CEREBRAL NEURAL NETWORKS IN CASES OF CONCOMITANT CHRONIC CEREBRAL ISCHEMIA AND TYPE 2 DIABETES MELLITUS

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With type 2 diabetes mellitus (DM2) as a concomitant disease, chronic cerebral ischemia (CCI) has a more severe course because of chronic hyperglycemia. Using resting state functional MRI (fMRI) data, this study aimed to investigate connectivity of cerebral neural networks in patients that have CCI with DM2 and without DM2. The study involved 257 CCI patients (81 male and 176 female, aged 50-85 years) some of whom had DM2. We assessed metabolic parameters, state of cerebral circulation, and cognitive functions. Resting fMRI was used for the analysis of structure of connectivity of cerebral neural networks. With false discovery rate (FDR) factored in, CCI patients with DM2 had values of some indicators of connectivity of cerebral neural networks at a level significantly lower than CCI patients without DM2 ($p_{(FDR)} < 0.05$). Namely, the indicators in question were those of connectivity of right hemisphere's speech neural network, left hemisphere's parahippocampal region, and angular gyrus of the right hemisphere, which is an integral part of the brain's passive mode network. Also, CCI patients with DM2 had significantly poorer connectivity of anterior cingulate gyrus, part of the salient neural network, and superior temporal gyrus. There are significant changes in the cerebellar networks, too. Overall, the size and intensity of most of the neural networks studied in resting state are lower in CCI patients with DM2.

Keywords: chronic cerebral ischemia, type 2 diabetes mellitus, resting state functional MRI, connectivity, size and intensity of neural networks

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Compliance with ethical standards: the study was approved by the local Ethical Committee of the Research Center of Neurology (Minutes #5-6/22 of June 1, 2022). All participants submitted signed informed consent forms.

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НЕЙРОСЕТИ ГОЛОВНОГО МОЗГА ПРИ СОЧЕТАНИИ ХРОНИЧЕСКОЙ ЦЕРЕБРАЛЬНОЙ ИШЕМИИ И САХАРНОГО ДИАБЕТА 2-ГО ТИПА

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Хроническая ишемия головного мозга (ХИМ), осложненная сахарным диабетом 2-го типа (СД2), характеризуется более тяжелым течением, связанным с хронической гипергликемией. Цель работы — исследовать организацию коннективности нейросетей мозга по данным функциональной магнитно-резонансной томографии (фМРТ) покоя у пациентов с ХИМ, страдающих диабетом 2-го типа, по сравнению с больными ХИМ без диабета. В исследовании приняли участие 257 пациентов: 81 мужчина и 176 женщин в возрасте 50–85 лет с ХИМ, часть из которых болели СД2. Оценивали метаболические показатели, состояние мозгового кровообращения, а также когнитивные функции. С помощью фМРТ покоя анализировали коннективную организацию нейросетей мозга. У больных ХИМ с СД2 показатели коннективности ряда нейросетей мозга с учетом поправки на множественность сравнений FDR (False discovery rate) статистически достоверно снижены ($p_{(FDR)} < 0,05$) по сравнению с больными ХИМ без СД2. Это коннективности речевой нейросети правого полушария с парагиппокампальной областью левого полушария и с угловой извилиной правого полушария, которая является составной частью сети пассивного режима работы мозга. Коннективность передней поясной извилины, входящей в салиентную нейросеть, с верхней височной извилиной была значимо ниже у больных ХИМ с СД2. Достоверные изменения затрагивают и мозжечковые сети. В целом, размер и нормированная интенсивность большинства исследованных нейросетей покоя ниже у больных ХИМ с диабетом.

Ключевые слова: хроническая ишемия мозга, сахарный диабет 2-го типа, функциональная МРТ покоя, коннективность, размер и интенсивность нейросетей

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Chronic cerebral ischemia (CCI) is a disease that degrades the flow of blood to the brain through main and small arteries, which leads to various cerebral disorders. As a rule, CCI develops in old and senile age. The typical concomitant conditions are narrowed cerebral arteries that are also growing less elastic due to atherosclerosis, hypertension, diabetic angiopathy, and other pathological processes. Comorbidity of CCI and type 2 diabetes mellitus (DM2) is common. DM2 aggravates ischemic

brain damage, but the effect of this comorbidity on cerebral connectivity has not been studied sufficiently [1].

