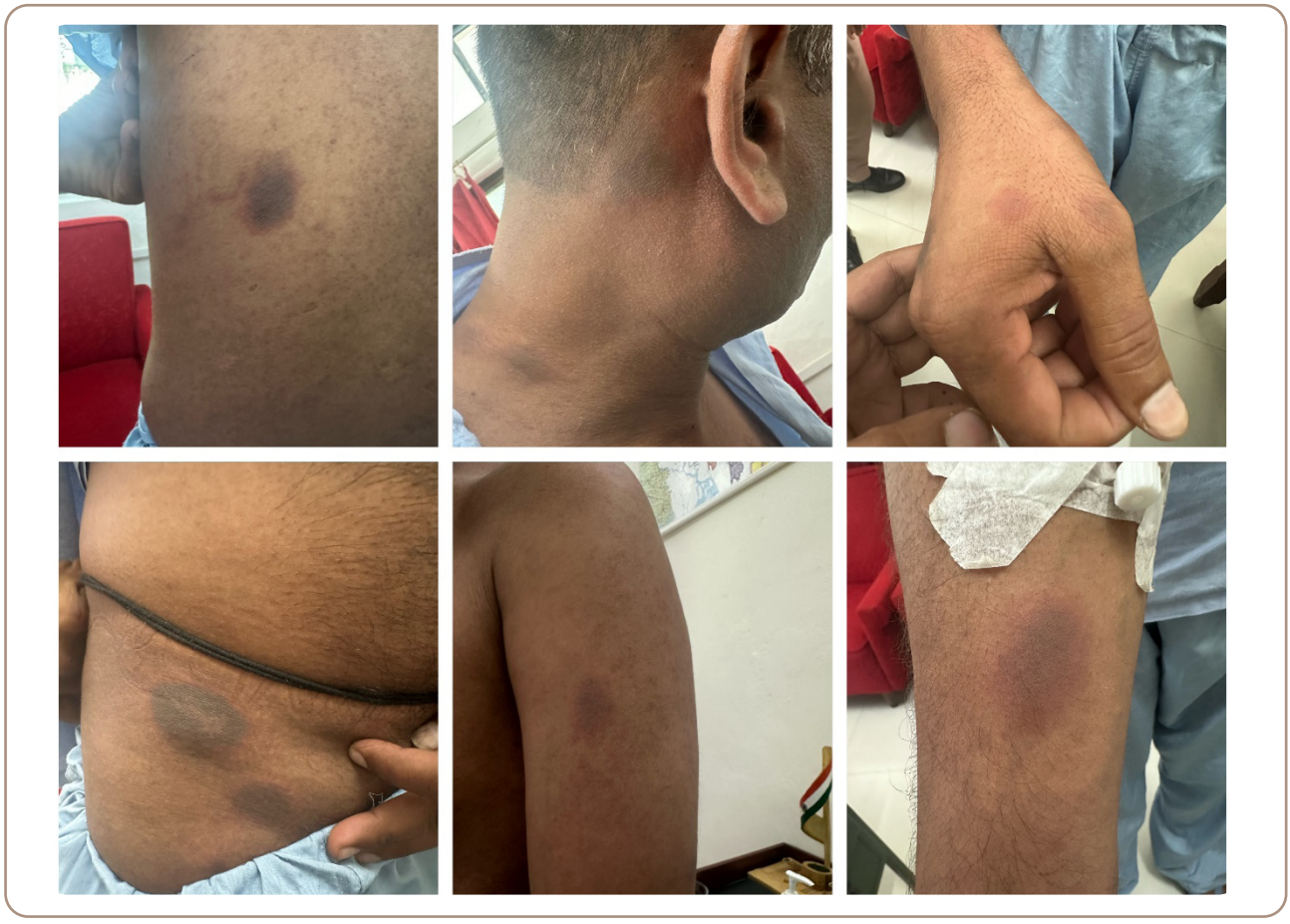

Figure 1. Resolving generalized bullous fixed drug eruptions involving multiple locations over the body following chlordiazepoxide administration.

Source: Singh et al., 2025.

liver functions are commonly observed in patients with long-term alcohol dependence, exceptions do occur, particularly in younger individuals with adequate nutritional status and no significant history of concurrent medical comorbidities).

Diagnosis

The patient was diagnosed as a case of:

1. Alcohol dependence syndrome, ADS (International Classification of Diseases, 10th revision, ICD-10, F10.2).
2. Alcohol withdrawal state (ICD-10, F10.3).

Therapeutic intervention

Pharmacological treatment

The patient was initially treated with chlordiazepoxide 60 mg/day for alcohol withdrawal. Within 24 hours of administration of chlordiazepoxide, he developed multiple vesicles over hyperpigmented erythematous targetoid macules located over both upper limbs, anterior and posterior trunk, and back of neck (Figure 1). There was no history of any constitutional symptoms. There was no involvement of any of the mucosal surfaces. Relevant hematological and biochemical investigations, including blood counts, liver/renal functions, blood glucose, lipid/thyroid profiles were repeated, and the results were within normal boundaries.

Concomitant diagnosis

A dermatology evaluation was conducted, and the patient was diagnosed as a case of GBFDE, with chlordiazepoxide being the offending drug. As per ICD-11, the patient was diagnosed as "Other specified adverse cutaneous reactions to medication" (EH7Y). The Adverse Drug Reaction Probability Scale (ADR Probability Scale) score for chlordiazepoxide was 7 (probable Adverse Drug Reaction, ADR [9]).

Follow-up and outcomes

Chlordiazepoxide was discontinued immediately. The patient was prescribed oral prednisolone (50 mg/day) and topical clobetasol cream (0.05% weight/weight) for 7 days. His lesions resolved gradually over a period of one week, leaving behind dark grey hyperpigmented lesions. He was advised to avoid chlordiazepoxide lifelong. His withdrawal was managed with oral diazepam, with no recurrence of dermatological symptoms. Subsequently, the patient was treated for ADS with psychosocial interventions and naltrexone (50 mg/day), without any ADRs.

Prognosis

The patient demonstrated a favorable prognosis. Following the discontinuation of chlordiazepoxide and initiation of oral prednisolone and topical clobetasol, the skin lesions resolved completely within one week, leaving behind residual hyperpigmentation. No recurrence of GBFDE was observed during subsequent treatment, and the patient successfully completed his treatment for ADS. The patient was reviewed on a monthly basis in an outpatient setting for ADS, and he was noted to have remained abstinent over the next three months.

Timeline

The patient timeline is presented in the Table 1.

DISCUSSION

Case report summary

This case report describes a 40-year-old male with a history of ADS, admitted for alcohol withdrawal management, who developed GBFDE following chlordiazepoxide administration. The patient initially developed transient vesicles on hyperpigmented erythematous targetoid macules, which resolved within one day of discontinuing chlordiazepoxide, leaving behind hyperpigmented lesions. The diagnosis was based on clinical criteria and confirmed with ADR Probability Scale score of 7, indicating a probable ADR. The patient was treated successfully with oral prednisolone and topical clobetasol, resulting in complete resolution of the lesions within a week.

Case report discussion

FDE is a delayed type IV hypersensitivity reaction, which occurs secondary to exposure to a causative agent. GBFDE is a rare and severe variant of FDE associated with blisters/erosions involving at least 10% of the BSA [10]. FDE has been linked to various medications, including anti-infective drugs such as β-lactam antibiotics, tinidazole, and acyclovir; analgesics like paracetamol, mefenamic acid, and metamizole sodium; non-steroidal anti-inflammatory drugs; anti-epileptic medications such as carbamazepine; psychoactive substances like barbiturates and codeine; and other agents such as allopurinol, contrast media, omeprazole, and loratadine [3]. Benzodiazepines such as chlordiazepoxide, lorazepam, and lormetazepam have also been implicated in the emergence of FDE, although rarely [11, 12]. Specifically, chlordiazepoxide triggers a variety of adverse cutaneous reactions, including urticaria, FDE, morbilliform erythema, systemic lupus erythematosus, drug-induced photosensitivity, purpura, and Stevens–Johnson syndrome [13, 14]. Blair in a case report in 1974 described a 48-year-old female on chlordiazepoxide (40 mg/day) who developed an erythematous maculopapular

Table 1. Patient chronology of disease development, key events and prognosis

Date	Key events	Condition
08 July 2024	Index patient voluntarily admitted in psychiatry ward to quit alcohol.	Patient diagnosed as a case of ADS and alcohol withdrawal state. Chlordiazepoxide 60 mg/day initiated.
09 July 2024	Developed multiple vesicles over erythematous hyperpigmented targetoid macules located over both upper limbs, anterior and posterior trunk, and back of neck.	Diagnosed as a case of GBFDE, with chlordiazepoxide being the offered drug. Chlordiazepoxide stopped immediately.
16 July 2024	—	Lesions resolved gradually over a period of one week, leaving behind dark grey huperpigmented lesions.
July–September 2024	—	For ADS treated with psychosocial interventions and naltrexone (50 mg/day). A monthly review was conducted in an outpatient setting, and it was noted that the patient maintained abstinence from alcohol for the following 3 months.

Note: ADS — Alcohol dependence syndrome; GBFDE — generalized bullous fixed drug eruption.

patch, 2.5 cm in diameter on the left side of her neck [15]. Chlordiazepoxide was discontinued, and she was treated with topical steroids and oral antihistamines, which led to a consequent improvement in the lesion. Upon reinstating chlordiazepoxide, the lesion returned to its erythematous and indurated state. The lesion again improved upon discontinuation of chlordiazepoxide. The author has, however, described the lesion as FDE rather than assigning the diagnosis of GBFDE [15].

Clinically, determining the culprit drug in the cases of FDE, especially those on polypharmacy, requires an oral provocation test, which involves administrating the putative offending drug, starting with a dose lower than the usual. However, the same procedure can trigger GBFDE and, hence, is contraindicated in patients who have had generalized forms of FDE [16]. A positive patch test over the previously affected area is a relatively safe course of action [16]. In the index case, the ADR Probability Scale score for chlordiazepoxide was 7 (probable ADR) [9]. The score was, however, spuriously low, as re-administration of the putatively offending drug is contraindicated in patients with GBFDE [16, 17]. Secondly, owing to the high mortality that accompanies the adverse reaction [4], chlordiazepoxide had to be abruptly stopped and any variation in the ADR (based upon an increased/decreased dose of the drug) could not be observed. Re-administration of the putative offending drug in ADRs with high mortality rates also comes with ethical considerations [16, 17].

