NEUROIMAGING APPROACH TO IDENTIFICATION OF WORKING MEMORY BIOMARKERS IN PATIENTS WITH CHRONIC CEREBRAL ISCHEMIA

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Verbal working memory (VWM) is a fundamental function responsible for temporary storage and short-term handling of verbal information. The study was aimed to determine the working memory biomarker associated with imaging of the source of infra-slow electrical activity in patients with chronic cerebral ischemia (CCI). A total of 50 patients with CCI took part in the study: 16 males and 34 females aged 50–85 years. VWM was evaluated by the Luria test. The subjects were divided into two groups matched by age with the VWM below and above the average level for the studied sample. The infra-slow, below 0.1 Hz, electrical activity, otherwise known as the DC potentials (DCPs) of the brain, was recorded with five monopolar leads: frontal, central, occipital, right and left temporal. The resting state fMRI was used to analyze brain regions with the activated BOLD (blood-oxygen-level-dependent) signal that were associated with the brain regions responsible for VWM and the DCP generation sources recorded with the non-polarizable electrodes. The differences in BOLD signal activation and infra-slow activity amplitude were found in two VWM groups. These resting-state neural networks, VWM and the neural network responsible for DCP generation, overlapped in frontal regions. There were significant differences in DCP recorded with the frontal lead in two VWM groups (p = 0.00004). In patients with CCI, infra-slow activity, recorded with the frontal lead that is generated by the neural network fragment representing an intersection of the VWM network and the part of the brain responsible for DCP generation in the frontal region, is a VWM biomarker.

Keywords: chronic cerebral ischemia, verbal working memory, resting fMRI, infra-slow electrical activity, DC potential, overlapping resting neural networks

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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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НЕЙРОВИЗУАЛИЗАЦИОННЫЙ ПОДХОД ДЛЯ ВЫЯВЛЕНИЯ БИОМАРКЕРОВ РАБОЧЕЙ ПАМЯТИ У БОЛЬНЫХ С ХРОНИЧЕСКОЙ ИШЕМИЕЙ МОЗГА

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Вербальная рабочая память (ВРП) — фундаментальная функция, ответственная за временное хранение и краткосрочную работу с вербальной информацией. Целью работы было определить биомаркер рабочей памяти, связанный с нейровизуализацией источника сверхмедленной электрической активности у больных с хронической ишемией мозга (ХИМ). В исследовании приняли участие 50 пациентов с ХИМ: 16 мужчин и 34 женщины в возрасте 50–85 лет. ВРП оценивали по тесту Лурия. Испытуемые были разделены на две группы, не различающиеся по возрасту, с ВРП ниже и выше среднего уровня в исследованной выборке. Регистрировалась сверхмедленная, менее 0,1 Гц, электрическая активность, иначе называемая уровнем постоянного потенциала (УПП) головного мозга в пяти монополярных отведениях: лобном, центральном, затылочном, правом и левом височных. С помощью фМРТ покоя анализировали области мозга с активированным BOLD (blood-oxygen-level-dependent) сигналом и связанные с областями мозга, ответственными за ВРП и за источники генерации УПП, регистрируемые неполяризуемыми электродами. В двух группах ВРП найдены различия в активации BOLD-сигнала и амплитуде сверхмедленной активности. Эти нейросети покоя, ВРП и нейросеть, ответственная за генерацию УПП, пересекаются в лобных областях. УПП в лобном отведении достоверно различался в двух группах ВРП (p = 0,00004). Биомаркером ВРП у больных ХИМ является сверхмедленная активность, регистрируемая в лобном отведении и генерируемая тем участком нейросети, который является пересечением сети ВРП и участка мозга, ответственного за генерацию УПП в лобной области.

Ключевые слова: хроническая ишемия мозга; вербальная рабочая память, фМРТ покоя, сверхмедленная электрическая активность, уровень постоянного потенциала, пересекающиеся нейросети покоя

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Verbal working memory (VWM) is a fundamental function responsible for temporary storage and short-term handling of verbal information that is necessary to solve a number of problems: reasoning, understanding, learning. Identification of VWM biomarkers can help us understand individual differences in cognitive ability, as well as diagnose and treat memory disorders [1]. The working memory deficit can also serve as an indicator of the cerebral disease process development. Functional magnetic resonance imaging (fMRI) studies revealed certain brain regions and networks involved in the VWM functioning, such as prefrontal cortex, parietal cortex, anterior cingulate cortex, hippocampus, etc., which can vary depending on the VWM assessment conditions, individual psychophysiological characteristics, and the disease type [2, 3]. In the prefrontal cortex, neurotransmitters dopamine and norepinephrine are involved in the VWM processes; these depend on the genes associated with dopamine receptors (for example, *DRD2*, *COMT*) and determine the working memory capacity and effectiveness [4]. fMRI and electrophysiological measurement, for example, performed when conducting the P300, N-back and other tests, provided valuable insights into neuronal activity associated with working memory and its capacity. Structural characteristics of the brain, such as grey matter volume and white matter integrity in the regions that support working memory (in the dorsolateral prefrontal cortex, anterior cingulate gyrus, etc.) can be correlated to the working memory indicators [5–6]. The VWM capacity decreases with aging; it is also reduced in individuals with neurodegenerative and vascular disorders, such as chronic cerebral ischemia (CCI) [2].