Excess glucose in patients with DM2 can cause neuron degeneration and the related neurological diseases and cognitive impairments. High blood glucose levels affect cells that can regulate its intake only in a limited fashion. These are, first of all, endothelial cells, as well as neurons of the peripheral and central nervous system [2]. Spikes in glucose levels modify microglial activity, which contributes to the development of inflammatory processes [3]. Chronic hyperglycemia causes a number of pathophysiological changes that aggravate its toxic effects on cells, tissues and organ systems. Some neurons begin to oversecrete neurotransmitters, including glutamate, one of the most common excitatory neurotransmitters that can have an excitotoxic effect [4]. Excess glucose dampens the ability of neurons to process information and disrupts interneuronal contacts. In part, this may be due to lower levels of glucose in the intercellular space, which conditions interaction between neurons [5–7]. There is evidence that brain plays an active role in glucose homeostasis, but the relative importance of this factor in comparison with others is still unclear [8].

Glucose is delivered to brains cells by transporter proteins, including Glut1 and Glut2, which facilitate glucose transfer across cell membranes. Insulin resistance associated with DM2 can handicap glucose's ability to enter brain cells, which hampers cerebral energy metabolism. Studies that employed positron emission tomography have shown that this compromises glucose metabolism in certain areas of the brain, such as prefrontal cortex and hippocampus, which are important for cognitive functions, memory, and decision-making. For example, it has been shown that, compared to healthy individuals, DM2 patients have less glucose metabolized in the prefrontal cortex, which translates into lower scores in cognitive tests. There is also evidence that this disease can disrupt mitochondrial dysfunction in the brain, which, again, translates into lower cognitive test scores as compared to those shown by people that do not have DM2 [9–12].

Disrupted glucose metabolism is associated with restructuring of interneuronal connections, which should be investigated in order to understand how the brain of CCI patients with DM2 works. Some studies designed for this purpose employ functional magnetic resonance imaging (fMRI), which allows examining connectivity, i.e., functional connections between different areas of the brain; such neuroimaging enables progress in neurology today [13]. Many published papers describe features of the structural and functional organization of the brain of CCI patients with DM2, but few address connectivity changes therein as registered with resting fMRI. BOLD signal is the ratio between oxidized and reduced forms of hemoglobin. It is assumed that synchronization of BOLD signals in different areas of the brain reflects synchronization of neural activity therein. This assumption has proven effective in practice, thus, the respective approach allows investigating communications between different areas of the brain. Assessment of synchronization of the BOLD signals yields quantification of the strength of interneuronal connections, and shows if the interaction is positive or negative.

Against the background of CCI, disruption of cerebral circulation can have significant consequences for functioning of the central nervous system, including deterioration of cognitive abilities and an increased risk of stroke. With DM2 as a concomitant disease, patients run a higher risk of microvascular and macrovascular complications, including ischemic stroke and small vessel disease, which significantly aggravates the overall pathogenic effect of the vascular dysfunction, and reduces the effectiveness of interactions between different regions of the brain [14].

Using the resting fMRI data, this study aimed to investigate connectivity of cerebral neural networks in patients that have CCI with DM2 and without DM2. We sought to understand the potential impact of DM2 on the organization of connectivity in a brain of a CCI patient, and assess the role comorbidity of these diseases plays in the development of cognitive and other disorders associated with CCI, such understanding and assessment potentially enabling development of the new methods of treatment and prevention of these diseases.

