RELATIONSHIP OF STABLE COMBINATIONS OF SALIVARY CATECHOLAMINES WITH CEREBRAL FUNCTION ORGANIZATION IN PATIENTS WITH CHRONIC CEREBRAL ISCHEMIA

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The study of the role of catecholamines (CAs) in cerebral organization of functions in patients with chronic cerebral ischemia (CCI) is relevant, since their important role as neurotransmitters is well known, along with the association with stress severity and cortisol. The study aimed to assess the impact of stable combinations of dopamine (DA), norepinephrine (NA), and adrenaline (ADR) on the organization of cerebral functions. A total of 76 patients with CCI were assessed based on the fMRI data (n = 21) converted into a network structure using the SPM-12 and CONN-18 software tools. Significance level estimation involved adjustment for multiple comparisons. Stable combinations of CAs reflecting mutual positive correlation of DA, NA and BP significantly affected cerebral organization of patients with CCI. CA combinations were associated with salivary cortisol ($F = 4.8$; $p = 0.038$) and memory ($F = 7.5$; $p = 0.011$) indices: the CA level increase was associated with increased cortisol levels and worse memory indices. Based on fMRI data the differences were revealed in connectivity organization of CCI patients with high and low levels of all three CAs. Patients with the CA content below median are characterized by the presence of closed neural networks extending to both brain hemispheres, which contributes to information integration and retention. It is assumed that such networks may be associated with the long-term potentiation mechanisms playing an important role in memory processes and changes in the synaptic connection strength. Thus, the use of non-invasive biochemistry testing methods and fMRI has made it possible to obtain new data on the ring organization of brain neural networks associated with stable CA combinations. Such neural network organization is likely to affect cognitive functions. High catecholamine levels in CCI patients are associated with increased cortisol levels, memory deterioration, and decreased connectivity in neural network of the brain.

Keywords: catecholamines, dopamine, norepinephrine, adrenaline, chronic cerebral ischemia, cerebral functions, connectivities, fMRI, neural networks

Author contribution: Fokin VF — manuscript writing; Abaimov DA — biochemistry testing; Ponomareva NV — physiological and neuropsychological testing design, general study design; Medvedev RB — Doppler tests and clinical assessment; Konovalov RN — brain imaging testing design; Lagoda OV — clinical assessment; Krotenkova MV — brain imaging testing management; Shabalina AA — biochemistry testing design; Tanashyan MM — clinical assessment management, general study design.

Compliance with ethical standards: the study was approved by the Ethics Committee of the Research Center of Neurology (protocol No. 5-6/22 dated 1 June 2022). The informed consent was submitted by all study participants.

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Received: 29.07.2025 **Accepted:** 13.08.2025 **Published online:** 21.08.2025

DOI: 10.24075/brsmu.2025.038

СВЯЗЬ УСТОЙЧИВЫХ СОЧЕТАНИЙ САЛИВАРНЫХ КАТЕХОЛАМИНОВ С ОРГАНИЗАЦИЕЙ ЦЕРЕБРАЛЬНЫХ ФУНКЦИЙ У БОЛЬНЫХ ХРОНИЧЕСКОЙ ИШЕМИЕЙ МОЗГА

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Исследование роли катехоламинов (КА) в церебральной организации функций у больных хронической ишемией мозга (ХИМ) актуально, поскольку известна их значительная роль как нейромедиаторов, а также связь с уровнем стресса и кортизолом. Целью работы было изучить влияние устойчивых сочетаний дофамина (ДА), норадреналина (НА) и адреналина (АДР) на организацию церебральных функций. Исследование выполнено на 76 больных ХИМ, с использованием данных фМРТ (n = 21), которые с помощью программ SPM-12 и CONN-18 преобразовывали в сетевую структуру. Оценку уровня значимости проводили с учетом множественности сравнений. Стабильные комбинации КА, отражающие взаимную положительную корреляцию ДА, НА и АДР, существенно влияли на церебральную организацию больных ХИМ. Комбинации КА были связаны с показателями саливарного кортизола ($F = 4,8$; $p = 0,038$) и памяти ($F = 7,5$; $p = 0,011$): повышение КА было ассоциировано с повышением кортизола и ухудшением показателей памяти. По данным фМРТ найдены различия в коннективной организации больных ХИМ с высоким и низким уровнем всех трех КА. Для пациентов с содержанием КА ниже значения медианы характерно наличие замкнутых нейронных сетей, распространяющихся на оба полушария головного мозга, что способствует интеграции и сохранению информации. Предполагается, что такие сети могут иметь связь с механизмами долговременной потенциации, играющими важную роль в процессах памяти и изменениями силы синаптической связи. Таким образом, использование неинвазивных методов биохимического анализа, а также фМРТ позволило получить новые данные о кольцевой организации нейросетей мозга, связанной с устойчивыми комбинациями КА. Подобная организация нейросетей, по-видимому, влияет на когнитивные функции. Высокий уровень катехоламинов у больных ХИМ связан с повышением уровня кортизола и ухудшением памяти и снижением коннективности нейросетей мозга.

