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Gender Differences in Neural Networks in Patients with Vascular Encephalopathy

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Abstract—Gender differences in cerebral connectivity in subjects with chronic vascular disease are pertinent due to the need for personalized medicine and the theoretical lack of development of the problem. Objective: to analyse the gender differences in neural networks in patients with vascular encephalopathy. The study involved 48 patients (30 women and 18 men) who underwent resting state functional MRI. The neural network graph of gender differences consisted of a small number of source nodes in the occipital fusiform cortex, and a large number of connections linking these nodes with other cerebral regions, located mainly in the left hemisphere. Connectivity measures showed that women have predominantly left hemisphere connections, while men have higher connectivity in the occipital regions of both cerebral hemispheres.

Keywords: neuroimaging, resting state fMRI, connectivity, gender differences in neural networks, chronic brain ischaemia

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Structural and functional differences in male and female brains are determined by several factors, the most obvious being hormonal and structural. The hormonal factor is primarily associated with sex hormones and those cerebral processes that depend on a predominance of these hormones and their changes with age. The second factor is due to the structural differences in the cerebral cortex and its cytoarchitecture, as well as the ratio of grey to white matter, the fractional anisotropy of white matter, and the linking of white matter connections. These differences are determined by genetic factors and appear under normal conditions and in various pathologies [1–7]. The need to further study sexual dimorphism is due to both the practical demands of personalized medicine and the theoretical requests to study the structural and functional organization of these differences.

Gender differences in vascular encephalopathy (VE) are extremely diverse and include cognitive, emotional, circulatory, metabolic, stress-inducing, age-related, and other aspects [8–11]. In this article, we investigate one of the main causes of sexual dimorphism in patients with VE—differences in the cerebral organization in men and women, while analysing the differences in the neural networks of the female and male brains [12, 13].

Not enough research is currently devoted to gender differences in the brain in normal and pathological ageing. Chronic cerebrovascular insufficiency, which usually begins in older age, has various adverse consequences for the individual, the most noticeable being progressive cognitive decline, as well as regulatory and executive dysfunction. The pathological consequences of this disease are largely associated with a decrease in regional cerebral blood flow (rCBF), which is accompanied by a decrease in functional connectivity [14, 15]. Recent studies have shown a close correlation between rCBF and changes in resting state connectivity in normal healthy people of different ages. At the same time, functional connectivity disruption is correlated with cognitive function status. A decrease in rCBF leads to an increase in deoxyhaemoglobin (dHb), which changes the MRI signal level and, ultimately, results in a reduction in neuronal activity [16]. Consequently, the BOLD (blood oxygen level dependent) signal and associated neuronal activity reflect the local changes in dHb content and are dependent on rCBF changes. This corresponds to the concept of neurovascular coupling, which presumes mutual conditioning of neuronal activity, rCBF and the BOLD signal.

It is impossible to say a priori how many connectivities that are significantly different in men and women, are distributed throughout the brain, whether evenly in both hemispheres or limited to a few areas. Most authors point to an age-related decrease in connectivity values, but this is observed until around

80 years of age, and can then undergo a compensatory increase [16].

Functional MRI (fMRI) methodology is widely used in cognitive neuroscience, while functional connectivity is an overall and effective measure of evaluating brain characteristics [15].

Study objective: to analyse the gender differences in brain neural networks in patients with VE.

PATIENTS AND METHODS

The study was conducted at the Research Centre of Neurology between 2017 and 2020. We examined patients with stage I and II VE, aged 50 to 85 years: 30 women (mean age 64.7 ± 1.7 years) and 18 men (mean age 67.4 ± 2.2 years). The age difference was statistically insignificant ($p = 0.34$). The groups of men and women also did not significantly differ during cognitive testing: proofreading, verbal fluency, Luria memory words test, Montreal Cognitive Assessment Test, and the serial 7s test.