GBFDE is a clinical diagnosis and generally does not require any biopsy [18]. A differential of Stevens-Johnson syndrome/toxic epidermal necrolysis was considered. The points in favor of GBFDE included rapid onset of symptoms (within 24 hours), presence of well-demarcated, marked hyperpigmented patches with adjacent skin being normal, characteristic absence of constitutional symptoms, and no mucosal involvement. However, some points against the diagnosis included no prior history of chlordiazepoxide use and no previous history of such reactions [17, 19].

In light of the rarity of GBFDE caused by chlordiazepoxide, the absence of prior reports, and the general predominance of antibiotics and non-steroidal anti-inflammatory drugs as causative agents, it is imperative to consider the possible mechanisms underlying this adverse reaction. One plausible explanation could be that chlordiazepoxide acts as a hapten, forming a complex with proteins in the skin, which subsequently triggers a delayed type IV hypersensitivity reaction. Another possibility is the role of genetic predisposition, which may make certain individuals more susceptible to benzodiazepine-induced immune-mediated reactions. Further research, including pharmacogenomic studies, is warranted to elucidate the mechanisms under chlordiazepoxide-induced GBFDE and to identify patients at higher risk of such ADRs.

The mainstay in the treatment of FDE/GBFDE is identifying and discontinuing the offending drug; in the majority of cases, no further treatment is needed [2]. Topical and oral corticosteroids (like prednisolone), and cyclosporine, have also been tried with success [2]. There is a lack of clinical trials evaluating the effectiveness of supportive care alone compared to treatments such as oral or topical steroids and cyclosporine in the treatment of GBFDE. It remains unclear whether these therapies accelerate symptom resolution or reduce mortality rates in comparison to a simple discontinuation of the causative drug [2].

Strengths and limitations

This case report has several strengths. It documents a rare case of ADR — GBFDE — caused by chlordiazepoxide, a widely used benzodiazepine. The report highlights the importance of early identification, prompt drug discontinuation, and effective management in achieving a favorable outcome. Additionally, it provides valuable insights into the potential cutaneous adverse effects of benzodiazepines, expanding the scope of clinical awareness.

However, there are limitations to this report. First, the transient nature of the vesicles meant they had resolved before photographic documentation could be obtained, reducing the illustrative value of the case. While the absence of bullae in the provided images could raise diagnostic questions, the overall clinical presentation, the response to the discontinuation of the drug, and the characteristic pattern of residual hyperpigmentation confirm the diagnosis. Second, the inability to perform a drug re-challenge due to ethical concerns limits a definitive confirmation of chlordiazepoxide as the causative agent. Lastly, the absence of histopathological examination/immunological studies of the lesions further constrains the case's scientific depth.

Despite these limitations, this case adds to the existing body of knowledge by reporting a novel association and underscores the need for vigilance when prescribing chlordiazepoxide.

CONCLUSION

This case report highlights the possibility of chlordiazepoxide as a rare, but potential, trigger of GBFDE. To the best of our knowledge, no prior reports have mentioned the same. We also recommend that clinicians maintain a high degree of clinical alertness when treating patients with chlordiazepoxide for developing GBFDE, owing to its rarity and potentially lethal outcome. This is even more the case in those patients who are being administered comparatively high doses of chlordiazepoxide (such as patients in alcohol withdrawal state). We also recommend the use of oral prednisolone and topical clobetasol in managing cases of chlordiazepoxide-induced GBFDE.

Informed consent: Informed consent was provided by the patient on 30 Jul 2024, prior to publishing this article. The participation of the patient was voluntary, and every step has been taken to maintain the patient's confidentiality and anonymity.

Article history

Submitted: 09 Aug 2024
Accepted: 14 Jan 2025
Published Online: 07 Mar 2025

Authors' contribution: Rishabh Singh — supervision, conceptualization, reviewing and editing the drafts. Vaibhav K. Sudhanshu and Mariam Shafiq — writing the original draft. Markanday Sharma — collecting study resources, reviewing and editing the drafts.

Funding: The research was carried out without additional funding.

Conflict of interest: The authors declare no conflicts of interest.

For citation:

Singh R, Sudhanshu VK, Shafiq M, Sharma M. Generalized Bullous Fixed Drug Eruption Induced by Chlordiazepoxide: A Case Report of a Potentially Lethal Adverse Effect. *Consortium PSYCHIATRICUM*. 2025;6(1):CP15563. doi: 10.17816/CP15563

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Motives for New Psychoactive Substances Consumption among Young Adults in Uzbekistan: A Qualitative Study Protocol

Мотивы употребления новых психоактивных веществ молодыми людьми в Республике Узбекистан: протокол качественного исследования

doi: 10.17816/CP15531

Study protocol

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ABSTRACT

BACKGROUND: New psychoactive substances (NPS) represent a global problem, especially among young people. In Central Asia, while the trafficking in NPS continues to grow, there remains a lack of data on the social, health and psychological consequences of their use.

AIM: To investigate the motives behind the NPS use among young people in the Republic of Uzbekistan, as well as the medical and social characteristics of this group.

METHODS: The study will include young people (18–35 years) who have used NPS in the preceeding 30 days (on the basis of self-reports) or are undergoing rehabilitation and plan to cease the NPS use within the next 12–18 months. Semi-structured interviews will reveal the reasons for NPS use, risk perception, stigma, barriers to seeking help, and the need for preventive and rehabilitation services. Interviews will take place at the Republican Mental Health Center and two specialized rehabilitation centers in Uzbekistan between November 2024 and the completion of enrollment (25–30 participants), but no later than May 2025. Additionally, a focus group of psychiatrists, psychotherapists, narcologists, and psychologists will evaluate the level of awareness amongst health care professionals as regards of NPS use and its prevalence, medical, and social implications.

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EXPECTED RESULTS: The study will identify the key motives of NPS use, usage patterns, and social and medical barriers of help-seeking. Findings will contribute to the development of prevention and rehabilitation strategies, including digital communication platforms and interactive educational programs.

CONCLUSION: The study focuses on raising awareness about the consequences of NPS in the Republic of Uzbekistan. This is essential for developing effective public health prevention and rehabilitation programs.

АННОТАЦИЯ

ВВЕДЕНИЕ: Новые психоактивные вещества (НПВ) представляют собой глобальную проблему, особенно среди молодежи. В Центральной Азии, на фоне увеличения трафика этих веществ, наблюдается нехватка данных о социальных, медицинских и психологических последствиях их употребления.

ЦЕЛЬ: Изучить мотивы употребления НПВ молодыми людьми в Республике Узбекистан, а также медико-социальные характеристики данной группы.

МЕТОДЫ: В исследование планируется включать молодых людей (18–35 лет), которые употребляли НПВ в последние 30 суток (по данным самоотчета) или проходят реабилитацию и планируют отказаться от употребления НПВ в течение последующих 12–18 месяцев. Для изучения мотивов употребления НПВ, восприятия риска, стигматизации, барьеров для обращения за помощью, потребностей в профилактике и реабилитации будут проведены полуструктурированные интервью. Интервью с потребителями НПВ пройдут в Республиканском центре психического здоровья и двух специализированных реабилитационных центрах Узбекистана в период с ноября 2024 года и до завершения набора участников (25–30 участников), но не позднее мая 2025 года. Осведомленность медицинских работников о распространенности и медико-социальных аспектах употребления НПВ изучат в фокус-группе с участием психиатров, психотерапевтов, наркологов и психологов.

ОЖИДАЕМЫЕ РЕЗУЛЬТАТЫ: По итогам исследования будут определены ключевые мотивы употребления НПВ, паттерны их использования, а также социальные и медицинские барьеры, препятствующие получению помощи. Также будут разработаны стратегии профилактики потребления НПВ и реабилитации потребителей, включая цифровые каналы коммуникации и интерактивные образовательные программы.

ЗАКЛЮЧЕНИЕ: Исследование нацелено на повышение осведомленности о последствиях распространения НПВ в Узбекистане. Его результаты будут способствовать разработке программ профилактики и реабилитации в системе общественного здравоохранения.

Keywords: *new psychoactive substances; youth; study protocol; Uzbekistan; qualitative study*
Ключевые слова: *новые психоактивные вещества; молодежь; протокол исследования; Узбекистан; качественное исследование*

INTRODUCTION

New psychoactive substances (NPSs) made their appearance on the market of addictive psychoactive substances in 2005 [1]. As defined by the United Nations Office on Drugs and Crime (UNODC), NPS is a substance susceptible to abuse, either in pure form or as a preparation, that is not covered by the 1961 Single Convention on Narcotic Drugs or the 1971 Convention on Psychotropic Substances but which may pose a "public health threat". In this context, the term "new" does not necessarily refer to novel preparations, but to substances that have only recently become available[1].

[1] United Nations Office on Drugs and Crime. The Challenge of New Psychoactive Substances. Viena: United Nations Office on Drugs and Crime; 2013 [cited 2024 Jul 23]. Available from: https://www.unodc.org/documents/scientific/NPS_Report.pdf

According to a report by the UNODC based on 2011–2016 data, an increase in NPS seizures and use in Central Asian countries associated with a surge in traffic from Russia and China is underway [2]. In particular, an increase in seizures of synthetic drugs in Kazakhstan has been observed since 2012, including the seizure of 10.6 kg of alpha-pyrrolidinopentiophenone in 2015 [2]. The same report noted a net increase in patients hospitalized with NPS dependence [2], while the prevalence of psychostimulant use among adolescents (13–18 years) is estimated to have increased to 2% [3]. In Tajikistan, 63 kg of methamphetamine was seized in 2012; in Kyrgyzstan, a methcathinone laboratory was dismantled in 2012 and 7 kg of amphetamine were seized in 2014[2]. An increase in documented cases of illicit cultivation of narcotic plants was recorded in Turkmenistan in 2012[2]. In 2013–2014, more than 6,500 drug-related crimes were registered in Uzbekistan, with an increase in the proportion of NPS-related offenses[2]. In the period from 2013 to 2016, all of the abovementioned countries, with the exception of Turkmenistan, reported the appearance of several dozen types of NPS[2].

The expanded presence of NPSs is largely due to their availability through online platforms and specialized outdoor outlets [4, 5]. The European Monitoring Centre for Drugs and Drug Addiction (now the European Union Drugs Agency, EUDA) reported more than 600 cases of NPSs between 2005 and 2016, with an annual increase of 13 NPSs in 2005 to 66 NPSs in 2016, with a peak of 101 cases of NPSs in 2014. This indicates a rapid, even exploding, availability of NPSs, combined with an increasing range of medical and social problems that includes attending issues such as the high toxicity of the drugs, poisoning, addiction and overdose, the sense of marginalization brought about by the use of these substances, the risks of accidental poisoning for others, the expansion of prisons, and increased overall violence [6].