Ключевые слова: катехоламины, дофамин, норадреналин, адреналин, хроническая ишемия мозга, церебральные функции, коннективности, фМРТ, нейросети

Вклад авторов: В. Ф. Фокин — написание статьи; Д. А. Абаимов — проведение биохимических исследований; Н. В. Пономарева — дизайн физиологических и нейропсихологических исследований, общий дизайн работы; Р. Б. Медведев — допплерографические и клинические исследования; Р. Н. Коновалов — дизайн нейровизуализационных исследований; О. В. Лагода — клинические исследования; М. В. Кротенкова — руководство нейровизуализационными исследованиями; А. А. Шабалина — дизайн биохимических исследований; М. М. Танашян — руководство клиническими исследованиями, общий дизайн работы.

Соблюдение этических стандартов: исследование одобрено локальным этическим комитетом Российского центра неврологии и нейронаук (протокол No 5-6/22 от 1 июня 2022 г.). Все участники обследований подписали добровольное информированное согласие.

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Статья получена: 29.07.2025 **Статья принята к печати:** 13.08.2025 **Опубликована онлайн:** 21.08.2025

DOI: 10.24075/vrgmu.2025.038

Catecholamines (CAs) represent a group of bioactive substances playing an important and sometimes crucial role in regulation of various body's physiological processes. These belong to the class of monoamines and include three major compounds: dopamine (DA), norepinephrine (NA), and adrenaline (ADR). All CAs are synthesized from the amino acid tyrosine. The sequence of CA synthesis is as follows: tyrosine — dioxyphenylalanine (DOPA) — dopamine — noradrenaline — adrenaline. CAs are produced primarily by adrenal glands, as well as in the neurons of the central and peripheral nervous systems. The above CA synthesis pathway is referred to as classic or major CA synthesis pathway. Non-classic synthesis pathways (for example, from microbiome) are insufficient to have an effect on the CA content in the brain or body as a whole.

Common CA functions include regulation of mood and emotional state. Dopamine is often associated with the feeling of pleasure and reward. NA and ADR represent the key components of stress response. These alter cardiac output and heart rate, contribute to dilation of blood vessels in certain regions [1].

CA functions are related to their molecular organization: DA acts primarily on dopamine receptors, affecting motor functions, attention, and motivation. DA has an impact on the functions associated with reward, mood, and motion, playing a role in motor control.

NA is involved in stress responses and is in demand for increasing attention and alertness. It acts on the alpha and beta adrenergic receptors, contributing to blood pressure increase, heart rate increase, and better concentration. ADR triggers bronchial dilation, blood glucose level increase, and metabolic activity enhancement. ADR is responsible for acute stress reactions, ensuring rapid physical activity increase (heart rate increase, blood pressure elevation, and increased blood supply to muscles). One more important aspect associated with the CA common origin is the lack of negative correlations between distinct CAs and tyrosine. Some indirect negative regulation methods have been found, for example due to competition for common receptors, but the role of such regulation is minor. Such features of CA metabolism result in mostly positive correlations between DA, NA, and ADR [1, 2].

Salivary catecholamine levels may vary depending on various factors, such as time of the day, health status, fact of having stress, and sample collection method. A certain role is played by the method to determine the CA content. According to the literature data provided by different authors, the CA content varied between several pg/ml and tens of ng/ml [3–5]. Since salivary CAs are very variable, it seems reasonable to consider relative, mostly qualitative, but not quantitative indices.

Catecholamines are easily detected in human saliva, but the origin of those is poorly understood. The majority of papers report that CAs enter the salivary glands through the bloodstream. It has been shown that some CAs, for example NA found in human saliva, come both from the bloodstream and sympathetic nerves of the salivary glands [5].