A diagnosis of VE was made in accordance with the classification of vascular lesions of the brain and spinal cord, developed at the Research Center of Neurology of the Russian Academy of Medical Sciences (1985), in the presence of a primary vascular disease (atherosclerosis and/or hypertension) and scattered focal neurological signs, combined with cerebral symptoms, such as headache, dizziness, tinnitus, memory loss, decreased working capacity and intelligence. All patients were right-handed. Lacunar infarcts were found in men and women on MRI, primarily in the white matter of the brain. The exclusion criteria were: dementia with a severity of 1+ on the Clinical Dementia Rating Scale [17], as well as a history of acute cerebrovascular accidents, traumatic brain injury, severe cardiac or metabolic (type 2 diabetes mellitus) disease, renal failure, uncompensated thyroid disorders, dysarthria, or contraindications to MRI.

All subjects underwent resting state fMRI of the brain in T2* mode to obtain a BOLD signal, using a Magnetom Verio magnetic resonance tomograph (Siemens, Germany) with a magnetic induction value of 3.0 Tesla. Subjects were instructed to relax as much as possible, lie quietly with their eyes closed (to avoid stimulating the visual system), and think about nothing in particular. MRI data were processed using the SPM12 program (Functional Imaging Laboratory at University College London; UK) in a MATLAB environment (MathWorks; USA). The CONN-18b application (McGovern Institute for Brain Research, Massachusetts Institute of Technology; USA) and the SPM-12 program were used to study connectivity [13]. Connectivity and group differences in connectivity were evaluated with adjustment for multiple comparisons, taking into account the false positive results error (FDR or false discovery rate). Connectivity was evaluated in various brain regions and neural networks, including the passive brain network, the frontoparietal network and others. Gender comparison of connectivity was performed in two patient groups of different sex. The comparison was performed in the Results Explorer sub-software. In these groups, the significance of differences was evaluated using a standardized regression coefficient adjusted for multiple comparisons of FDR. The assessment was made using two-way and one-way (positive and negative) tests. The difference in the results obtained using one-way and two-way tests stems from the different sensitivity of these approaches to the level of false positive results [18]. Therefore, the neural network graph obtained using the two-way test is not exactly equal to the sum of positive and negative graphs, but rather provides a semiquantitative picture with positive and negative connectivity parameters, but with the same qualitative ratio.

Abbreviations of anatomical and functional terms used in the figures and table (see below):

AG—angular gyrus; Cerebel 10—cerebellum 10 (cerebellum, posteroinferior part), DorsalAttention FEF—dorsal attention network FEF (frontal eye field), Frontoparietal PPC—frontoparietal network, posterior parietal cortex; Frontoparietal LPFC—frontoparietal network, lateral prefrontal cortex; FP—frontal pole, HG—Heschl's gyrus; IFG tri—inferior frontal gyrus, pars triangularis; iLOC—lateral occipital cortex, inferior division; MidFG—middle frontal gyrus; OFusG—occipital fusiform gyrus, OP—occipital pole; pSTG—superior temporal gyrus, posterior division; PP—planum polare (upper temporal gyrus near the temporal pole); PT—planum temporale; Salience. SMG—salience network supramarginal gyrus; TOFusC—temporal occipital fusiform cortex; Ver 8 or 12—cerebellar vermis, lobules 8 or 12, R or L—right or left hemisphere.

RESULTS

The correlation (regression) coefficient is a measure of the connectivity of two brain regions. Many connectivities in the female and male brains do not show statistically significant differences according to this test. However, there are a statistically significant gender differences for several connectivity indicators, with two options possible: the female brain connectivity indicators are higher or lower than the male brain based on statistical measures (correlation or regression coefficient). A graph made up of these different connectivities can be considered a neural network of gender differences, which consists of two sub-networks – positive and negative (Fig. 1).