The widespread use of fMRI provided a separate source for the development of ideas about the neurovascular unit (NVU), the cellular complex ensuring interaction between the BOLD signal and the neuronal activity. NVU consists of neurons, glia, endothelial cells, and some other components [7–8]. The processes that ensure working memory result in the NVU activation, due to which increased activity of BOLD signals, neuronal responses, and infra-slow activity shifts are observed. In the Russian literature, the term “infra-slow activity” is used along with the term “DC potential (DCP)”. Active functioning of neurons associated with working memory activation can lead to changes in the NVU pH and, as a result, to the dynamics of potential difference between blood and cerebrospinal fluid. The normal resting state pH of cerebrospinal fluid is 7.31–7.34, while that of arterial blood is slightly more alkaline, 7.35–7.45. According to the calculations based on the Nernst equation due to differences in hydrogen ion concentration (https://www.physiologyweb.com/calculators/nernst_potential_calculator.html), the BBB membrane steady potential shift of up to 9 mV can be normally observed. Additional shift is possible due to differences in concentrations of other ions (potassium, sodium, chloride). The dynamic changes in acidity change the hemoglobin's affinity for oxygen, thereby affecting the BOLD signal (Bohr effect) and cellular acidosis [9]. Thus, infra-slow activity in the millivolt range reflects primarily complex energy processes occurring in the NVU and can serve as an indicator of the state of VWM and other cerebral functions, since disturbances of the acid base balance on both sides of the BBB are associated with changes in the functioning of neurons. The dynamics of infra-slow oscillations of potentials in the millivolt range reflecting the energy characteristics of metabolism could potentially play a role of the energy process biomarker [10–14]. The association of DC potential with neuronal activity is ambiguous. Higher neuronal activity normally corresponds to higher DCP values. In case of disorder, for example neurodegenerative or cardiovascular disease, DCP tends to rise due to the brain acidity increase resulting from neurodegenerative and atrophic processes, as well as vascular incompetence, as it happens in Alzheimer's disease [15].

Conventional VWM biomarkers, such as the previously mentioned P300 and N-back tests, are often correlated to various fMRI characteristics in the paradigm of tasks, when the subjects execute certain cognitive tasks. These tasks ensure direct activation of the working memory networks and direct measurement of cognitive functions and related brain activity indicators. At the same time, the resting state fMRI records spontaneous brain activity fluctuations, when the subjects are in the resting state and do not execute any specific tasks, however, these rather accurately reflect the VWM state. The resting-state neural networks represent brain regions exerting synchronized activity in the relaxed wakefulness state. Obviously, the state preceding the cognitive task has a decisive influence on the cognitive test performance. In the resting state, neural networks can overlap with the networks associated with the tasks; such a relationship is likely to be important for assessment of cognitive function using the resting-state networks, as well as for the search for biomarkers. The evidence, that regions of the brain functionally connected in the resting state facilitate transmission of information related to cognitive tasks between these brain regions, is provided [16]. The authors of this paper have developed an approach for demonstration of the relationship between the network topology in the resting state and transmission of information in the networks during execution of tasks. The resting-state neural networks also can overlap with each other, which reflects some fundamental pattern of internal organization of the brain. Correlations between brain regions measure statistical relationships (correlations) between the neuronal activity in various brain structures and show the degree, to which two brain regions are synchronized (in-phase or out-of-phase) in these areas in different states of the brain. The brain regions, for which strong correlations are reported, are inherent to the same resting-state neural network. It is theoretically possible that neural networks can exist in two different states and their size would be different in these two states. It is also possible that neural networks can be correlated to several neural networks due to their multilayered structure. Significant overlapping of some neural networks with each other suggest that there are strong functional relationships between the networks reflecting their common functional roles and coordinated models of activity in the brain [17–18].

The study was aimed to search for a biomarker being a component of the VWM neural network in patients with chronic cerebral ischemia. This biomarker must be inherently involved in the working memory process, which makes it a useful tool for solving the research and applied problems. The currently known working memory biomarkers are compared with the fMRI data in the paradigm of tasks. To date, no biomarker has been found that could be considered within the resting fMRI paradigm. This approach is aimed to fill the gap.