The common source of CAs suggests mutual conditioning of those. However, the associated influence of catecholamines on brain function is still poorly understood. With mutual correlations of distinct CAs, resulting, in particular, from their common origin, a synchronized CA alteration can be observed [6]. In this regard, the study aimed to assess the impact of salivary CA combinations on connectivity of the brain neural networks, memory indices, and cortisol levels, when the quantity of all three CAs is above or below median, in patients with chronic cerebral ischemia (CCI), the disorder characterized by chronic disorder of cerebral circulation and the related diffuse or focal brain lesions, as well as cognitive and neurological deficits. The diagnosis of CCI is established based on the comprehensive assessment of clinical, instrumental, and neuropsychological data [7–10] (for details see Methods).

METHODS

The study involved 76 patients with CCI (42 females and 34 males aged 58–82 years). Salivary levels of catecholamines (DA, NA, ADR) were assessed. The patients were different from each other mostly in quantitative characteristics of memory impairment, performance, irritability, brainstem symptoms, etc. The main CCI etiological causes were as follows: atherosclerosis, hypertension (including hypertensive heart disease), venous insufficiency, diabetic angiopathy, vasculitis of various etiology, blood disorders, etc. Inclusion criteria: initial manifestations and subcompensated CCI; no need for permanent care from others in patients' daily life. Exclusion criteria: dementia severity score 1 or more (Clinical Dementia Rating) [11]; history of acute cerebrovascular accident, traumatic brain injury, severe cardiac or metabolic disorder (type 2 diabetes mellitus); renal failure, uncompensated thyroid dysfunction. All patients were right-handed.

The diagnosis of CCI was established based on the comprehensive assessment of clinical, instrumental, and neuropsychological data. Cognitive deficits represent the key sign of CCI often manifested by mild cognitive impairment. Assessment involved the use of neuropsychological tests: mini-mental state examination (MMSE) for general cognitive function assessment; Montreal Cognitive Assessment (MoCA test) more sensitive to mild impairment, especially affecting executive functions and attention; Luria's verbal memory tests.

Typical CCI symptoms were as follows: deterioration of memory, attention, decreased information processing speed, executive function (planning, decision making) impairment.

Structural MRI was focused on determining the white matter damage extent (leukoaraiosis). Fazekas score was used to estimate the damage severity.

MRI was used to detect lacunar infarctions, small foci (3–15 mm) in deep brain structures (basal ganglia, thalamus, pons). Mild-to-moderate ventricular dilation or cortical atrophy was one more CCI sign.

Neurological assessment revealed motor and sensory deficits typical for CCI: mild hemiparesis, dysmetria, reflex asymmetry, abnormal reflexes (for example, Babinski's sign); gait disorders; autonomic nervous system dysfunction, such as orthostatic hypotension; extrapyramidal symptoms, such as tremor.

Neuropsychological testing was used to clarify the nature and severity of cognitive impairment affecting memory (verbal, visual), executive functions, speech activity, visual-spatial abilities.

Differential diagnosis with neurodegenerative disorders took place.

fMRI

A total of 21 patients underwent T2* weighted resting state fMRI of the brain in order to record BOLD signal in the Magnetom Verio magnetic resonance imaging scanner (Siemens, Germany) with the magnetic field strength of 3.0 Tesla. Functional scans were acquired in the resting state using the T2* weighted EPI sequence: TR = 1500 ms, TE = 30 ms, flip angle 70°, slice thickness 2 mm, FOV 190 mm, FOV phase 100.0%. The patients were previously instructed to relax as much as possible, lay still with the eyes closed (to avoid stimulation of visual sensory system), not to think about anything in particular. MRI data were processed using the SPM12 software in the MATLAB computing environment. The CONN-18b application being part of the SPM-12 toolbox was used to assess connectivity.

Biochemical tests

Determination of salivary catecholamines. Salivary levels of monoamines, including DA, NA, ADR, and their metabolites were determined by high performance liquid chromatography (ion pair chromatography) with electrochemical detection (HPLC-ED) using the System Gold liquid chromatography system (Beckman Coulter Inc., USA) equipped with the RECIPE EC 3000 electrochemical (amperometric) detector (RECIPE Chemicals + Instruments GmbH; Germany), with the Rheodyne 7125 injector, 20 µL sample loop. Catecholamines were separated by chromatography on the reverse-phase Nucleodur C18 Gravity column, 4.6–250 mm, pore diameter 5 µm (Mashery-Nagel GmbH & Co. KG, Germany). The System Gold 125 pump (Beckman Coulter Inc., USA) was used; the mobile phase flow rate was 1 mL/min at the pressure of 200 atm. atm. The mobile phase for catecholamine separation was as follows: 0.1 M citrate-phosphate buffer containing 1.1 mM of octanesulfonic acid, 0.1 mM of EDTA, and 9% of acetonitrile (pH 3.0). Measurement was performed using the RECIPE EC 3000 electrochemical detector (RECIPE Chemicals + Instruments GmbH; Germany) equipped with the ClinLab ECD-Cell, Model Sputnik, glassy carbon working electrode (+ 0.85 V), and silver chloride reference electrode Ag/AgCl. Prior to chromatography, catecholamines were isolated from saliva by solid phase extraction using the activated aluminum oxide as an extractant.