Yet, the results of surveys looking into the use of NPSs remain highly volatile and context-specific, with considerable variations being observed between different countries and populations[3] [7]. In particular, such surveys have identified the geographic, cultural, and socio-economic factors that are associated with the easy availability of NPSs, the reasons for and how they are used, the specifics of the media coverage of the problem, and the degree of social stigmatization that comes with that use. The reasons behind the use of NPSs, the mechanisms of dependence, as well as the health consequences, including toxicity and the development of dependence, are also determined by the pharmacological profiles of the substances in this group [8, 9]. Considerably more complex relationships and health outcomes are related to the practice of poly-drug use of NPSs [9].

It is, therefore, not surprising that the reasons behind the surge in the use of NPSs vary and include curiosity, the seeking of pleasure or pursuit of a warped sense of sociability, and the desire to escape from reality, with the chief reasons varying depending on the region, cultural, and social contexts [5, 10]. Moreover, people using NPSs often perceive these substances as safer alternatives to traditional illicit drugs, which leads to stronger temptation to ignore barriers to their use and, as a result, an increase in their availability and associated risks [5]. At the same time, the proliferation of information about NPSs on the Internet has led to changes in drug use patterns, as many users seek these substances because of the hitherto unexperienced sensations they afford them [5]. Age-specific patterns and characteristics of NPS use have also been reported. In particular, according to a literature review by Coombs et al. (2022), the level of use of NPSs is highest among young people aged 16 to 24 years (data for Australia, New Zealand, Poland, Spain, the United Kingdom, and the USA)[3].

Public health measures to counter the spread of NPSs include innovative surveillance methods to identify new trends and the risks associated with these substances. For example, the French Addictovigilance Network uses a multifactorial approach (collection of data from different sources, analysis of abuse signals, early identification of drug use patterns) to monitor drug use patterns and related health effects, which has proven to be effective in the early detection of substance abuse signals and the prevention of adverse health effects [6]. Such systems are necessary for developing public health care strategies and interventions aimed at reducing the risks associated

[2] United Nations Office on Drugs and Crime. Central Asia Synthetic Druds Situation Assessment. Viena: United Nations Office on Drugs and Crime; 2017 [cited 2024 Jul 23]. Available from: https://www.unodc.org/documents/scientific/Central_Asia_November_2017_FINAL.pdf

[3] European Union Drugs Agency. European Drug Report 2017. Lisbon: European Union Drugs Agency; 2017 [cited 2024 Jul 23]. Available from: https://euda.europa.eu/publications/edr/trends-developments/2017/html_en

with the use of NPSs, which justifies the development of similar monitoring and prevention tools in other regions, including in Central Asia.

Under the current circumstances, the Government of Uzbekistan is taking comprehensive measures to increase oversight of the illegal circulation of narcotic drugs and psychotropic substances[2], including a review of the list of controlled substances, legislation, and the fostering of interdepartmental cooperation. In particular, the Narcotics Control Committee of the Republic of Uzbekistan regularly updates its lists of controlled substances and coordinates activities related to their legal circulation, including the issuance of permits for the import, export, and transit of NPSs[4]. In 2024, the national strategy for fighting drug addiction and drug-related crime for 2024–2028 was approved and centered on improving the legislation, drug monitoring, and public safety[5]. The National Center on Drug Control has been established, with the responsibility to interact with international organizations, develop preventive measures, and regularly submit reports to the UN[6]. At the same time, the issue of the development, implementation, and expansion of programs for prevention of the short- and long-term health consequences of the use of NPSs, including transient psychotic conditions [11, 12], psychoses [13, 14], and suicide [15], remains relevant for Uzbekistan.

In the current literature, the Central Asian countries are mentioned only as a starting point on the route of NPSs to other countries [14]. The lack of data is critical in the development of regional public health care programs, as the socio-economic and cultural factors that influence drug use behavior in Central Asia may have a different structure and impact compared with countries where the reasons for NPS use have been studied. The need for the development of these programs has to do with the inefficacy of simply raising awareness about the risks associated with psychoactive substances in stopping their use by adolescents and other youths [16]. In addition, the need for developing personalized strategies for countering illegal substance use through a deep look into the reasons behind such behavior and the application of interventions adapted to the individual's reasoning profile is being discussed [17]. The fact of change in behavior and, as a result, decrease in the level of substance use among young people as a result of motivational interviews also support the idea that a comprehensive solution to motivational problems is the key to effective countering of NPS use [18, 19]. It is important to note that the reasons for the use of classical psychoactive substances and NPSs can differ significantly, which also points to the need for the development of targeted (adapted to NPSs) prevention strategies and programs [20]. According to Jatau et al., such community-centered measures aimed at changing behavior through the implementation of motivational and cognitive behavioral strategies may be useful [21].

The aim of this study is to investigate the motives for NPS use among young people in the Republic of Uzbekistan, as well as the medical and social characteristics of this group.

This aim was dictated by the following objectives:

1. To study the reasons why young people use NPSs.
2. To assess how aware young people are about the consequences of using NPSs on their health and social well-being and their perception of the harm caused by NPSs.
3. To identify NPS use patterns.
4. To assess how young people perceive the stigma that comes with the use of NPSs and its impact on their willingness to seek help, as well as the barriers to seeking and accepting medical, psychological, and social assistance.
5. To evaluate the necessity for preventive measures and assistance for young people when problems arise in relation to their use of illicit drugs.

METHODS

Study design

This qualitative study will use a phenomenological approach to investigate the characteristics and patterns of the use of NPSs from the point of view of substance consumers

[4] Narcotics Control Committee [Internet]. Tashkent; 2024 [cited 2024 Jul 23]. Available from: https://www.uzpharm-control.uz/en/departments/the-drug-control-committee

[5] National Strategy to Combat Drug Addiction and Drug Crime in the Republic of Uzbekistan for 2024–2028. 2024 [cited 2024 Nov 3]. Available from: https://www.project-leica.eu/en/uzbekistan-developed-the-national-strategy-to-combat-drug-addiction-and-drug-crime-in-the-republic-of-uzbekistan-for-2024-2028

[6] On strategic measures to eliminate the negative impact of narcotic drugs and psychotropic substances on the health of the population and the gene pool of the country by ending the illegal circulation of narcotic drugs and psychotropic substances in the Republic of Uzbekistan: decree of the President of the Republic of Uzbekistan No. UP-73 of May 6, 2024. 2024 [cited 2024 Jul 23]. Uzbek. Available from: https://lex.uz/docs/6912475

in this group. The theory of social learning was chosen as the basic theory for the planned study, which focuses on the interaction of behavioral, cognitive, and environmental factors (in particular, the social environment and the context of the surrounding community) [22]. The immediate environment of the person (family, friends, and colleagues) will be regarded as the social environment, while cultural, economic, and social conditions, and the specific regional features or national traditions will be considered in the context of the surrounding community.

An inductive method of qualitative data analysis will be used to identify the key patterns and aspects of use of NPSs. Instead of being formulated in advance, study hypotheses will be based on the information collected, a method predicated on insufficient knowledge of the issue of the NPSs use by young people in Uzbekistan. However, the study will test a number of baseline assumptions about the reasons why young people in particular use NPSs, as well as their medical and social characteristics:

1. The use of NPSs is rooted in a combination of psychological factors, such as the desire to reduce stress and experience pleasure, social conditions, including the influence of the environment and the availability of substances, as well as economic circumstances, such as low cost and ease of access.
2. Young people who use NPSs have insufficient information about the long-term risks associated with their use, and the strength of the motivating reasons outweigh the assessed risks, which increases the likelihood of continued use.
3. Patterns of NPSs use, including the frequency and conditions in which they are used, the methods of purchase, and the types of substances used, vary and are linked to the availability of substances, the social context, and the individual preferences of those using them.
4. The high level of stigmatization of NPSs users in society suppresses their willingness to seek medical, psychological, and social assistance, which raises additional barriers towards accessing the necessary support.
5. From the perspective of young NPSs users, the most effective measures to tackle the problem would be to enlist interactive educational programs and digital communication tools, as well as making available anonymous treatment services and social assistance.

Our study will consist of three parts: two rounds of interviews with users (a pilot and a main survey) and a focus group with specialists. *The pilot survey* will involve interviewing NPS users to improve and adapt our questionnaires (data collection tools) for the main survey by testing questions for clarity and consistency for the participants in the pilot interview. *The main survey* will include a series of individual interviews with NPS users (current users of NPS or undergoing rehabilitation); the meetings will be held in a location convenient for the interviewer. The interviews in *focus groups* with health care professionals (psychiatrists, psychotherapists, drug addiction specialists, psychologists) will be conducted at clinics and rehabilitation centers participating in the study (more details below). Focus groups with specialists will also be held in other regions of Uzbekistan. The regions will be selected later among those with the highest prevalence of NPS use as based on updated data for 2024. As a result of the interview, it is planned to assess healthcare professionals' awareness of the prevalence and medical-social aspects of NPS use.

No compensation is planned for study participants.

Investigator characteristics and reflexivity

The principal investigator (G.A.Z.) is a highly qualified psychotherapist with more than 10 years of experience working with patients, including psychoactive substance users. Drug addiction specialists, all with more than 5 years of experience in the treatment and rehabilitation of patients suffering from substance dependence, will also participate in the study. The task of the principal investigator and drug addiction specialists is to conduct interviews, analyze data, including transcript encoding, and keep reflection diaries to minimize bias.

The research team includes a psychiatrist (T.S.S.) with more than 20 years of experience in treating patients with comorbid mental and behavioral disorders, a Candidate of Medical Sciences. His task would be to control for bias throughout the independent data analysis, including checking the accuracy of the data coding and interpretation conducted by other members of the team; reviewing and discussing reflection diaries from other investigators to identify additional patterns and reasons behind the use of NPSs and to ensure consistency in data interpretation; participating in data triangulation; and participating in joint data discussions to align interpretations and minimize subjectivity.

Study conditions

The interviews of NPS users will be conducted at the Republican Mental Health Center of Uzbekistan and two rehabilitation centers, Detox and Gratus (all in Tashkent, Uzbekistan). These institutions provide specialized assistance to users of psychoactive substances. The choice of location for the interviews (options: a psychotherapist office, a free room in a rehabilitation center, a cafe) will be left to the discretion of the participants in the survey.