A. Distribution of connectivities that are different in men and women. Positive t-test values (scale at the top of the figure) are red and orange, negative values are blue and dark blue. Positive connectivities correspond to a predominance of such connections in

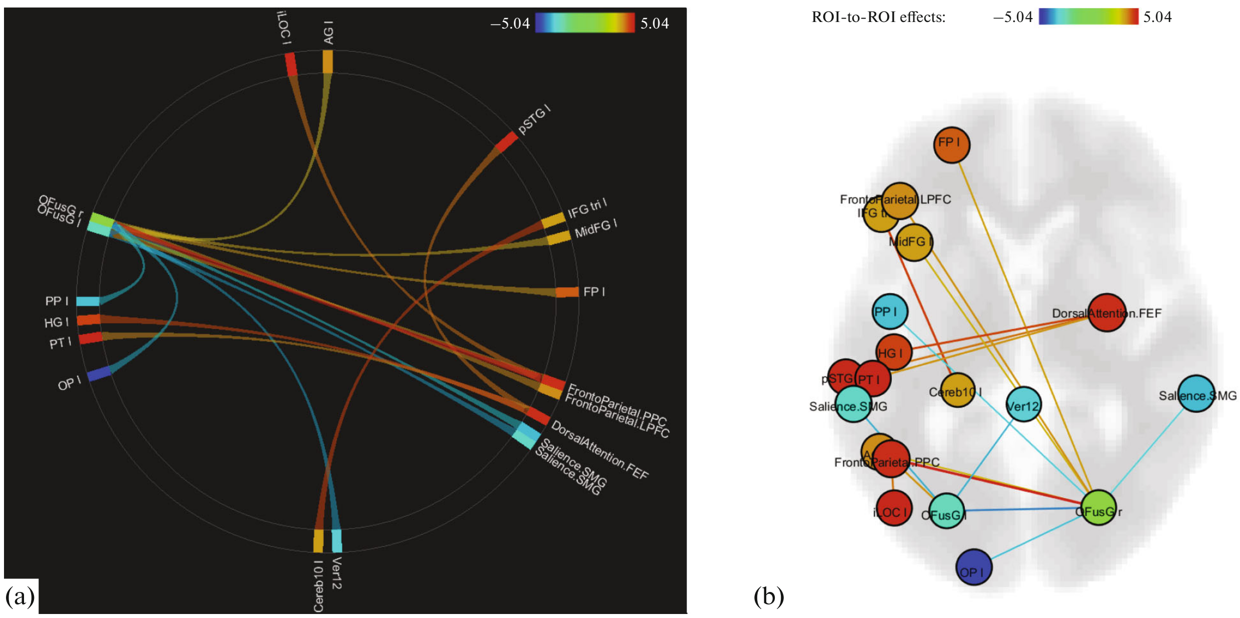

Fig. 1. Distribution of connectivities that are different in male and female patients with VE.

women compared to men, and negative connectivities indicate the predominance of this connection in men compared to women. A two-way test was used that considered the positive and negative connectivity parameters. B. Distribution of connectivities relative to the axial section of the brain. The list of abbreviations is provided in Methods.

Figure 1a shows that connectivities do not form closed loops, with one exception: the two main nodes located in the right and left occipital fusiform cortex are linked to the lateral prefrontal cortex in the frontoparietal network of the left hemisphere, as well as to each other. The main connectivity part is in the left hemisphere, moreover, these connectivities are "female," i.e., they predominate in women (Fig. 1b). The negative neural network is formed by negative differences, since connectivity in the male brain is higher than in the female brain, in this case. Subtracting connectivities means subtracting the correlation (regression) coefficients, which are a measure of brain connectivity.

Exact values of connectivities that predominate in women or men are provided in the Table 1.

The table shows that the number of main source nodes in the virtual "neural network" of gender differences is six, with two located in the right and four located in the left hemisphere. The number of targets in the left hemisphere is fourteen, four of which are negative. The number of targets in the right hemisphere is two (one positive and one negative). Thus, women have higher connectivity parameters compared to men (11), and lower connectivity values—about half as much as men (5). The differences are statistically significant ($p = 0.03$). There are also significant differences in the number of targets in the left and right hemispheres ($p < 0.0001$).