The patients' salivary cortisol levels were determined with the Abbott i2000 ARCHITECT immunochemiluminescence analyzer (Abbott Laboratories, Illinois, USA) using the reagent kits of the same brand.

Saliva samples were collected in accordance with the previously reported protocol [9]. The patients did not drink alcohol for a week, tea or coffee for 1 h before saliva collection; they rinsed their mouth with water 10 min before this. Saliva collection was accomplished through spitting into a test tube with the volume of at least 1.5 mL. Saliva samples contaminated with blood were excluded from the study. For that the ELISA kit for detection of saliva contamination with blood was used [12].

Other tests

The patients were tested for verbal memory using the Luria's test involving control of immediate and delayed recall of 10 words. They were through verbal fluency test, correction test. Furthermore, blood pressure was recorded, pulse pressure (difference between systolic and diastolic blood pressure) was calculated, and heart rate was registered.

Statistical analysis

The data obtained were analyzed using the Statistica-12 software package (Dell, USA). The distribution was tested for normality using the Kolmogorov–Smirnov test and Lilliefors test. The mean and standard error were calculated, and one-way analysis of variance and correlation analysis were performed. Spearman's rank correlation coefficient was calculated. To analyze neural networks, Student's *t*-test was also calculated, and adjustment for multiple comparisons was applied — FDR (False Discovery Rate).

RESULTS

CA content distribution: the salivary DA, NA, and ADR distribution associated with chronic cerebral ischemia was significantly different from normal (Gaussian) distribution (Fig. 1).