METHODS

The study involved 257 patients, 81 male and 176 female, aged 50–85 years, all diagnosed with CCI (Table 1). Part of them, 80 people (31%), also had DM2. Table 1 presents demographic characteristics of the participants. The average duration of CCI was 10.1 ± 0.7 years. The patients were divided into two groups: without DM2 (group 1) and with DM2 (group 2). The key causes of CCI were atherosclerosis, arterial hypertension, venous insufficiency, diabetic angiopathy, vasculitis of various etiologies, etc. The duration of DM2 was 15.8 ± 1.1 years; no patient had severe macrovascular complications nor ran the risk of severe hypoglycemia. The inclusion criteria were: initial manifestations and subcompensation of CCI, no need for constant care from others [15–17]. The exclusion criteria were: score 1 up dementia as per the Clinical Dementia Rating Scale [18], a history of acute cerebral circulatory disorders, traumatic brain injuries, severe cardiac, renal insufficiency, uncompensated thyroid dysfunction. All the patients were right-handed.

Body mass index (BMI) was higher in both male and female patients with DM2 (p = 0.006 and p = 0.009, respectively). There were significantly more men that graduated from an higher education establishment than women (both groups; $p < 0.01$).

There were no differences in statistical BMI, age indicators for men and women in both groups; the number of male participants in the groups was similar (difference insignificant). Thus, it is possible to investigate the organization of neural networks in combined groups.

Table 1. Demographic characteristics of CCI patients with DM2 and without DM2

	Number of men	Number of women	BMI, men	BMI, women	Age, men	Age, women	Education higher / secondary, men	Education higher/secondary, women
CCI patients w/o DM2 (group 1)	59	120	27.1 ± 0.5	27.6 ± 0.5	64.7 ± 1.4	67.2 ± 0.7	*35/23	57/52
patients with DM2 (group 2)	23	57	*30.2 ± 1.3	*30.2 ± 0.9	67.2 ± 2.1	68.9 ± 1.1	*14/8	24/25

Note: the table shows mean values ± standard errors.

Table 2. Biochemical, psychometric, and hemodynamic indicators significantly different in the two groups of CCI patients (with and without DM2), as revealed by ANOVA, as well as means and standard errors of the indicators

	Analysis of Variance (ANOVA)			Mean ± standard error	
	n	F	*p*	Group 1	Group 2
Glucose, mmol/l	257	154.9	0	5.2 ± 0.03	7.1 ± 0.22
Triglycerides, mmol/l	247	24.4	0.000001	1.4 ± 0.005	1.9 ± 0.12
IL6, pg/ml	112	4.1	0.045333	157.03 ± 8.2	188.95 ± 14.2
ESR, mm/hour	248	16.2	0.000075	14.4 ± 0.7	19.5 ± 1.1
Fibrinogen g/l	236	10.9	0.001088	3.6 ± 0.06	3.9 ± 0.08
Left MCA resistance index	92	7.8	0.006389	0.52 ± 0.009	0.57 ± 0.016
LP proofreading test (K = F/A)	242	9.4	0.002424	0.86 ± 0.0106	0.78 ± 0.0229

Note: *n* — number of subjects, F — Fisher's test, *p* — level of significance, MCA — middle cerebral artery, LP — letter patterns, K — proof-reading test success rate.

Resting fMRI

The participants (83 CCI patients, 27 of them with DM2) underwent brain fMRI aimed at registering the BOLD signal. The tomograph was Magnetom Verio (Siemens; Germany), with magnetic field strength of 3.0 Tl. T2 weighted EPI sequence was used to obtain the resting functional scans: TR = 1500 ms, TE = 30 ms, flip angle = 70°, section thickness — 2 mm, FOV = 190 mm, FoV phase — 100.0%. The participants were instructed to fully relax, lie calmly with eyes closed (to exclude stimulation of the visual analyzer) and not think about anything specific. The MRI data were processed in the MATLAB SPM12 software. With the help of CONN-18b application on the SPM-12 platform, we analyzed connectivity in various neural networks of the brain; CONN-18b is an open source toolkit based on MATLAB [19].

Using CONN-18b, we compared connectivity in two groups of CCI patients, with and without DM2. The reliability of differences was assessed by a standardized regression coefficient adjusted for false discovery rate (FDR).