The context of the study is marked by a high level of stigmatization of NPS users in society. In this regard, special attention will be paid to creating conditions for participants to freely share their experiences and opinions, as well as to create a trusting atmosphere and ensure confidentiality. All potential survey participants will be availed of detailed explanations regarding the study's goals, objectives, and methods; after such explanation, they will be asked to sign an Informed Consent Form as survey participants (see Appendix 1 in the Supplementary).

Data collection began in November 2024; it will conclude after completion of the scheduled number of interviews, but no later than May 2025.

Selection strategies and eligibility criteria

Two strategies will be used to design the study sample. The first one involves inviting NPS users who have sought psychotherapeutic help, or persons undergoing a rehabilitation program at the above-mentioned centers (a convenience sample). The second one is when participants of the first sample invite acquaintances of NPS users and are not undergoing rehabilitation in clinics or rehabilitation centers on a voluntary basis (a snowball sample). For all persons undergoing rehabilitation and agreeing to participate in the study, the medical documentation used in the routine practice of the relevant health care facility will be taken as a source of information. For participants who are not undergoing rehabilitation, medical records will not be completed, and information required by the study protocol, including socio-demographic data, will be recorded only in the study documentation.

Inclusion criteria: men and women aged 18 to 35 years, residents of Uzbekistan who, by self-admission, have used NPSs in the last 30 days or are in rehabilitation, have stopped using NPSs and plan not to resume using NPSs for the next 12–18 months. Participants must have sufficient knowledge of the Uzbek or Russian language to participate in the interview. The age range of 18–35 years is chosen based on data showing that the majority of cases of drug use were registered in this age range[7].

Exclusion criteria: evidence of coercive hospitalization or rehabilitation in the medical records; dependence on other psychoactive substances (alcohol, opioids, amphetamines) declared by the potential study participant or documented in their medical records; clinical signs of a psychotic disorder at the time of the interview.

Ethical considerations

The Ethics Committee of the Ministry of Health of the Republic of Uzbekistan has approved the protocol of a research study titled "Medical and social aspects of the use of new psychoactive substances among the young people of Uzbekistan (Tashkent). A qualitative interview" (Minutes No. 6/10-1916 dated September 05, 2024). In case of changes in the key parameters of the study protocol (number of interviews, remuneration for participation, use of promotional materials to attract participants to the study) or any other information that potentially affects the participants' consent to participate in the study, the necessary documents will be re-submitted for review to the Ethics Committee.

A signed Informed Consent Form (see Appendix 1 in the Supplementary) will be sought from all study participants. The Informed Consent Form has been developed and approved by the Ethics Committee and contains information about the study purpose and objectives, planned procedures, possible risks, and benefits for study participants.

Personal information (sex, age, interview number in the voice recorder, date of the interview) about the persons included in the study, as well as their consent for participation, signed with a name chosen by the participant, will be held by the principal investigator.

Data collection methods

An audio recording of the interviews with NPS users and health care professionals in focus groups will be made. The estimated duration of an interview is 40–90 minutes. Investigators' notes, including data from reflection diaries, will also be recorded.

[7] European Monitoring Centre for Drugs and Drug Addiction. Guidelines for the prevalence of problem drug use (PDU) key indicator at local level [Internet]. Lisbon: EMCDDA; 1999 [cited 2024 Sep 18]. Available from: https://www.euda.europa.eu/html.cfm/index58064EN.html_en

Tools and technologies used for data collection and storage

The interview with NPS users will be semi-structured, using a guide containing questions about the socio-demographic characteristics of the study participants (sex, age, education, marital status, employment) and 33 questions related to the study topic. We used material from the study by Gittins et al. [6], including an introduction explaining the study objectives and discussing confidentiality issues, issues related to the history of substance abuse, the types of NPSs used, frequency of use, places of purchase and user experience. In addition, to address the study aim, we included questions to investigate the motivation for the NPSs use (questions about the needs that the respondent is trying to meet and the purposes of the use) (see Appendix 2 in the Supplementary). Guidelines in Russian and Uzbek will be used to conduct interviews with NPS users (see Appendix 2 in the Supplementary). The interview will be conducted in the Russian and Uzbek languages at the convenience of the interviewee. A focus group guide will be used to conduct focus groups with specialists (see Appendix 3 in the Supplementary). The focus group will be conducted in the Uzbek and Russian languages.

The guidelines texts may change depending on the results of the analysis of the pilot stage.

Audio recordings of interviews will be made using portable voice recorders. Permission to record will be secured from the interviewee. At the end of the interview, the records will be copied to a personal computer to which only the principal investigator will have access. Audio records and text data will be encrypted using AES256 technology, and access to the files will be protected with passwords.

Number of interviews

About 25–30 interviews are planned. This number was set based on consultation with experts and experience from similar studies. However, the actual sample size will be determined by sampling saturation; i.e., the qualitative study threshold when data collection stops yielding new ideas and topics.

Source data processing, data analysis, and data reliability security techniques

The saved audio recordings will be transcribed manually in the interview language, verbatim, with subsequent translation into Russian for ease of analysis and coding. The quality of the translation will be ensured by back translation of all the interviews by an independent professional translator and comparison of the back translation with the original text.

The MAXQDA software (VERBI GmbH, Germany) will be used for data organization and analysis. Encoding of key topics, concepts, and categories in MAXQDA will be performed using an open-label approach (studying text data without a pre-specified code set) simultaneously by two investigators. Coding discrepancies will be resolved through discussion and consensus. Codes are the key ideas expressed by respondents, reflecting the most important aspects of their experience, such as reasons for use, perception of the consequences, stigma, barriers to seeking help, and assessment of existing prevention programs. For further analysis, the open-coded data, which will highlight key citations, ideas, and concepts, will be grouped into categories based on which the main topics will be determined, allowing one to assess the patterns and phenomena related to the study matter. At the next stage, through the comparison of topics, identification of convergences, and determination of key patterns, hypotheses reflecting key aspects of the study will be formulated and conclusions will be drawn.

Data analysis will be performed simultaneously with collection to ensure an iterative process and an inductive nature of the study. An analysis of the first 5–10 interviews during the iteration is planned in order to identify potential new topics and check the wording of the questionnaires in terms of whether they are adequately understood. If necessary, changes will be made to the wording of questions or new topics will be added for further interviews. For example, if participants actively raise topics that were not initially included, these topics will be added in subsequent interviews. To triangulate the data, the results of the interview, the data from the investigators' reflection notes, as well as the answers of the participants to various interview questions, will be compared.

When accessing the MAXQDA software, the coded data will be organized according to subjects' IDs (depersonalized identification number, sampling center, and interviewer), structured, and prepared for analysis. The data will be checked for accuracy and consistency through random control: the second investigator (T.S.S.) will compare randomly selected fragments of the decoded texts with the audio recordings. In addition, data from the interview will be compared with information extracted from the investigators' notes to reinforce the soundness of the analysis.

The principal investigator and drug addiction specialists will conduct the primary data coding, and the principal investigator and the second investigator will perform an independent analysis to verify the accuracy of the codes and the consistency of the topics. All investigators will participate in the discussion and the finalizing of the topics.

An inductive approach will be used to analyze the data, allowing the key themes of the narrative to emerge based on the actual data obtained.

When analyzing the codes for topics and reasons, the questionnaire items predefined for the study aims will be taken into account, as specified below:

1. To investigate the reasons why young people use NPSs, including the psychological, social, and economic factors that underpin the need for their use (questions 10, 11).
2. To assess the awareness of young people about the consequences of using NPSs on their physical and mental health, social well-being and their perception of the harm caused by NPSs (questions 12, 15–18, 21, 25).
3. To identify NPS use patterns (the frequency and conditions of use, methods of purchase, types of substances used) (questions 1–9, 13, 14).
4. To explore young people's perceptions of the stigma associated with NPSs use and its impact on their willingness to seek help, as well as the barriers to seeking and receiving medical, psychological, and social assistance (questions 22–24, 31).
5. To determine young people's needs for prevention measures regarding NPSs use and support in case of problems related to their use, including information support tools and identification of effective communication channels, as well as the development of recommendations for ensuring access to treatment and social support services for users of psychoactive substances (questions 19, 20, 26–30, 32).

DISCUSSION

Limitations

The planned study has several sources of possible systematic problems. First, there is the use of a convenience sample and a snowball sample, as well as the selection of participants aged 18 to 35 years in health care facilities in the city of Tashkent (a capital city with young people with specific socio-demographic and cultural characteristics). These circumstances may lead to the formation of a biased sample that does not reflect the composition and characteristics of the general population (all users of NPSs in Uzbekistan), which, in turn, will limit the possibility to extrapolate the study results.

Second, questions about the past (e.g., "*when and how did you first start using NPSs*"?) can be influenced by memory lapses; i.e., participants may distort or forget details of their first episodes of using NPSs. This may corrode the reliability of the information about the triggers and circumstances of the initiation to NPS use and associated factors.

Third, we assume that the semi-structured questionnaire does not cover the full range of motives, reasons, and context in the use of NPSs, as well as the barriers faced by young people living in Uzbekistan when seeking help. However, we plan not to limit the interview's cope to just the text of the guidelines, and if new topics arise, allow the interviewer to ask additional questions. In addition, we plan to take into account the results of the analysis in the pilot stage of the study in order to refine and improve the text of the questionnaire.

Fourth, objective confirmation (e.g., chromatographic studies, test strips) of isolated episodes of NPSs use (without other narcotic drugs) is not planned in this study. At the same time, we understand that poly-drug addiction usually follows a more severe course, which will enrich the phenomenology of reasons and warrants their study [9, 23].

Data sharing

The results of our study will be shared through the publication of articles in scientific journals, in the form of reports at conferences, or other public events. There are no plans to open access to the source data of the study.

Registration of the study protocol

The study was registered as a dissertation work at Bukhara State Medical University (the work was approved by the Scientific Council at a meeting on February 16, 2022, Minutes No. 002759).

Article history

Submitted: 07 Apr 2024
Accepted: 22 Jan 2025
Published Online: 11 Mar 2025

Authors' contribution: Guzalkhon Zakhidova (principal Investigator): conceptualization, data curation, investigation,

methodology, writing — original draft, writing — review and editing. Uladzimir Pikirenia: conceptualization, project administration, supervision, writing — review and editing. Timur Syunyakov: formal analysis, validation, visualization, writing — original draft, writing — review and editing. Mariya Prilutskaya: conceptualization, data curation, methodology, writing — review and editing.

Funding: Financially supported by the DAAD with funding from the Federal Ministry for Economic Cooperation and Development (BMZ).