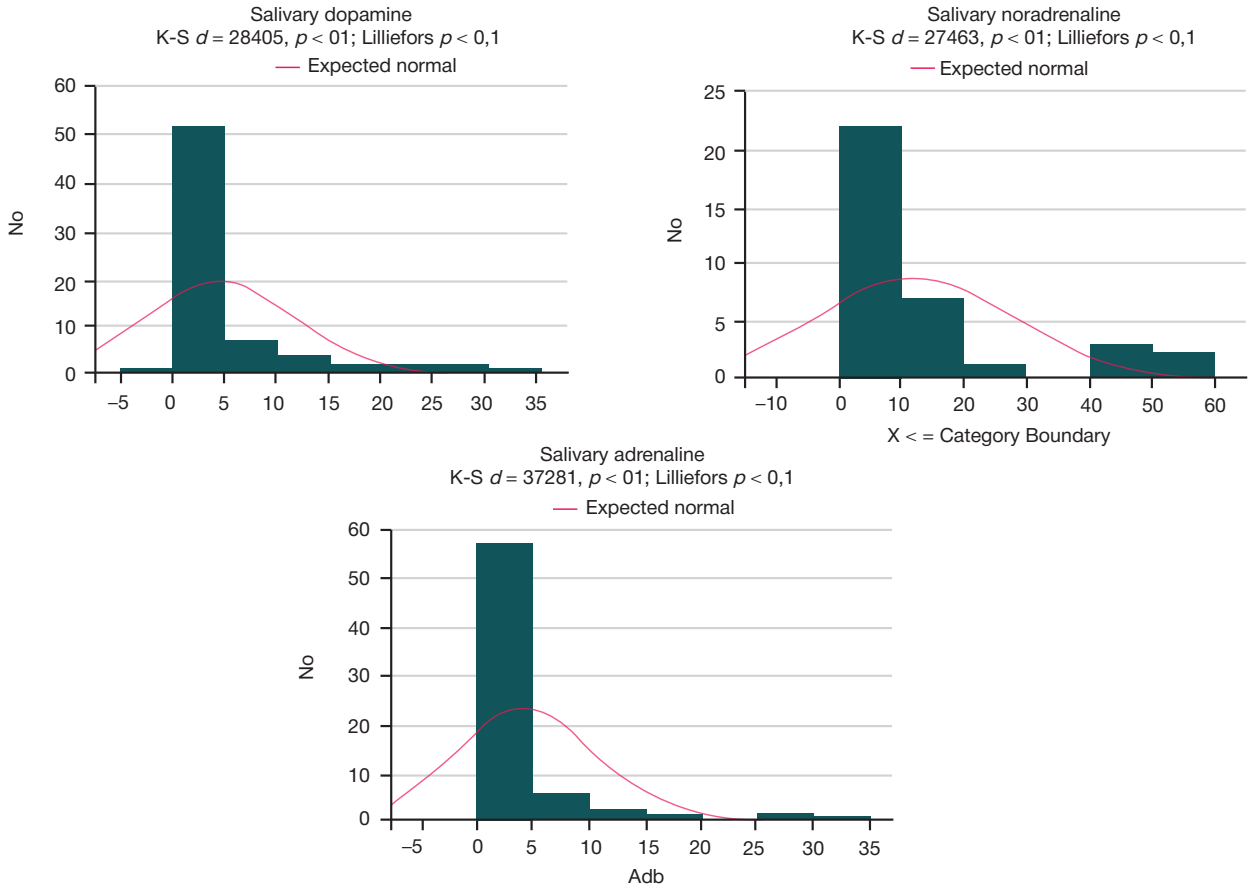

Fig. 1. Bar charts of salivary dopamine, norepinephrine, and adrenaline distribution (ng/mL). Vertical axis (Y) — number of subjects; horizontal axis (X) — catecholamine concentration (ng/mL). K-S — Kolmogorov–Smirnov test, Liliefors — Lilliefors test

Table 1. Spearman's rank correlation (R)

Pair of variables	Number	Spearman's rank correlation coefficient(R)	t(N-2)	*p*-value
NA & ADR	76	0.511801	5.12474	0.000002
NA & DA	65	0.509447	4.699123	0.000015
ADR & DA	62	0.490695	4.362181	0.000051

Note: NA — norepinephrine; ADR — adrenaline; DA — dopamine; R — Spearman's rank correlation coefficient; t — Student's *t*-test; *p* — significance level.

The Kolmogorov–Smirnov test and Lilliefors test values suggest significant difference of experimental distributions from normal (Gaussian) distribution. Fig. 1 presents bar charts of the distribution of salivary dopamine, norepinephrine, and adrenaline. The range of changes of these monoamines is consistent with the above literature data [3–6].

Distribution of various catecholamines in saliva was generally close to log-normal. For testing, logarithms of all baseline values were taken. It was found that based on the Kolmogorov–Smirnov test d (maximum difference between the theoretical and empirical distributions) was as follows: for NA $d = 0.069$; for ADR $d = 0.086$; for DA $d = 0.092$. P-values > 0.2 obtained for these logarithmic distributions suggest that there is no reason to believe that these logarithmic distributions are different from normal for the test CAs.

Due to the common origin, contingency of catecholamines between pairs of CAs in the background is not surprising. Table 1 presents the correlation coefficient values obtained when using nonparametric rank statistics.

The use of Spearman's rank correlation analysis revealed a moderate positive correlation between all CA pairs. All the rank correlation coefficients were significantly different from zero (Table 1). The squared correlation coefficient demonstrates the share of the influence or factors explaining variation of a single variable through the relationship with another one, since it shows what proportion of the overall variability of a variable is due to the linear relationship with another variable. That is why the share of factors determined by joint effects of CAs on each other is about 25%. Such contingency suggests that in patients with chronic cerebral ischemia the probability of having high (or low) levels of all three catecholamines at once is higher, than the probability of having any other inconsistent combination of CA levels.

All patients were divided into two subgroups: in each subgroup, CA content was above or below median.

The share of cases, when the levels of all three CAs were above or below median, was slightly more than a half (28 cases out of 50 possible). This means that the conditions, when all three CAs at once are above or below median levels, account for at list a half of all possible variants. The median value for dopamine was 1.447 (min — 0; max — 30.341) ng/mL; for norepinephrine — 5.577 (min — 0.954; max — 56.647) ng/mL; for adrenaline — 2.408 (min — 0.057; max — 90.257) ng/mL.

The number of patients with the levels of all three CAs below median was 13 (group 1), and that of patients with the levels of all three CAs above median was 15 (group 2).

Groups 1 and 2 differed from each other in that the levels of all three CAs were below or above median. Patients of these groups were significantly different based on the number of psychophysiological characteristics. Thus, patients of group 1 had significantly lower cortisol levels, and their delayed word recall scores (Luria's test) were better, than that of group 2 representatives (Fig. 2).