Analysis of the neural networks relied on their two main features, size and intensity. These indicators are convenient and natural tools for describing connectivity graphs [20–22]. Size of a neural network is the number of connections it has to other formations. Its intensity is the sum of T-test values (absolute) describing connectivities of the given neural network. We used normalized connectivity, i.e., the network's intensity-to-size ratio.

Cognitive tests

The patients did a proof-reading test: for 3 minutes, they searched for two adjacent similar letters (letter patterns) in a text without spaces. This test is based on Kirchner's n-back test; in our case, n equaled 1, since at n > 1 the test was difficult for most participants. Evaluating the participants' performance, we factored in the number of letter patterns found as it related to the total number of such combinations and to the number of lines viewed, the total volume of text viewed, and the difference between all letter patterns and the number of patterns found. In addition, patients undertook verbal fluency test, Luria's memory words test and the MoCA test. These cognitive tests were described before [23].

Duplex scanning

At this stage, we evaluated the linear velocity of systolic and diastolic blood flow in the right and left internal carotid, middle cerebral (MCA) and brachial arteries. The system used for the purpose was Toshiba Viamo. To assess systolic linear blood flow velocity and index of peripheral resistance in the arteries, we relied on the generally accepted method and used a linear sensor with a frequency of 5.0–12.0 MHz.

Biochemical studies

The patients donated blood for a blood panel, which assessed levels of glucose, triglycerides, fibrinogen, ESR (erythrocyte sedimentation rate) and other indicators. To learn the level of interleukins, we used saliva samples, same as for cytokines, which were established using a sandwich solid-phase enzyme immunoassay (ELISA). The content of IL6 was determined with the help of Vector-Best kits (Vector-Best; Russia). The measuring range was 1–2000 pg/ml. In all studies, we used calibrators provided by manufacturers of the reagents, and additional calibrators purchased for the purpose.

The study was done in duplicates, on a VICTOR 2 microplate reader (Perken Elmer; USA), using control samples with low and high content of the studied parameters. Saliva samples were collected from the patients; they refrained from alcohol for a week before sampling, did not drink neither tea nor coffee 1 hour before that, and rinsed their mouth with water before spitting at least 1.5 ml of saliva into a test tube. Saliva samples contaminated with blood were excluded from the study, with contamination tested for using an enzyme immunoassay kit [23]. In addition, we registered blood pressure and heart rate.

Statistical data processing

Statistica 12 software package (Dell; USA) was used to statistically process the data acquired. Kolmogorov-Smirnov test was used to establish whether the distribution is normal or abnormal. We calculated arithmetic means, standard errors, and did one-factor variance and correlation analyses. The analysis of neural networks involved determination of Student's *t*-test and adjustment for FDR. The size and normalized intensity of neural networks were evaluated.

RESULTS

The registered difference between patients with DM2 and without it was evident in a number of biochemical, hemodynamic and cognitive indicators, and in the characteristics of inflammatory processes, which point to serious metabolic and other differences in the activity of the brain and the body (Table 2).

The resulting data indicate serious differences between the groups that concern carbohydrate and lipid metabolism (glucose, triglycerides), inflammatory processes (IL6, ESR), hemodynamic parameters and cognitive functions. All the participating patients exhibited high values of inflammation

indicators, but those with DM2 had the respective symptoms more pronounced. The results of proof-reading test in group 2 (with DM2) were inferior to those in group 1.

The revealed differences may have a connection with the organization of neural networks. Figure 1 and Table 3 show data on the cerebral neural networks that had values of all the significantly different connectivities significantly higher in group 1 compared to group 2.

Thus, between the two groups, we identified neural networks that have different connectivity parameters, the difference being significant with p(FDR) < 0.05 factored in. The resulting data indicate that altered connectivities are associated with large neural networks (default network, salient, cerebellar, speech networks). This suggests that potential changes in the organization of neural networks may affect their performance and significant regions of the brain.