METHODS

A total of 50 patients with chronic cerebral ischemia (CCI) took part in the study: 16 males and 34 females aged 50–85 years. There were no significant differences in the average age between the samples of males (64.3 ± 2.7) and females (66.2 ± 1.5); significance levels were as follows: $p = 0.78$ for differences between males; $p = 0.42$ for differences between females. All patients were right-handed.

In CCI, cerebral blood flow through the main and small arteries of the head is disturbed, which can result in various functional disorders of the brain. The disorder often occurs

in elderly and senile individuals. This is usually accompanied by atherosclerosis, hypertension, diabetic angiopathy, and other diseases. Inclusion criteria: initial manifestations and subcompensated CCI; no need for permanent care from others in patients' daily life [19–21]. Exclusion criteria: dementia severity score 1 or more (Clinical Dementia Rating) [22], history of acute cerebrovascular accident, traumatic brain injury, severe heart or renal failure, uncompensated thyroid dysfunction.

Cognitive function assessment

Verbal working memory (VWM) was evaluated by the Luria test. The test was modified taking into account the capabilities of patients with CCI. The subjects were offered to memorize 10 unrelated words repeated five times and immediately reproduce them. The final fifth value for the correctly reproduced words was counted.

Infra-slow electrical activity was recorded: DC potential of the brain. DCPs of patients with CCI were measured with the 5-channel Neuroenergokartograf unit (Statokyn; Russia) using the non-polarizable silver chloride electrodes. Active electrodes were placed on the head, and the reference electrode was placed on the right wrist. The electrode placement scheme was as follows: along the sagittal plane — inferior frontal (F), hereinafter frontal, central (C), occipital (O) leads; parasagittal plane — right and left temporal leads (Td) and (Ts). Recording was performed after applying the measures aimed to control and radical reduction of electrode artifacts with virtual elimination of the skin potentials. The electrode placement matched the international 10–20 scheme, standard topographic symbols are provided in parentheses. The details of DCP recording were reported earlier [11].

Resting state functional magnetic resonance imaging (fMRI)

The subjects underwent T2* weighted fMRI to obtain the BOLD signal in the Magnetom Verio magnetic resonance imaging scanner (Siemens; Germany) with the magnetic field strength of 3.0 Tesla. The subjects were offered to relax as much as possible, lay still with the eyes closed (to avoid stimulation of visual sensory system) and not to think about anything in particular. The MRI data were processed using the SPM12 software (UK) in the MATLAB computing environment (USA). The MAGNETOM Verio magnetic resonance imaging unit (Siemens; Germany) had 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 resting state fMRI was used to assess brain areas showing the BOLD signal activation and intersecting with the sources generating infra-slow brain activity recorded by the non-polarizable electrodes in the inferior frontal lead.

Additional Doppler tests were performed in order to exclude abnormal circulation asymmetry.

Statistical processing of the data obtained was performed using the Statistica-12 software package (Dell; USA). The Kolmogorov–Smirnov test was used to test the distribution for normality. We calculated mean values, standard deviations, standard errors, and variance, conducted one-way analysis of variance and correlation analysis.

RESULTS

The average number of words reproduced by 50 patients with CCU after five repeats of 10 words was 7.6 words (standard error ± 0.2 words). The subjects were organized into two groups: group 1 (25 individuals) reproduced seven words or less after five repeats, subjects of group 2 (25 individuals) reproduced eight words or more, respectively. The average number of words memorized in the first group was 6.4 ± 0.2 words; in the second group it was 8.9 ± 0.2 words. The groups were matched by age (significance of differences in age $p = 0.91$). The average age of group 1 was 66.7 ± 2.0 years, while that of group 2 was 64.4 ± 1.8 years.

Fig. 1 shows brain regions, in which the BOLD signal values are higher in the second group of subjects.

When assessing the BOLD signal difference, the regions with high T-value are highlighted. Then MNI (Montreal Neurological Institute) brain coordinates are provided in parentheses, followed by the anatomy name and in some cases network name. The most activated region with the MNI coordinates (–27 –67 6) corresponds to the left lingual gyrus — Visual network, *L. lingual gyrus*, which in this situation is activated primarily as a working memory structure. In Fig. 1 this region is located at the coordinate axes intersection. Among other the following should be noted: left postcentral gyrus — Somatomotor network, *L. postcentral gyrus* (–28 –26 60), left cingulate gyrus — Default mode network, *L. cingulate gyrus* (–28 –51 38), and left inferior frontal gyrus — Language network, *L. inferior frontal gyrus* (–28 25 8).