Such differences in psychophysiological characteristics of two groups support the idea that there are differences in cerebral organization of these patients. To estimate the differences in cerebral organization of groups 1 and 2, we assessed connectivity difference in the groups with the levels of all three CAs below or above median: group 1 — group 2.

Considering False Discovery Rate (FDR), all the connectivities, that were different with lower CA levels, were significantly higher, than with higher CA levels (Fig. 3).

We chose not the conventional pFDR < 0.05, but the lower significance level pFDR < 0.02, to consider more significant patterns, in which the plethora of connectivities of two groups were different (Fig. 3).

Thanks to the cyclic (closed) organization of the connections (Fig. 3) most common in group 1 with the lower CA levels, stable excitation circulation is generated engaging the large

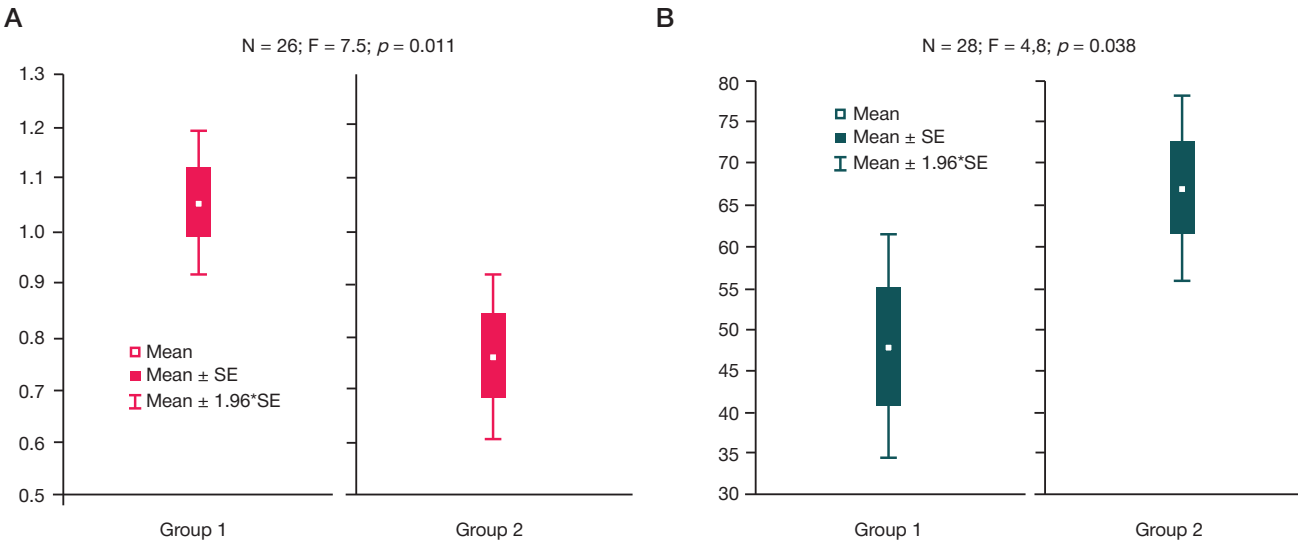

Fig. 2. Differences in memory characteristics **(A)** and salivary cortisol levels **(B)** in two groups with different CA values. N — number of subjects; F — F-test; *p* — significance level. **A**. The vertical axis shows delayed word recall relative to the average level of direct recall of 10 words (Luria's test). **B**. The vertical axis shows salivary cortisol levels (nmol/L)

number of neural centers, which contributes to more optimal functional organization of the brain, as also confirmed by the results of psychophysiological tests (Fig. 2).

Circulation of excitation is possible, for example, in the following chain of the neural structures linked with the common excitation process synergy:

Cerebellum (including the Vermis) — right lateral sensotimotor network (Sensori Motor Lateral) — left superior frontal gyrus (SFG) — left supramarginal gyrus (SMG) — cerebellum. This circuit engaging both hemispheres can maintain generalized synchronization of excitation processes.

DISCUSSION

In our studies, salivary cortisol and catecholamine levels were determined by biochemical methods. According to the literature data, salivary levels of these substances in individuals with CCI are considerably higher, than in healthy individuals. In the morning, salivary cortisol levels usually reach a few to tens of nmol/L (the levels of about ~10–20 nmol/L are often reported in the literature). Higher values are reported for CCI. In this study, cortisol levels associated with CCI were about 3–3.5 times higher compared to normal based on the literature data [12–14].