Therefore, it can be assumed that with DM2 in the background, rearrangement of connections in the brain extends beyond the four mentioned connectivities; moreover, this disease probably triggers other changes in each network, less significant yet characteristic of most neural networks, which are often disregarded. There are two parameters used to describe a network: its size and its intensity [24]. The latter depends on the former: the larger the size, the higher the intensity. Therefore, it is feasible to consider a normalized neural network intensity indicator, i.e., intensity divided by size. Table 4 presents values of these parameters peculiar to the two groups of this study.

The resulting data suggest that patients with DM2, as a rule, have less significant connectivity indicators than patients not suffering DM2. Moreover, the normalized intensity of most neural networks in them is lower. Based on both parametric and non-parametric criteria, these data are reliable; the latter includes the sign test, which confirms reliability (p < 0.01) of the observation showing that CCI patients without DM2 have greater size and normalized intensity of neural networks than CCI patients with DM2.

Figure 2 presents distribution of connectivities coming out of the dorsal attention network in the right hemisphere.

The right hemisphere's dorsal attention network in group 1 is almost twice as large as that in group 2 (86 and 44, respectively). As for the left hemisphere, the difference in size is only 1.7, but CCI patients without DM2, which comprise group 1, have normalized intensity 2.2 greater than registered in CCI patients with DM2, group 2; this is more than recorded for the right hemisphere (Table 4). The differences in connectivity of this neural network are most noticeable in the frontal medial gyrus of left hemisphere, in the dorsal attention network of right and left hemispheres, in the right half of the cerebellum, in the right parietal region and other regions. However, some of the high-intensity connectivities remain stably high in CCI patients with DM2. This applies, first of all, to the left hemisphere's dorsal attention network, postcentral gyrus, additional motor area of both hemispheres and some other formations.

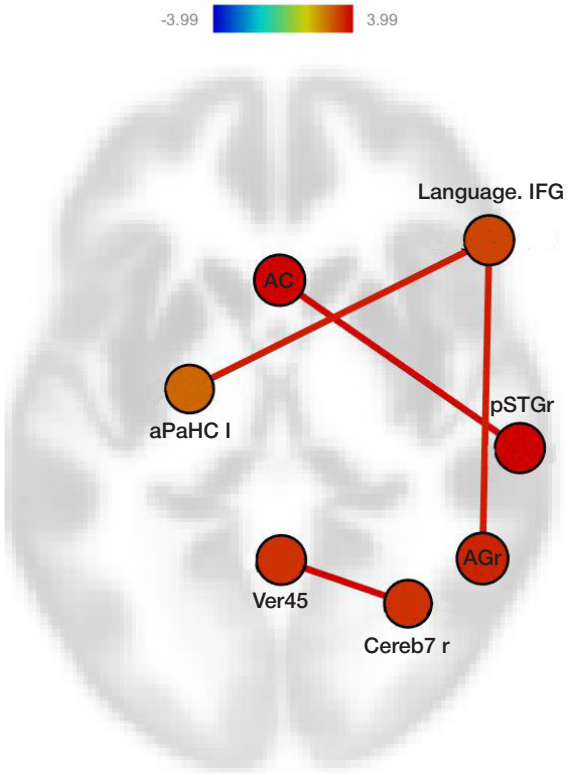

Fig. 1. Statistically significant prevalence of positive connectivities in group 1 (CCI patients without DM2) compared to group 2 (CCI patients with DM2). Distribution of connectivities by brain regions. At the top — T-test color scale. Legend: Cereb — Cerebellum; Ver — Vermis; Language — speech neural network; IFG — Inferior Frontal Gyrus; AC — Cingulate Gyrus, anterior division; pSTG r — Superior Temporal Gyrus, posterior division, right hemisphere; aPAHC l — Parahippocampal Gyrus, anterior division, left hemisphere; AG r — Angular Gyrus, right hemisphere. The numbers after Cereb and Ver are regions of the cerebellum and the vermis.

Comparison of the data from Table 2 shows what changes neural networks' reorganization triggers in carbohydrate, lipid metabolism, inflammation, hemodynamics and cognitive functions. Further studies will help to understand reliability of network reorganization in patients with DM2 as a marker of these changes.