Conflict of interest: The authors declare no conflicts of interest.

Supplementary data

Supplementary material to this article can found in the online version:
Appendix 1: https://doi.org/10.17816/CP15531-145489
Appendix 2: https://doi.org/10.17816/CP15531-145490
Appendix 3: https://doi.org/10.17816/CP15531-145491

For citation:
Zakhidova GA, Pikirenia Ul, Syunyakov TS, Prilutskaya MV. Motives for New Psychoactive Substances Consumption among Young Adults in Uzbekistan: A Qualitative Study Protocol. *Consortium PSYCHIATRICUM.* 2025;6(1):CP15531. doi: 10.17816/CP15531

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Dialogical Structure of the Brain and the Ternary System of the Mind: The Neurosemiotics of Yuri Lotman

Диалогическая структура мозга и троичная система психики: нейросемиотика Юрия Лотмана

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Opinion

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ABSTRACT

Yuri Lotman (1922–1993) was a semiologist, literary critic, and cultural historian from Soviet Russia. He is credited with founding the multidisciplinary Tartu-Moscow School of Semiotics. As a cultural theorist and humanist, he was highly influential across many fields, but his contributions to theories about the brain as a semiotic system have often been overlooked.

Topics such as the asymmetry of the brain hemispheres, the "untranslatable" specialization of their respective "languages", interhemispheric dialogue, and the unity of consciousness were frequent subjects of discussion within the scientific community that formed around the multidisciplinary Tartu-Moscow (and Leningrad) group. Recently, scholars such as E. Andrews and T.V. Chernigovskaya have highlighted the influence and relevance of the "neurosemiotic" model proposed by Yu.M. Lotman in the late 1970s. However, our impression is that a fundamental aspect, which Yu.M. Lotman considered indispensable for the functioning of any "thinking system", has been overlooked in the application of this model to contemporary studies of neurophysiology. This aspect is the intersemiotic translation device that Yu.M. Lotman calls the "semiotic boundary". We can consider this as a "third" structure of intersection between the two hemispheres, which actively operates to translate specialized information systems reciprocally. In this paper, we will attempt to restore its significance according to an interpretation updated to the most recent discoveries in cognitive neuroscience.

АННОТАЦИЯ

Юрий Михайлович Лотман (1922–1993) — советский семиотик, литературовед и культуролог. Ему приписывают основание междисциплинарной Тартуско-московской семиотической школы. Как теоретик культуры и гуманист, он оказал большое влияние на многие области человеческого знания, но его вклад в теории о головном мозге как семиотическом устройстве часто отходит на второй план.

Такие темы, как асимметрия полушарий головного мозга, «непереводимая» специализация используемых ими «языков», межполушарный диалог и единство сознания, были частыми предметами обсуждения в научной среде, сформировавшейся вокруг междисциплинарной московско-тартуской (и ленинградской) группы. В работах последних лет ученые Э. Эндрюс и Т.В. Черниговская заострили внимание на актуальности нейросемиотической модели Ю.М. Лотмана, которая зародилась еще в конце 1970-х годов. Однако сложилось впечатление, что при применении этой модели в современных нейрофизиологических исследованиях был упущен из виду фундаментальный аспект, который Ю.М. Лотман считал неотъемлемым в функционировании любой «мыслящей системы». Этот аспект представляет собой средство интерсемиотического перевода, называемое Лотманом «семиотической границей». Его можно рассматривать как «третью» структуру пересечения двух полушарий, активно работающую над двусторонним переводом специализированных информационных систем. В настоящей статье мы попытаемся восстановить его значение, опираясь на интерпретацию, обновленную с учетом последних открытий в области когнитивной нейронауки.

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Keywords: *Yuri Lotman; hemispheric asymmetry; multimodal semiotics; semiotic boundary*
Ключевые слова: *Юрий Лотман; межполушарная асимметрия; мультимодальная семиотика; семиотическая граница*

A "NEUROSEMIOTIC" MODEL

Tatiana Chernigovskaya in [1] revisited theoretical framework of Yuri Lotman, highlighting the generative role of "noise" in semiosis as a dynamic force stemming from the asymmetry of the cerebral hemispheres. She interprets noise not as an obstacle to communication, as in Jakobson's classical model [2], but as a creative tension fostering new meanings through the interplay of the hemispheres' distinct cognitive styles [3]. While my approach builds upon Lotman's dialogism and the semiotic potential of hemispheric asymmetry, it diverges by introducing the concept of *semiotic boundary*, which Yu.M. Lotman originally used in cultural analysis but largely overlooked in neuroscience. Here, the semiotic boundary is not merely a site of tension but an active mediator, translating and integrating the "languages" of the left and right hemispheres. By reframing Lotman's insights, this paper proposes a novel explanation of interhemispheric communication as a structured process generating cohesive cognitive and cultural outputs.

In the article by Tatyana Chernigosvkaya [4], it is mentioned that Yuri Lotman delivered a significant lecture at a seminar in Tartu in 1981, focusing on the "problem of semiogenesis and the functional specialization of the brain hemispheres as a model of intellectual processes". The researcher, who was present at the event, recalls that this seminar was an important platform for discussing experimental findings from the *Laboratory of Functional Asymmetry of the Human Brain* (Institute of Evolutionary Physiology, Russian Academy of Sciences) [4]. Reflecting on these discussions 40 years later, Tatyana Chernigovskaya acknowledges Lotman's remarkable foresight in *conceiving the bipolar structure of the brain as a minimal semiotic unit*, anticipating by decades the neuroscientific discoveries on cerebral lateralization. Although "he did not speak directly about physiology", Yu.M. Lotman had intuited that the bipolarity of the hemispheres is not only a functional organization but also a key principle in the generation of meaning, applicable to both the brain and culture. Lotman's insights, T.V. Chernigovskaya emphasizes, remain highly relevant even today [1].

Thus, from the standpoint of cultural semiotics, we have a direct and remarkable testimony that not only did Yuri Lotman conceive his own neurocognitive theoretical model, but that it was held in high regard among Russian cognitive neuroscience researchers [5]. In the vast literature of criticism and commentary on Yuri Lotman, many complex cultural concepts such as the Semiosphere or the concept of "explosion" are interpreted in various ways, often neglecting that, even within the system of culture, the concept of "mind" was fundamental to Yu.M. Lotman. His central international compendium of writings is titled Universe of the Mind [6]. The subtitle of The Semiosphere is "Asymmetry and Dialogue in Thinking Systems" [7]. In theoretical interpretations, these concepts tend to disappear, despite Lotman's constant reiteration of the fundamental concept of his epistemology: the isomorphism between individual and the collective of minds, the latter understood as culture.

The "mind" of a culture, its collective consciousness, is the result of interaction between different languages that are often incomprehensible to each other (language but also dance, music, painting, and even fashions or everyday behavior). It is also the result of interactions with other cultures, which bring new languages and customs through exchanges, like an intersubjective exchange [8]. Yuri Lotman believed that the brain, as a semiotic system where sensory and cognitive information circulates in different patterns between the hemispheres, and between the individual mind and its interlocutor, operates according to the same mechanisms. In fact, as Yu.M. Lotman explained, semiotics as an autonomous discipline was born as the science of information [9]. From this position, the study of culture was integrated into the study of complex information systems and was interested in many scientific fields, including cybernetics and biological or physical systems. Semiotics sought to uncover the general laws governing complex systems [10]. In this context, Lotman's work on brain semiotics, particularly the concept of the "semiotic boundary" [6] as an interhemispheric translation device, plays a pivotal role in bridging the fields of semiotics and cognitive neuroscience.

KEY ARTICLE

The article "Kul'tura kak kollektivnyj intellekt i problemy iskusstvennogo razuma" (Culture as a Collective Mind and the Problems of Artificial Intelligence) is fundamental for understanding the multidisciplinary approach of Yuri

Lotman and the Tartu-Moscow group [10]. The Italian translation of this work was published in the same year in the proceedings of the annual international semiotics congress, in an edition that Yu.M. Lotman personally oversaw [11]. To introduce the problem of culture as a collective mind and as a model for instructing intelligent machines, Yuri Lotman begins with the formula of an immutable law of cybernetics, according to which "the stability of the system increases with the variability of its elements". This law also applies to the information processed and shared by the brain's hemispheres, which, to achieve homeostatic stability (unity of consciousness), must resolve their specificity and asymmetry through mutual exchange (dialogue). Observations made on cultural mechanisms highlighted that only humans were capable of processing data from experience into not only abstract concepts, but also new ideas, through dialogue with other individuals, groups, and cultures. These studies, which were also conducted by R. Jakobson [12], L.S. Vygotsky [13, 14], and V.V. Ivanov [15, 16], led Yu.M. Lotman to assert that the difficulties in translating languages did not block the circulation of information, but rather qualitatively transformed it, favoring the emergence of new texts and messages capable of reinterpreting new states of systems [1, 2, 17]. Translation between languages needed to be mediated by devices that were not reversible, term-by-term exchanges, but rather metaphorically elaborated, leaving space for idiosyncratic interpretations. Yu.M. Lotman believed that this was the true source of human semiotic creativity.

The brain operates in the same way, as inferred from the article [11], because an individual's creativity emerges from the ability to metaphorize otherwise untranslatable information, given that the codes of the respective hemispheres are specialized for very different functions. Yu.M. Lotman explains these concepts whenever he talks about the artistic abilities of poets, writers, painters, etc. [6]. The "new thought" that emerges through creative interhemispheric dialogue is not merely information added quantitatively to one or the other hemisphere. Here, we seem to discover the distinction Yu.M. Lotman identified between the brain and the mind: the mind exists as the qualitative emergence of an informational surplus "new" information generated by translations as metaphorizations, which arises from the joint work of the two hemispheres but is semiotized by humans in the texts of culture. This occurs in intersubjective relationships, in inter- and intra-cultural relations, and also in inner mental dialogue [6].

We think this hypothesis is of immense importance for current neurosemiotic studies, as it anticipates the issue raised by G. Tononi's Integrated information theory about consciousness in its "physical substrate": the more specialized the information of each brain hemisphere is, the more the total information requires integration at the metal-level of the global system [18]. While Tononi "solves" the problem through a mathematical formula that measures a certain quantity of integrated information required for the emergence of consciousness, Yu.M. Lotman proposes a qualitative model of extended consciousness, where cultural information exceeds biological information in the metasemiotic systems that are isomorphic to both individual and collective minds.