In CCI, an upward trend of salivary catecholamine levels is reported, which reflects enhancement of sympathetic activity and impaired vascular regulation. However, measurement in saliva requires standardization for clinical use. The difficulty is that catecholamine measurement has not been standardized, and only a few authors report exact numbers: normal salivary noradrenaline are 20–30 pg/mL, and adrenaline levels are approximately 3–4 pg/mL [5]. Another paper reports rough equivalence of adrenaline and norepinephrine (0.1 pmol/L) [4], and dopamine level is approximately 0.5 pmol/L [4–5].

Traditionally, assessment of distinct CAs is often considered without taking into account their association with other ones. Such an approach has the following shortcoming: since CAs are related due to common origin, it is rather difficult to isolate the features of distinct CAs, and in some cases these should be considered in combination with other CAs. The CA activity largely reflects the functional state of the brain, for example, due to positive correlation between the levels of some CAs (ADR and NA) and cortisol levels. One variant of the “contextual” consideration is the above analysis of the synchronized CA states. Such functional states affect both cognitive and metabolic indices, especially the ones associated with stress severity. The range of CA changes is different on both sides of the median. This is probably due to the fact that CA production is altered under exposure to stress, and dysfunction of the negative feedback mechanism limiting the release of CAs is possible, which can also be due to stress [15, 16]. In healthy individuals, the quantity of CAs released by the adrenal glands and sympathetic nervous system is regulated by the negative feedback mechanisms. When a certain CA level is reached, further CA production is inhibited, which prevents excess activation of the sympathoadrenal system. In prolonged or chronic stress, permanent stimulation of the sympathetic nervous system and adrenal glands is observed. This results in the permanently high blood catecholamine levels. The negative feedback mechanism begins to fail, i.e. the control over adrenaline and norepinephrine production is lost, which leads to negative effects on the brain function.

The main distinctive feature of the brain's connective organization in the group with lower CA levels is the presence of the closed circuit of connectivities, which can result in the prolonged potentiation processes. Closed neural networks are networks, in which inputs and outputs represent the closed cycle, ensuring information storage and processing within the closed structure [17]. The neural networks of the patients different in salivary NA levels only were earlier considered; these networks were not cyclic (closed) [18].

It can be assumed that excitation circulation in the closed circuit of neural structures can really maintain synergetic processes between various brain regions. Consider some characteristic features of this circuit.

It is well known, that the cerebellum plays a key role in motor coordination and maintaining balance. It is also involved in cognitive functions, such as learning and memory. Its capability of integrating sensory information and motor output makes it an important link of this circuit. The cerebellum also can integrate information from various sensorimotor sources, ensuring coordination between various body parts and modulating the activity of cortical structures. The link between the right lateral sensorimotor network and the left cortical structures (superior frontal gyrus and supramarginal gyrus) can be associated with the mechanisms underlying cross-modal sensory processing, enabling processing and integration of information from both sides of the body and sensory inputs. Furthermore, the left superior frontal (SFG) and supramarginal (SMG) gyri are involved in higher cognitive functions, such as attention, problem-solving, and planning. Excitation increase in these regions can enhance cognitive information processing and improve the controlled actions related to motor activity. The above chain can effectively use the feedback mechanisms. Excitation initiated in one node can be returned to the previous nodes to ensure stable activity and possible enhancement (potentiation)