Connectivities that are better expressed in women or men, are unevenly distributed across the cerebral hemispheres. Figures 2 and 3 show individual neural network sections with a predominance of connectivities in women or men.

Figures 2a, 2b show the significant asymmetry in connectivity prevalence in the left hemisphere compared to the right. Meanwhile, the two main sources of these parameters—the occipital fusiform cortex and the frontal visual field, which is part of the dorsal attention network—are found in the right hemisphere. Moreover, the neural network of connectivities prevailing in women does not contain loops (Fig. 2a).

Figure 3 demonstrates that the distribution of negative connectivity parameters, indicating a greater intensity of these connections in men, is more or less uniform in the posterior parts of both hemispheres. The neural network that is composed of connectivity parameters predominant in men also does not contain loops (Fig. 3a).

Therefore, positive and negative networks represent true neural network regions in women and men, whose connectivity is significantly higher in these groups. The identified gender differences in neural networks in patients with VE consisted of positive and negative connectivity parameters, and were asymmetrically distributed throughout the cerebral hemispheres. The asymmetry was mainly associated with connectivities that predominate in women; more pronounced connections in men were relatively evenly distributed across both cerebral hemispheres. In general, the predominant connectivity parameters were

Table 1. Statistical characteristics of the gender difference in connectivities

Connectivity (two-way test)	T-test	Uncorrected significance level	FDR-corrected p-values
R OFusG			
L Frontoparietal PPC	5.04	0.0000	0.0013
OFusG L	–3.99	0.0002	0.0194
L Frontoparietal LPFC	3.84	0.0004	0.0202
L FP	3.67	0.0006	0.0255
L MidFG	3.47	0.0011	0.0349
L OP	–3.40	0.0014	0.0349
L AG	3.38	0.0015	0.0349
L PP	–3.25	0.0022	0.0439
R Salience.SMG	–3.20	0.0025	0.0447
L OFusG			
L Frontoparietal LPFC	3.81	0.0004	0.0337
L Salience.SMG	–3.54	0.0009	0.0448
Ver12	–3.48	0.0011	0.0448
L Frontoparietal PPC			
L L iLOC	4.09	0.0002	0.0141
L HG			
R Dorsolateral, FEF	4.50	0.0000	0.0076
R DorsalAttention, FEF			
L pSTG	4.10	0.0002	0.0137
L PT	3.82	0.0004	0.0217
L Cereb10			
L IFG tri	4.57	0.0000	0.0059

Symbols: T—Student's t-test; pFDR—significance level adjusted for multiple comparisons; FDR (false discovery rate)—false-positive decision error, the method used to test the null hypotheses when conducting multiple comparisons; bold type indicates sources, normal type indicates targets. The other abbreviations are the same as in Fig. 1.

higher in women than in men (the differences are statistically significant, $p = 0.003$).

DISCUSSION

The development of neuroimaging methods [19] now allows us to analyse neural network gender differences and identify the connectivities prevailing in women and men. Most of these parameters, which are more closely correlated with each other in women, are located in different regions of the left hemisphere. The parameters prevailing in men are less numerous and are found in both posterior hemispheres. Results of diffusion weighted MRI show that cortical networks in women have greater anatomical connectivity and more effective organization in many networks, including the default mode network, as compared to men. However, the opposite is observed in the salient network, with higher connectivity in men [20, 21]. The anatomical differences that lead to gender differences in neural networks are obviously accompanied by functional differences. The existence of neural networks without a corresponding morphological substrate, despite a functional connection, seems unlikely, especially if false-positive correlation effects are excluded. Nevertheless, this possibility exists if we imagine that two or more targets are connected to the same source. The BOLD signals of these targets can be synchronized, and in this case, the neural network graph should have loops (closed contours). However, the figure shown has no such loops, with one exception mentioned in the Results: two nodes located in the right and left occipital fusiform cortex, connected to the lateral prefrontal cortex of the frontoparietal network in the left hemisphere. The BOLD signals from these three areas are synchronized with each other. Nevertheless, the correlations between both occipital fusiform cortices were negative. There were no loops when considering only positive or negative connections (see Figs. 1–3 and the Table 1), which indicates the low probability of false correlations in these cases.