CONTINUOUS AND DISCRETE

The analogy of cultural asymmetry and brain structure asymmetry (also) implies the relationship between discrete languages and continuous languages and the problem of their reciprocal equivalence in texts based on them [11]. By continuous languages, the author refers to the language of painting, sculpture, architecture, or continuous sound, where "reading" does not occur by arranging elements along a temporal line, but rather where symbolic configurations appear as immediate, spatial, and timeless states. Discrete languages include natural language, writing, logical thought, articulated movement, and others in which the code is organized into segments oriented along a temporal line toward a result. For the study of these latter languages, Yu.M. Lotman observes, we have many tools of analysis, while for investigating continuous languages, we have none. "Among other things, their role (like that of right-hemisphere consciousness) is not secondary" [11]. What does the scholar mean by "right-hemisphere consciousness"? He evidently refers to the problem of inner dialogue. We know that the debate on this theme was vibrant during those years. V.S. Bibler [19] had written a paper on the "process of internal dialogism as a clash of radically different thinking logics" [1]. Meanwhile, V.V. Ivanov, considered the co-founder of Cultural Semiotics, was working on different forms of sensory processing on the different semiotic languages in the asymmetric brain [15]. If one were to design an artificial thinking machine, Yu.M. Lotman states, it would need to be equipped with a mechanism describable as an "infant consciousness block" or a "mythological birth mechanism" because *only the "polar opposition between texts formed in such a framework and those formed within*

the logical-discrete mechanism provides the metaphorism necessary for elaborating new communications" [11].

Let us attempt to penetrate Lotman's complex language. The concept of "infant consciousness block", if understood as the interruption of childhood psychological development following trauma in affective relationships, was a psychological condition described by the Italian child neuropsychiatrist Giovanni Bollea [20]. Although Yuri Lotman does not explicitly cite G. Bollea, his works had been widely known since the 1960s. This "block" manifests in children as difficulty in understanding and integrating their emotions, thoughts, and perceptions, leading them to retreat into a parallel reality that serves as a defense mechanism against emotionally painful self-experiences. The affected child avoids verbal communication, struggles to articulate their emotions, and fails to develop a coherent sense of self. As a result, they seek refuge in a fantasy world dominated by reassuring symbolic entities that provide an alternative to an intolerable reality. Lotman's concept may also be linked to disruptions in child-adult relationships, as explored by L.S. Vygotsky [14] in his notion of the "zone of proximal development (ZPD)", (as his interpretation of artistic thought), which describes the gap between what a child can achieve independently and what they can accomplish with guidance. So Yu.M. Lotman appears to be referring to a childlike mind that operates recurrently through images and symbols. As further confirmation of this interpretation, Yu.M. Lotman also discusses the "mythological birth mechanism" as a mode of narrative construction by symbols [6], where relationships between phenomena are considered not through logical connections but through associations in a magical-mythological continuum. Here, the reference can be aptly directed toward the concept of "savage thought" described by C. Lévi-Strauss, whom Yu.M. Lotman cites in the article along with M. Mauss. Thus, the world is read "like tarot cards", where the relationships between the figures provide the required information, rather than the order in which the cards are drawn or the spatial arrangements. For an extremely rational person (who heavily uses the left hemisphere), this "primitive" or "childish" language is utterly nonsensical (insane). To explain this incompatibility of thoughts, our semiologist guides us through one of his most elegant yet complex insights: (A thinking system) "can be defined as a mechanism that, in addition to intelligent behavior, possesses potential capacities for non-intelligent (insane) behavior, and thus can choose at any moment between the two opposite strategies" [11]. It is tacitly evident that in this study Yuri Lotman critiques the cybernetic theory of the "metaphorical brain" proposed by M.A. Arbib [21] (cited by Yuri Lotman in the article), according to whom there are no issues of dialogue and integration between the two hemispheres. For the same reason, Yu. Lotman would probably not have agreed with Arbib's theory of language learning [22] through imitation via embodied simulation [23] based on the discoveries related to mirror neurons [24], which the semiotician did not have the opportunity to know in time. We believe, instead, that he would have drawn different conclusions from the role of intermodal translation performed by mirror neurons, as we will propose below.

THE SEMIOTIC BOUNDARY AND THE BRAIN

A hypothetical mediation mechanism between the two hemispheres would functionally be located at the center of the polar-tension axis, not only maintaining the system's homeostatic balance but also bringing elements of the hemispheres' languages closer together in a shared field of tension. The further apart the two elements are on the axis, the more difficult it will be for them to be mutually translated. But it is precisely in this tension effort that the most effective metaphors are realized and the most unpredictable thoughts capable of sometimes "exploding" the order of a previous system and forcing its components to find a new balance for an effective renewal of thought [8]. These are phenomena that occur only in the conscious emerge, thinking activity of the individual, such as the "mad" thought of a physics genius or the unheard-of metaphors of a poet, which, in turn, can trigger sense-explosions leading to epochal renewals, such as historical artistic genres.

Lotman's semiotic boundary is a semiotic mediation structure described extensively in The Semiosphere [7]. In culture, it can be explained through various examples and one we propose is that of a mercantile border city where merchants and buyers from many languages meet, and are forced to understand each other in simple market exchanges. Not only can the languages be mutually incomprehensible, but so can the objects themselves, whose uses or artistic values may be unknown, thus complicating exchange values. In these cases, mediators, evaluators, customs officers, experts, bilinguals, etc., are essential to populate the border spaces, making possible a continuous enrichment mechanism for cultures, where the main exchanges are of new ideas and thoughts. However,

even this Samarkand has its own cultural conception of itself, emerging from the languages of power, institutions, dominant culture, and the nobility, shaping a widespread local sentiment. Thus, enveloping the spheres of semiotic interaction, a sphere emerges in which culture seeks to identify itself, in a self-description mechanism that, in constructing the "we", also defines the "others": foreigners, the marginalized, the uneducated.

Interhemispheric communication, even within an individual's consciousness, does not consist merely of input-output circulation but includes self-awareness that arises from metaphorical translations between discrete and continuous languages and would not be possible outside a world of intersubjective semiotic interactions.

THE INTERHEMISPHERIC METAPHORICAL TRANSLATION SYSTEM

It is natural to think of the interhemispheric boundary translation zones as analogous to the various brain commissures. We propose that these commissures collectively form a coherent interhemispheric translation zone. The functions of the corpus callosum were known to Lotman, thanks to the pioneering work of R. Myers, R. Sperry, and others on split-brain studies [25]. As previously mentioned, Russian neuroscience was highly advanced in the study of cerebral asymmetry and, thanks to the profound contributions of A.R. Luria, it also made significant progress in understanding the cognitive development and the systemic functions of the brain [26].

More recent studies suggest that the commissures are involved not only in pre-selecting messages but also in controlling balance, coordinating sensorimotor functions, and mediating proprioceptive signals [27]. This latter function is especially intriguing, as it seems to suggest a functional continuity with the other commissures.

We first examine the anterior commissure. The metaphorical interparietal dialogue, particularly in the interaction between the two inferior parietal lobules (IPL), has been studied in depth by Indian neuroscientist V.S. Ramachandran [28]. He noted that the IPL (both right and left) is a true hub for the integration and exchange of different sensory (visual, auditory, tactile) and motor languages [29]. The cross-modal interactions of these languages, depending on the qualitative interference of their components, allow the human mind to combine new ideas through metaphorization processes. In this way, the researcher formulates hypotheses about creative thinking, particularly in archaic Indian art. For example, the statues of the Indian deity Shiva with four arms do not represent monstrous humans but rather a being who, in his cosmic dance, dominates the heavens and the earth. The movement of the arms is what spins the cosmic wheel in which the figure is inscribed, according to the cycle of time. V.S. Ramachandran and E.M. Hubbard [30] hyphothesizes that this is a metaphorical way to merge the discrete language of sequential execution of individual gestures with the continuous language of holistic vision. The IPL is deeply involved in embodied simulation of movements and their mirrored understanding, to the point that this lobule is densely populated with mirror neurons.

The IPL, situated at the intersection of various specialized areas, according to the authors, selects and coordinates sensory and motor languages, laying the foundation for cognitive metaphorization. It is also involved in proprioception, which aligns with the function of the corpus callosum that we highlighted. Imaging studies have shown that neuronal activity in the right IPL increases when there is an incongruity between observed and executed movement, suggesting that this region is involved in internal control of posture, closely linked to the mirror neuron system [31].

Now, let's turn to the hippocampal commissure. The hippocampus is primarily known for its role in memory and spatial orientation, but its connections with other brain areas, including motor and sensory systems, make it important for regulating posture and balance, engaging the proprioceptive system [32]. Proprioception is the ability to perceive and recognize the position of the body and its parts in space without external sensory input (seeing oneself, being touched). The interconnection between the two parts of the hippocampus via the commissure allows bilateral integration of proprioceptive information from muscles, joints, and tendons. This proprioceptive function allows us to have an awareness of the body's totality in relation to the environment, such as when we must prepare for unexpected external reactions, where we do not yet know which muscles or joints will need to be activated. It also enables us to mentally reach the smallest muscles of the body, which are part of our embodied experience, and to consciously recall and sequentially execute all the gestures required for complex procedures like playing the piano [33].

If we place these two functions on a bipolar axis, the first will appear as a continuous, unarticulated vision,

suspended from goal-oriented action, like when we perceive danger or face a choice but do not yet know what to do. The second will appear as the execution of a proprioceptive program, studied segment by segment, as in a solo concert performance or competitive dance, where the subject focuses on each muscle and joint in the continuous feedback between perception and proprioception.

The proprioceptive system also allows us to internalize and become aware of the axial coordinates of movement [34]: back/forward and the maintenance of an upright posture, as well as the low/high axis that passes through the body's center of gravity. We become aware of these axes (as well as the right/left "balance") when the body moves toward an object of interest (goal-oriented procedure) or when the body "plays" with proprioceptive balance, such as when a child learns to stand and walk, or in the "wild" movements of dance [35]. Proprioception is perceived as both bilateral and lateral/subtle (as in fine manual work), making its function "third" in relation to hemispheric specializations. Because it is involved in intersubjective relationships through the mirror neuron system, proprioception lends itself to the role of an extended "collective proprioception", allowing an entire culture to order and share the meanings of its world. For example, the high/low axis hosts entire symbolic systems that vary across cultures, such as heaven/earth; divine/human, importance/futility, royalty/subjugation; prestige/disdain, and so on. This third, metaphorical-tensional function allows us to describe proprioception as a boundary or metaphorical filter for translation between perception and cognition.