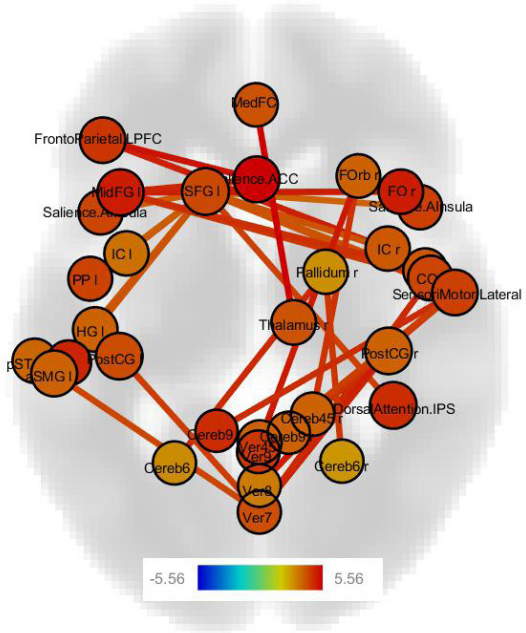

Fig. 3. Connectivity difference with the more low and high levels of all catecholamines (group 1 — group 2), pFDR < 0.02. There is a Student’s t-test color chart below the figure. r, l — right and left hemispheres; Ver — Vermis, Cereb — cerebellum; digits following Ver, Cereb — share of the vermis or cerebellum; AC — Cingulate Gyrus anterior part; ACC — Anterior Cingulate Cortex; Cuneal — Cuneal Cortex; CO — Center Operculum Cortex; Forb — Frontal Orbital Cortex; HG — Heschl’s Gyrus; IC — Insular Cortex; sLOC — Lateral Occipital Cortex superior division; MedFC — Frontal Medial Cortex; PC — Cingulate Gyrus posterior division; aPaHC — Parahippocampal Gyrus anterior division; PaCiG — Paracingulate Gyrus; PostCG — Postcentral Gyrus; PreCG — Precentral Gyrus; PP — Planum Polare; SMA — Juxtapositional Lobule; SFG — Superior Frontal Gyrus; aSMG — aSTG — Superior Temporal Gyrus anterior division; toITG — Inferior Temporal Gyrus temperooccipital division; toMTG — Middle Temporal Gyrus temporooccipital part

of synaptic strength in these areas. Such a “closed contour” can contribute to the neuronal activity synchronization between various brain regions, which is important for maintaining behavior stability and motor coordination. Excitation circulation can contribute to alteration of structure at the synaptic level, since repeated activation can result in the processes related to synaptic plasticity (such as long-term potentiation and long-term depression) that can strengthen the connections between appropriate neuronal structures.

Thus, excitation circulation in the above neural circuit demonstrates a complex interplay between motor coordination and cognitive processing. Such interplay can maintain effective functioning in both sensorimotor and cognitive spheres, ensuring a synergistic mechanism for adaptation and learning. In the closed circuits of connectivities, such as neural networks, excitation can circulate, generating repeated launches of neuronal activity. This process can contribute to the long-term potentiation through the following mechanisms.

1. Enhanced neuronal activation. Prolonged excitation circulation can maintain high intracellular calcium levels in the neurons. The increase in calcium levels contributes to more potent release of neurotransmitters and enhances synaptic transmission being the most important component of both short-term and long-term synaptic plasticity [19].

2. Creating positive feedback. In the closed circuit, excitation can result in active return of the signal through the excitatory synapses. Such a mechanism can yield the state contributing to potentiation, since the neurons connected are still activated, which enhances transmission of information and prepares synapses for further activation [20].

3. Neuronal activity modulation. Mutual modulation of neurons in the circuit can result in the long-term synaptic strength modulation, which provides the basis for synaptic plasticity. This phenomenon, in turn, contributes to the long-term potentiation [21]. Synaptic strength is a measure of the effectiveness of signal transmission between neurons at the synaptic level. Synaptic strength determined by how much a postsynaptic neuron responds to the presynaptic neuron activation reflects the amount of neurotransmitters released into the synaptic cleft, as well as the sensitivity of postsynaptic receptors to these neurotransmitters.

Potentiation can be modulated via different mechanisms, such as upregulation of receptors or synaptic structure alteration, which can consolidate changes in the neural network related to the learning and memory processes.

Thus, it can be assumed, that prolonged excitation circulation in the closed circuit can maintain the conditions for long-term potentiation. This is especially important in the context of neuroplasticity, learning and memory processes, since alteration of synaptic transmission can result in the lasting neural network alteration.

However, elevated cortisol and catecholamine levels disturb blood supply to the brain and cause cessation of excitation circulation in the neural networks of the brain [22].

CONCLUSIONS

We have revealed a significant correlation between stable salivary catecholamine combinations and organization of cerebral functions in patients with chronic cerebral ischemia. The findings confirm that comprehensive simultaneous analysis of salivary DA, NA, and ADR levels can be an informative marker of the brain functional state associated with this disorder. In the group of patients with CCI showing high contingency of salivary CAs with the relatively low CA levels (below median), the presence of closed neural networks was reported. It is assumed that such networks can contribute to higher long-term potentiation, possibly through which this group of patients has higher cognitive indices. High catecholamine and cortisol levels associated with disturbances of blood supply to the brain negatively affect connectivity of the brain neural networks. The noninvasive method to assess catecholamines and the qualitative analysis of those can be useful for investigation of the brain network organization associated with the cerebrovascular disease.

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