DISCUSSION

DM2 is a common concomitant disease in patients with chronic cerebral ischemia. According to our own research data and published reports, up to a third of CCI patients have DM2 [25]. This disease damages vascular endothelium, which is vitally important with its part in paracrine, endocrine and autocrine functions that maintain normal vascular balance of the body. Endothelium regulates integrity of blood vessels, their permeability, angiogenesis, hemostasis and immune responses. It controls vascular tone, vasodilation and vasoconstriction, migration and proliferation of smooth muscle cells, fibrinolysis

Table 3. Neural networks' connectivity differences prevailing in group 1 compared to group 2

Neural network connectivities	T-test (71)	p(unadjusted)	p(FDR)
Cereb7 r — Ver45	3.99	0.0002	0.0259
AC — pSTG r	3.89	0.0002	0.0364
Language, IFG r — aPaHC	3.62	0.0006	0.0472
Language, IFG r — AG r	3.6	0.0006	0.0472

Note: legend for Figure 1 applies; T-test is a two-tailed sided Student's T-test, numbers in parentheses — number of degrees of freedom; p(unadjusted) — level of significance unadjusted for FDR; p(FDR) — level of significance adjusted for false discovery rate.

Table 4. Quantity of cerebral neural networks' connectivities (size) and their normalized intensity, based on fMRI data, group 1 (CCI without DM2) and group 2 (CCI with DM2)

	Size			Normalized intensity		
Groups	1	2	1–2	1	2	1–2
Default Mode Network, Lateral Prefrontal (L)	105	69	36	5.2	4.8	0.4
Default Mode Network, Lateral Prefrontal (R)	93	60	33	6	5.5	0.5
Sensory Motor Lateral (L)	115	90	25	7.3	6	1.3
Sensory Motor Lateral (R)	114	94	20	7.5	6.1	1.4
Visual Lateral (L)	91	72	19	5.9	5.8	0.1
Visual Lateral (R)	94	67	27	6.1	6.3	–0.2
Salience anterior Insula (L)	95	66	29	6.9	6.7	0.2
Salience anterior Insula (R)	108	83	25	7.1	6.7	0.4
Dorsal Attention, Frontal Eye (L)	55	32	23	5.3	3.1	2.2
Dorsal Attention, Frontal Eye (R)	86	44	42	5	4.9	0.1
Fronto Parietal, Posterior Parietal Cortex (L)	95	103	–8	6.2	4.8	1.4
Fronto Parietal, Posterior Parietal Cortex (R)	70	69	1	6.5	5.8	0.7
Language posterior, Superior Temporal Gyrus (L)	87	57	30	6.1	5.4	0.7
Language posterior, Superior Temporal Gyrus (R)	86	59	27	6.3	5.3	1
Cerebellar Anterior	97	76	21	6.5	5.1	1.4
Cerebellar Superior	112	93	19	6.5	5.5	1
Average sizes of neural networks	93.4 ± 3.8	69.3 ± 4.5	23.7 ± 3.1	6.3 ± 0.18	5.5 ± 0.22	0.78 ± 0.16

Note: (L) — left hemisphere, (R) — right hemisphere; 1 and 2 — group 1 (without DM2) and group 2 (with DM2); 1–2 — difference between the parameters' values registered in the groups.

and thrombogenesis. Disruption of endothelial regulation can lead to endothelial dysfunction, which is often observed in DM2 cases [26]. With complications of microvascular nature, this dysfunction primarily causes lower secretion of NO, higher oxidative stress, increased production of inflammatory factors, expression of proinflammatory cytokines and impaired angiogenesis [27]. According to our data, compared to CCI patients without DM2, patients suffering both of these diseases have more proinflammatory interleukin 6 in saliva, significantly higher ESR, disrupted lipid metabolism, as well as increased MCA resistance index and impairments of some of the cognitive functions [28]. Our research has shown that DM2 affects organization of neural networks and handicaps their functioning.