CONCLUSION

In this article, we have proposed interpretations of some of Yuri Lotman's profound ideas, which could still shed light on current debates in cognitive neuroscience. The semiotic boundary, as part of a ternary structure of the brain-body system, should be understood as follows: the corpus callosum facilitates the transfer of already processed information, ready to be quickly implemented in the contralateral system, functioning as a pre-selection and mediated routing mechanism.

The anterior commissure modulates the tension between the two associative parietal lobes, regulating the selection of sensory and sensorimotor message exchanges. The hippocampal system regulates, via the commissure, the oscillation between static and dynamic proprioception and between body balance/imbalance. By recording new movements marked by emotional significance, it reinforces its importance for long-term memory. The translation system could be further supported by other commissures, such as the cerebellar vermis or the recently discovered interthalamic commissure. According to this vision, the two hemispheres communicate along the continuous/discontinuous axis as follows.

Information emitted by the left hemisphere on articulated segments of actions or sensory languages, passing through the boundary system, would be decomposed into symbolic units according to semantic configurations influenced by the environment. In these atemporal grids, each symbol derives meaning from immediate relationships with other symbols, based on topological and metaphorical criteria. A symbol can either fit into an already established cognitive configuration or demand new interpretive grids around its evocative power. These atemporal configurations of symbols would then present themselves to the opposite hemisphere as "nodes" for possible fragments of new, creative (or corrective) syntactic chains to be integrated into goal-oriented action.

Since the exchanged elements are "bent" toward a function not predicted by the natural behaviors of the species, this metaphorical distortion brings new ways for the mind to know or recognize the world. This is the key to human creativity. The structure of the mind is ternary because proprioceptive and cognitive consciousness functions as a metalinguistic layer above cerebral bilingualism. However, the individual mind cannot function unless it is immersed in broader systems, from intersubjectivity to culture and interculture. The semiosphere, as Yu. Lotman defines it, is a "system of systems".

While this work aims to provide a theoretical reflection on Yuri Lotman's ideas and their potential applications within the framework of cognitive neuroscience, we acknowledge its intrinsic limitations as a speculative endeavor. Specifically, the absence of empirical integration or practical evaluations stems from the independent position of the author, without access to research centers or laboratories capable of experimentally testing the proposed hypotheses. The arguments presented here are intended primarily to stimulate theoretical and interdisciplinary discussion, offering an interpretative model that necessitates further exploration and validation through empirical research. We encourage the scientific community to consider these insights as a starting point in future investigations that may examine the practical implications of the neurosemiotic

model and its potential contributions to understanding cognitive and cultural functioning.

Article history

Submitted: 17 Dec 2024
Accepted: 13 Feb 2025
Published Online: 05 Mar 2025

Funding: The research was carried out without additional funding.

Conflict of interest: The author declares no conflicts of interest.

For citation:

Sanna M. Dialogical Structure of the Brain and the Ternary System of the Mind: The Neurosemiotics of Yuri Lotman. *Consortium PSYCHIATRICUM*. 2025;6(1):CP15606. doi: 10.17816/CP15606

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Comments on the Article “Dialogical Structure of the Brain and the Ternary System of the Mind: The Neurosemiotics of Yuri Lotman”

Комментарий к статье «Диалогическая структура мозга и троичная система психики: нейросемиотика Юрия Лотмана»

doi: 10.17816/CP15627

Commentary

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Marco Sanna, the author of the article, “Dialogical Structure of the Brain and the Ternary System of the Mind: The Neurosemiotics of Yuri Lotman”, written in the format of a popular science essay, reflects on the complex structure of the human mind’s information systems as they manifest in everyday life, the origins of “semiotic creativity”, and the mechanisms involved in creating abstract symbols and meanings [1]. The author alerts us to the importance of synchronizing semiotics with the neurosciences and to the usefulness of the Yuri Mikhailovich Lotman model. He invites further discussion amongst experts involved in integrative neuroscience, including psychiatrists, medical psychologists, neurolinguists, evolutionary psychologists, anthropologists, and cultural scientists. The essay can be considered an introduction to the problem. The correct structuring of the context of the article allowed us to highlight a number of promising ideas from Yu. Lotman and to consider the expediency of applying some provisions of his theory in modern research. With this comment, I would like to support the initiative to revive interest in the research of this world-renowned scholar and to consider the idea of a semiotic space and the methods of Lotman in the context of the development of interdisciplinary neurocognitive research.

The author focuses on the ambient underestimation of the theoretical work of semiologist and culturologist Yuri Lotman, which was conducted in the second half of the 20th century. Yet his contributions remain highly relevant if we want to take neurosemiotics to the next level of integrative science and post-non-classical philosophy [2]. This idea forms the core of the article and justifies its title. Works on neurolinguistics and semantics of that period in science evolution were influenced by the ideas of the famous psychophysiologist Alexander Romanovich Luria; about secondary systemic speech disorders that go beyond the understanding of local topical distribution of primary functions [3]. Based on the above-mentioned achievements of that time, Lotman developed a theory of a semiotic space (“semiosphere”) with its internal and external boundaries, which extended beyond the scope of natural sciences and philology. One cannot but agree with the author that the specialization and translation of information through both the dialogue of an individual with the external world and the internal “dialogue of the two hemispheres”, which is based on functional asymmetry, can be considered Lotman’s significant contribution [4, 5]. The author’s view constitutes the quintessence of the article and justifies the choice of its title. According to Lotman’s explanation, the idea of a semiotic space resulted from the development of mathematical and natural sciences: “The success of non-Euclidean geometry and the emergence of the theory of relativity put forward the ideas of the relativity of space, the

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multiplicity of spaces, their asymmetry, and symmetrical complementarity" [6]. Relying on his approach, Yu. Lotman was able to identify significant differences between natural language and actual speech and texts: the unexpressed versus the expressed, the ideal versus the structural and materialized, respectively, which is important for understanding the specifics of neurolinguistic and cultural studies. In the late 20th century, Lotman's ideas about the semantic network of lexical and syntactic units, his concept of cognitive processes and a neurosemiotic model, were innovative, widely discussed at conferences, published in academic literature, and highly regarded in the Russian researchers community. Yet, these ideas are now rarely mentioned in the development of contemporary cognitive theories or in applied research on an international scale. The possible reasons for such a state include the difficulties involved in interpreting the key concepts put forth by Yu. Lotman and the lack of vigorous efforts to integrate of interdisciplinary principles into the study of deep brain processes at the interface with Lotman's semiotics.

It becomes clear that Lotman's ideas today align with modern scientific perspectives on connectomics, functional plasticity, and the cognitive elasticity of the human brain. They also resonate, to some extent, with the concept of the cognitome of Konstantin Vladimirovich Anokhin, which describes mental functions and consciousness as the activity of a neural hypernetwork. A comparison of Lotman's structural-functional approach to complex mental functions with Anokhin's latest ideas on the principles upon which the brain functions reveals that both address problems of a similar character [7, 8]. K.V. Anokhin, developing the concept of a high-order hypernetwork model of the brain, noted a serious overall shortcoming affecting modern studies into higher mental functions and consciousness processes [7]. That shortcoming is the lack of a fluid neurobiological theory that explains information systems devices and consciousness; in other words, a theory of how rich subjective experience is gained through brain activity [9, 10]. Konstantin Anokhin insists on a radical restructuring of ideas about the brain from the position of functional systems theory to overcome the "gap" between conventional neurophysiology and psychology. He offers a bridge in the form of an alternative "mind-brain" theory with holistic functional systems. At the same time, the scale of the functional unit can vary depending on the required set of processes. This perspective introduces a new fundamental dimension in neurobiological systems that "elevates them to the category of cognitive systems" [7]. According to the theory of functional systems, the activity of a cognitive organism and its adaptation are shaped by the accumulation of subjective experience and the development of the ability for "anticipatory reflection of future interactions with the environment" [7]. In Vyacheslav Borisovich Shvyrkov's research, which builds on this theory, it is demonstrated that neurons are specialized in relation to holistic elements of subjective experience rather than isolated physiological or psychological functions [11].

The theoretical approaches to information processing by the mind-brain proposed by Yuri Lotman and Konstantin Anokhin offer prospects for identifying the fundamental underpinnings of human cognitive and mental functions. Notably, Lotman's approach aligns with contemporary views on the technological sophistication of cognitive studies, including "thinking machine" technologies. Optogenetics methods have brought about a revolution in neurobiological research. These technologies have the potential to help clarify the most controversial points in Lotman's theory and the views of the author of this article. With their help, it would be possible to test the biological aspect of the phenomena of cerebral bilingualism and continuous interaction of the two hemispheres during resting state or specific tasks, as referenced in the manuscript. In Lotman's era, such possibilities remained in the realm of imagination. Moreover, it is now evident that artificial intelligence and machine learning are no longer just research tools. Modern AI technologies already contribute to the modeling of cognitive processes that diverge from the analog modes of perception and thinking most familiar to us. However, fully understanding these processes requires the development of appropriate neurocognitive theories.

Over time, the trends in neurolinguistic research have changed under the influence of neuroscience discoveries. Today, the semantic structures of language are well-studied, with consideration given to the distribution and association of language functions in the brain's cortical hemispheres and the relationship between speech and thought. In recent years, research into the interaction between cortical speech areas and the non-speech sensorimotor regions of the brain has identified neural networks that involve deep subcortical structures. This has clarified the operational and regulatory roles of particular areas. The brain functions in a highly integrated fashion, with interhemispheric connections playing a crucial role in sensory, motor, and cognitive processes. These points of contact involve transitions

between hemispheres through both "mirror" and "non-mirror" tracts, the latter including functional loops such as those between Broca's and Wernicke's areas. The corpus callosum, consisting of approximately 100 million fibers, enables both hemispheres to process the same task within an extremely short interval [11]. To explore how the hemispheres communicate, different functional speech networks, including semantic networks, are being studied. One hypothesis suggests a strong interaction between left-hemispheric processing of syntax and right-hemispheric processing of prosodic information via the corpus callosum, allowing these two types of linguistic information routes to influence each other [13, 14]. Generalized data from more than 100 brain imaging investigations (fMRI and PET) have shown that physical speech signals exist in the brain as multiple distinct choice points within both the information input and output systems. Around 730 areas of increased activity have been identified in the left hemisphere, which are responsible for phonology, semantics, and sentence or text processing, with a significant overlap between them [15].

When analyzing neurobiological data related to semantics, it is important to consider their potential mobility over short periods of time, particularly as a language's working vocabulary expands and its syntax becomes more simplified. These processes are characteristic of many modern languages. All of this suggests a distributed network of speech production which is similar to the World Wide Web.