The highlighted graph of gender differences resembles a so-called scale-free network with its uneven

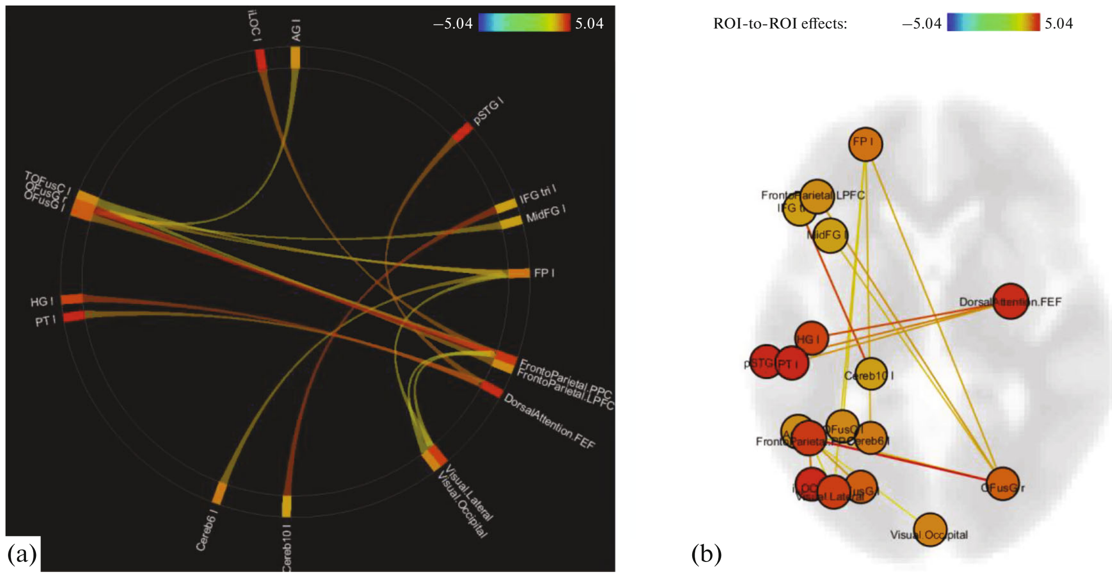

Fig. 2. Distribution of connectivities predominating in women with VE compared to men. The abbreviations are the same as in Fig. 1. One-way positive test.