This study has shown that, compared to people that have CCI only, the significantly lower connectivity values registered in CCI patients with DM2 is associated with a number of large neural networks: right hemisphere's speech neural network and its connections with the left hemisphere's parahippocampal region and right hemisphere's angular gyrus, which is part of the brain's passive mode network. Also, CCI patients without DM2 had significantly better connectivity of anterior cingulate gyrus, part of the salient neural network, and superior temporal gyrus. There are significant changes in the cerebellar networks, too. Thus, a relatively small number of altered connectivities is associated with large neural networks: the default network, speech, and salient networks. There are also numerous changes in other neural networks, evident in the dropping normalized intensity of connective links in CCI patients with DM2 (compared to those without DM2). Also, in such cases, reorganization of neural networks results in them shrinking by a fourth. It is clear that if the correlation of individual nodes of a neural network deteriorates, the accuracy of information transmission is compromised. Other researchers have

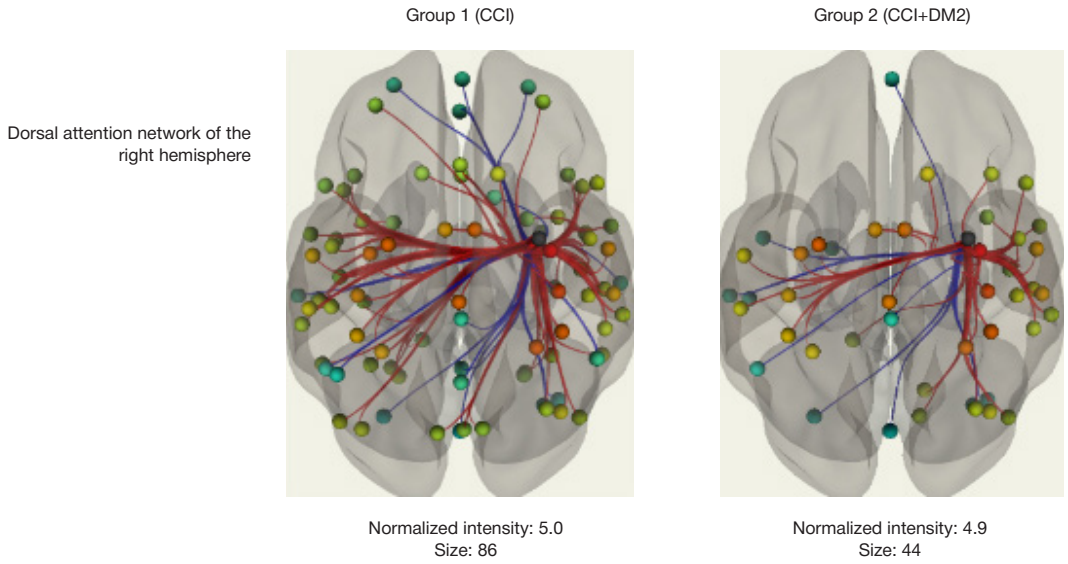

Fig. 2. presents distribution of connectivities coming out of the dorsal attention network in the right hemisphere.

also shown that DM2 can affect neural networks of the brain [29, 30]. They used various methods, including resting fMRI. These studies suggest that DM2 can alter neural networks, increasing the risk of significant cognitive decline and dementia, which seems likely due to the reduction of a large number of connectivity indicators significantly different from zero.

CONCLUSIONS

DM2 is a common concomitant disease in CCI cases; it exacerbates chronic inflammation and endothelial dysfunction. We registered significant differences in carbohydrate, lipid metabolism, inflammation, hemodynamics, and cognitive functions between CCI patients without DM2 and CCI patients without DM2. All the participating patients exhibited high values of inflammation indicators, but those with DM2 had the respective symptoms more pronounced. As expected, we detected significant changes in neural networks in patients with DM2, especially in the parahippocampal region, angular, anterior cingulate and superior temporal gyri, cerebellar networks. These changes entail decrease of the size and intensity of neural networks, deterioration of their synchronization, which is obviously associated with compromised accuracy of information transmission between different brain structures. Further studies may aim at finding markers of initial changes in the organization of neural networks shaped by DM2 in CCI patients, and developing means of their prevention.

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