For these studies, Lotman's concepts of information flow and schematic models could prove valuable. One can nod to the author's formal logic in correlating Lotman's theoretical predictions with the accumulated empirical neurobiological data and the modern frameworks that reflect them, including those addressing the role of human subjective experience, reflection, and the relationship between personality and culture.

The greatest difficulty is the part of the article in which the author offers an interpretation of Lotman's notion of the "semiotic boundary" (a necessary entity to ensure interhemispheric translation and dialogue in perceptual and thinking systems) as an independent structure functionally connected to the hemispheres. The article's discussion of the controversial and multifaceted phenomenon of the "semiotic boundary" as a functional brain unit and semiotic space is positioned as the core of the work, advocating for the relevance of Lotman's ideas. To support this argument, the author includes several examples from modern neurobiology but does not explore the limitations of these findings. In particular, the concept of the boundary, as interpreted here, requires analysis grounded in a broader body of scientific evidence. This is especially important given that the phenomenon of the border, as stressed by both Yu. Lotman and the author, suggests not only changes in its extent — such as becoming wider — but also shifts in the degree of involvement of specific structures. Modern neuroscience sheds light on the variability of the brain in the context of neuroplasticity, which, as part of humanity's genetic heritage, reshapes the brain under sociocultural influences throughout cultural development. With each new stage of cultural evolution, individuals acquire skills that drive significant neural changes. For instance, studies have documented more extensive interhemispheric connections in musicians who began training at an early age. It is interesting that Lotman's predictions about entirely new forms of information, described as the metaphorization of untranslatable information during interhemispheric interaction, have gained validation in neuroscience. According to Yu. Lotman, this phenomenon arises from the differing specializations of the hemispheres. Such a phenomenon of total information (not just added), when the interplay of brain regions amongst each other leads to a qualitative transformation when a new whole is not the result of a simple addition of separate elements, fits the description of emergentism. It is to be expected that the study of the semiological boundary in neurobiological studies will be difficult given the myriad changes involved in synaptic activity, the receptor density, and the brain cells and that occur for a variety of reasons. Additionally, the author provides only a cursory discussion of the cerebellum's role, despite the emerging research that underscores its relevance in this context. A more in-depth exploration of its functions could further enrich the discussion.

Some of the important topics raised by the author include the influence on the brain biology of factors related to the cultural space, as well as possible biological and psychosocial mechanisms and the links between them. Given that the evolutionary history of the human species is linked to the development of language in the pursuit of personal and sociocultural goals, the consideration of culture in Lotman's neurosemantic model is an important issue that requires a separate study. The work builds on Lotman's pivotal article, which presents culture as collective intelligence, proposing an epistemology of isomorphism between the individual and collective minds. In the context of two-way

directionality, we now consider the reciprocal influence of cultural learning and brain activity (a type of counter-movement), in which cultural experience rearranges neural connections, reprograms circuitry, and modulates functional relationships between brain regions. This has been shown in numerous studies to the point that performing certain cultural tasks can lead to the formation of specific brain modules. Cross-cultural analysis shows that it is important to take into account the established differences between the thinking of people belonging to the "Western" culture as opposed to those of the "Eastern" culture.

Lotman's understanding of the influence of cultural factors is important in studying the mental activity of a "reflective", "creatively thinking", "creative" person — a position detailed by the famous philosopher Merab Konstantinovich Mamardashvili in terms of cultural-dialogical reflection [16–18]. The link between the individual and the collective mind through the dialogue of people with cultural forms in Lotman's theory is manifestation of the principle proposed by Russian philosophers and psychologists. M.K. Mamardashvili likens the relationship between man and culture to a kind of influence of "cultural forms" (art, science, philosophy, others) as "man-forming machines"; i.e., building in man what "could not be otherwise" done [16]. Lev Semyonovich Vygotsky's publications trace the idea that culture, particularly art, performs psychotechnical work and can transform human thinking [19]. In search of a link between culture and man, L.S. Vygotsky uses the concept of the word, while M.K. Mamardashvili, building his ideas on the basis of ancient and postmodernism/post-non-classical philosophy, uses the concepts of logos and topos. The significance of language units, speech systems, and the role of reflection in the works of L. Vygotsky, Yu. Lotman and M. Mamardashvili are considered from different vantage points, but the essence of their ideas is rooted in the same space of a reflection on the content and mechanisms of formation of cultural forms. Yuri Lotman and Merab Mamardashvili sought to grasp the nature of the mechanism that undergirds the process of transformation of a person in their contact with cultural forms and the emergence of redundant properties in human biology — rhythms and intonations of the soul. In the framework of this approach, the emergence of redundancy requires a dialog between a person's self and his/her reflective position, which is designated as the Other. It is the formed redundancy in the course of reflection that allows one to transform known perceptions and become a source of new knowledge about the studied reality, its development, and regulation. Thus, a reflective person emerges not simply due to the mastering of a word-concept, but due to cultural forms, logos, and topos. It is in dialogue with these elements that the individual shapes and creates their own identity.

The manner in which Yu. Lotman approaches his ideas for interdisciplinary research in medicine is based on the biopsychosocial model of mental and neurological disorders. However, data on the biological effects of numerous factors related to everyday experiences and cultural influences remain insufficient. The latest version of the ICD-11 international classification of mental disorders emphasizes this issue. The concept of "dialogue between hemispheres" raised by the author is quite relevant when discussing difficult cases with speech and other cognitive impairments, especially in the context of ontogenetic development. There are known cases of cognitive brain mobility — recovery of speech, or semantic functions in severe lesions of the dominant hemisphere in early childhood. Potential models for studying the role of hemispheres can be variants of the progressive neurodegenerative diseases caused by old age, which often begin as localized disorders of synaptic activity, focal brain atrophy, and isolated symptoms. Neuroplasticity and compensatory mechanisms often contribute to cognitive impairment developing gradually and subtly at first, becoming clearly manifested as both hemispheres and paired brain regions become involved. According to neuroscientists, most cognitive functions in humans are duplicated in the left and right hemispheres in cortical areas (prefrontal, motor, sensorimotor cortex, secondary associative cortical centers) and basal nuclei (hippocampus, amygdala, striatum, others), and they are functionally identical. Interhemispheric communication allows for the development of a compensatory mechanism and the maintenance of a normal functional asymmetry.

Typically, normal and pathological ageing processes begin in the non-dominant (usually right) hemisphere responsible for speech function and semantic functional networks. Often, the compensatory mechanism becomes exhausted only at late stages of neurodegenerative diseases, with a gross deficit of higher mental functions. For example, in a typical form of Alzheimer's disease, cognitive disorders manifest themselves in amnestic syndrome, which involves both the left and right hippocampus (a strategically important structure for the memory processes). At the same time, the preservation of speech in patients plays

a compensatory role and helps them remain socially active for a relatively long time, until pronounced bilateral brain atrophy begins to set in, leading to impaired semantic interpretation and encoding of information. In the later stages, the patient first experiences difficulty recalling the right name of a familiar object, and then they lose the name altogether, not understanding what it is and what it serves, and they also lose the rules of verbal communication. But in a human neurodegenerative pathology, there also exists a localized lesion of the dominant brain hemisphere at the onset of the disease. The clinical picture is dominated by the syndrome of isolated primary progressive aphasia, with pronounced limitations as relates to daily life. These cases, with unilateral lesions (including neuroimaging data), come with a low chance of rehabilitation. It is probably a lesion in a strategically important area responsible for speech, but unpaired in a functional sense. In psychiatric and neurological practice, there are cases where patients experience a loss of categorical understanding of the world, along with speech disorders, such as impoverished vocabulary and the erosion of syntactic grasp. It is often challenging to determine whether these impairments stem from deficits in working memory, attention, slower information processing speeds, or other related issues. The causes and mechanisms behind these speech disorders, particularly in the context of neurodegenerative diseases, remain a topic of debate, because of mounting evidence indicating that speech semantic functions are not limited to the dominant hemisphere. For example, the right hemisphere plays a crucial role in the processing of complex aspects of perception and expression, such as metaphor, humor, and contextual meaning, while the left hemisphere is primarily responsible for literal and rational interpretation [20]. The development of neurosemantic methods for diagnosis and neurorehabilitation is crucial.

In conclusion, to summarize my thoughts on the article "Dialogical Structure of the Brain and the Ternary System of the Mind: The Neurosemiotics of Yuri Lotman", I believe it is important to highlight the potential value in integrating Lotman's approach in the shaping of the objectives and the means to achieving them in contemporary cognitive neuroscience, psychiatry, and neurology. His theory provides a framework for studying highly organized constructs linked to intellectual perception and behavior, the predictive role of brain processes, and their influence on the development of complex cultural forms. Another strength of Lotman's concept is its epistemological foundation, centered on the isomorphism between the information systems of the individual and collective mind. When developing Lotman's ideas, it would be beneficial to integrate the principles of post-non-classical philosophy, particularly interdisciplinarity. At the same time, it is also important to highlight the limitations of Lotman's approach, especially the real challenges in interpreting key concepts, such as the "semiotic boundary" between the two hemispheres, the underdevelopment of interdisciplinary integration, and the dearth of reliable experimental data. Still, these ideas merit to be explored further, for example, through a narrative review approach, which could help define the potential scientific applications and limitations of Lotman's concept in research. It should be noted that the article is somewhat overloaded with the ideas of both Yu. Lotman and the author, and that some topics and concepts are presented in a speculative way, without sufficient scientific validation. The most controversial part of the article is on the "hard problem" of consciousness, which, outside of medicine and neuroscience, is often treated as a private, philosophical category. The author discusses the unity of consciousness in the context of interhemispheric dialogue, referring to Yuri Lotman, but not referencing modern research or the views of leading figures in neuroscience. This is a critical field, and incorporating contemporary perspectives is essential when dealing with one of the most ambiguous aspects of our understanding of living organisms. Anokhin's cognitome theory could also be valuable in this context [2]. The author is encouraged to address these limitations by presenting contemporary views and substantiating Lotman's theories with reliable empirical evidence. I wish the author success as he continues to explore this topic.

Article history
Submitted: 30 Jan 2025
Accepted: 17 Feb 2025
Published Online: 15 Mar 2025

Funding: The research was carried out without additional funding.

Conflict of interest: The author declares no conflicts of interest.

For citation:
Andriushchenko AV. Comments on the Article "Dialogical Structure of the Brain and the Ternary System of the

Mind: The Neurosemiotics of Yuri Lotman". *Consortium PSYCHIATRICUM*. 2025;6(1):CP15627. doi: 10.17816/CP15627

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