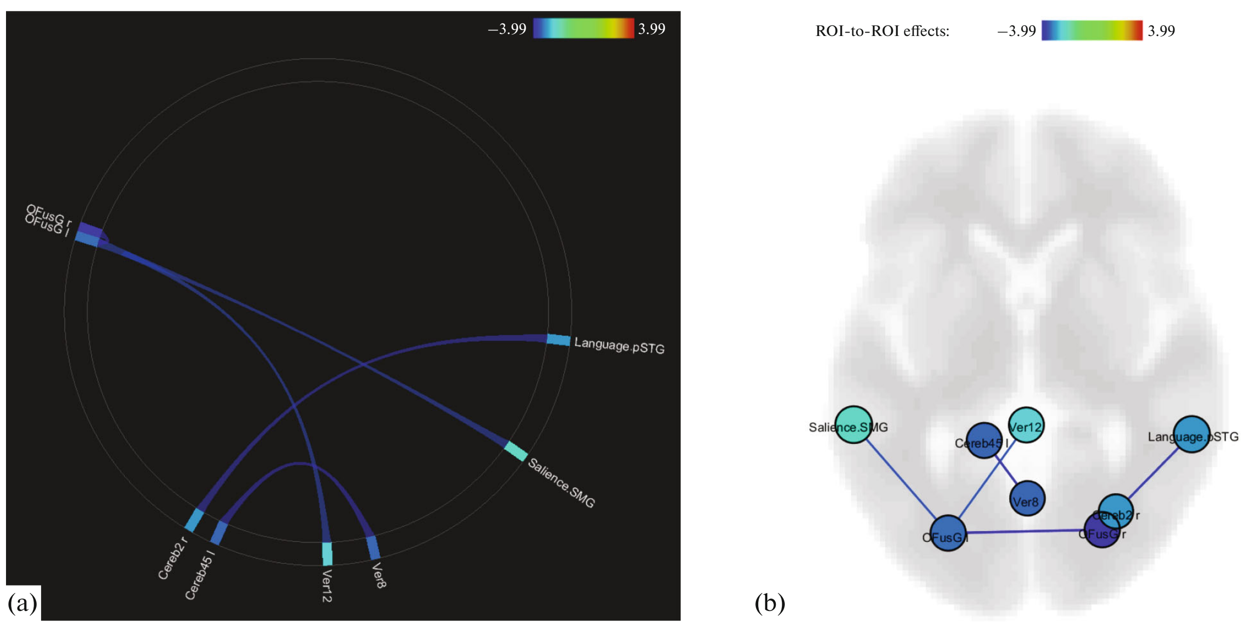

Fig. 3. Distribution of connectivities predominating in men with VE compared to women. The abbreviations are the same as in Fig. 1. One-way negative test.

connectivity distribution: both hub nodes, located in the occipital fusiform gyrus bilaterally, are connected to more than 70% of the targets, while the remaining 5 sources are connected to less than 30% of the targets [22, 23].

If we consider the neural network represented by connectivities that are more pronounced in women, the main source nodes are in the occipital fusiform gyrus, the area of the brain involved in facial recognition and memory processes; other parts of the fusiform cortex are involved in the regulation of muscle tone. The role of hub nodes is not fully understood. Analysis of neural networks in patients with Alzheimer's disease, recorded several years apart, showed amyloid accumulation around these nodes. The metabolic cascades related to this disease may increase in these areas [24]. It is possible that in chronic cerebrovascular insufficiency, areas of concentrator nodes are at higher risk of cerebrovascular events, due to a greater need for oxygen than in other areas.

The connections in the right and left occipital fusiform cortex are unusual in their asymmetry. The right node has more connections than the left one. One explanation for this phenomenon is that the right hemisphere plays a greater role in facial recognition compared to the left, while the large number of targets in the left hemisphere may reflect different stages of cognitive information processing (these processes are very intense in the female brain).

To what extent are these patterns specific for patients with VE? No fundamental differences were found in the organization of the connectome in small vessel disease versus normal in one study [25], with a slight decrease in the total number of connectivities in patients. Another study [6] found that in a normal sample, which corresponded in age to our sample, the number of connectivity parameters predominating in women and men was approximately the same. In middle age, the interhemispheric connectivity parameters on EEG are normally higher in women than in men [26].

Thus, the number of connectivities decreases with age, furthermore, the difference between the age norm and VE is probably due to both an overall decrease in connectivity parameters and a decrease in connectivity in the male sample.

CONCLUSIONS

(1) In patients with VE, the gender differences in connectivity graph has two distinct source nodes, with a large number of connections located bilaterally in the occipital part of the fusiform cortex, and a larger number of target nodes with 1–2 connections located primarily in the left hemisphere.

(2) The network of gender differences, represented by connectivity parameters predominant in women, is larger in the number of entities involved than the connectivity parameter network predominant in the male sample.

(3) The connectivity parameter network predominant in women is mostly located in various regions of the left hemisphere, while the connectivity parameter network better expressed in men is found in the posterior parts of both hemispheres.

(4) It is likely that gender differences in connectivity may have a predictive value in some cases, indicating further development of VE in men and women.

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Compliance with ethical standards: this study was approved by the Ethics Committee of the Research Centre of Neurology (Minutes no. 11/14 dated November 19, 2014); all subjects signed an informed consent form to participate in the study.

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