In the group of patients with good working memory, the fMRI BOLD signal activation was significantly higher, than in patients with poor working memory, which is due to higher neuronal activity in the regions shown in Fig. 1. This is also associated with higher energy exchange in these areas and adjacent regions, which suggests the pH change and, therefore, differences in DCP. However, cerebral circulation is often disturbed in patients with CCI. Therefore, neurodegenerative processes resulting in higher DCP in individuals with poor memory are activated. Individuals with high VWM have no acidosis, so DCP is lower. ANOVA revealed significant differences in DCP recorded with the frontal lead in individuals with high and low VWM values reported in the resting state and when performing cognitive tests (Fig. 2A, B).

What's interesting is that the differences between two groups are more significant in the resting state, than during execution of a cognitive task (Fig. 2A, B). This supports the idea that neural networks in the resting state and during execution of cognitive tests largely overlap, especially those implementing similar tasks related to solving verbal problems and concentration, as in this case.

The intergroup differences in DCP recorded with other leads are less pronounced (see Table).

Consider fMRI differences in the subjects differing in DCP recorded with the frontal lead. The first group included the subjects with the DCP recorded with the frontal lead below 6.5 mV, the second group included those, whose DCP recorded with the frontal lead exceeded 6.5 mV (Fig. 3).

Fig. 3 shows distribution of the difference of activated voxels associated with the groups of patients differing in DCP recorded with the frontal lead.

Comparison of fMRI in two groups of patients different in terms of VWM indicators and with two groups with low and high DCP is used. This makes it possible to identify the areas of activation caused simultaneous by these two factors, since overlapping of the regions associated with both working memory and generation of DCP recorded with the frontal lead is one of possible reasons for the relationship between DCP and cognitive functions. We have found such areas (Fig. 4).

Thus, we can understand, which regions are responsible for DCP generation and why DCP is a working memory marker in this situation.

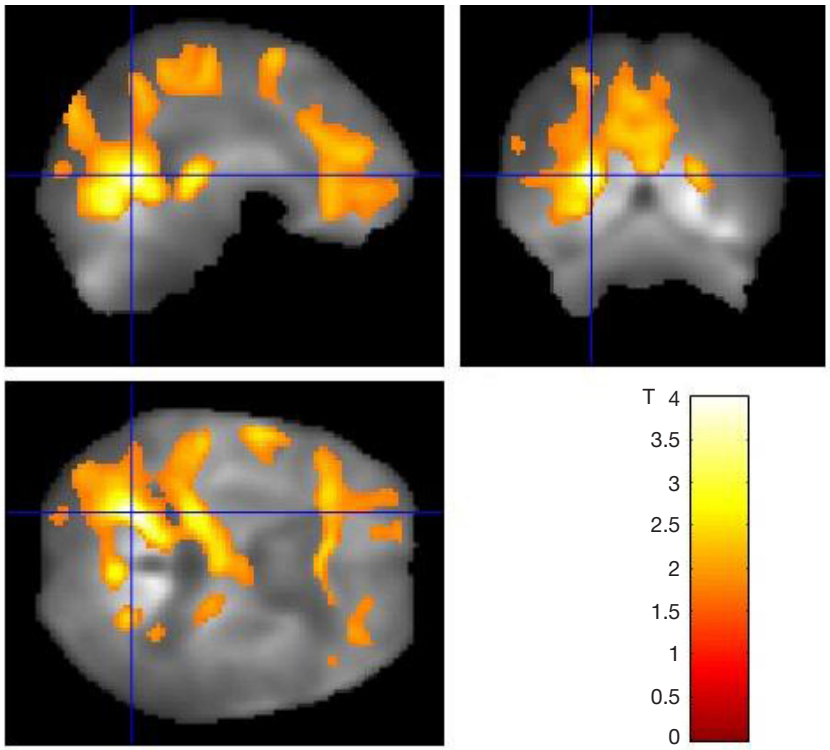

Fig. 1. Brain regions corresponding to the activated voxel difference in patients with high and low working memory indicators based on fMRI data. Lower right — T-value scale. The activated voxel difference at the significance level below 0.05 corresponds to the T-value exceeding 1.68

DISCUSSION

In our sample, the patients included in group 2 having higher VWM showed almost normal indicators. This resonates with the data provided by other authors about the fact that there is often no objective evidence of cognitive decline in patients with the early stage vascular disorders, even if the patients have subjective complaints [23]. In patients with CCI included in the first group with lower VWM, the VWM indicators were typical for patients with vascular or neurodegenerative disorders showing no signs of dementia [23]. In individuals having higher VWM, the voxels activated were located primarily in the left hemispheric structures, while the regions of visuospatial working memory are located primarily in the right hemisphere [2, 3]. Certain parallel between the fMRI activated voxel difference in two groups and DCPs in patients with good and poor working memory was found. The ideas about the association of infra-slow activity in the millivolt range with the resting-state neural networks have been discussed in the literature for a long time and have been confirmed by the study [24]. The authors of the paper do not preclude the relationship between these potentials and the BBB potentials. This study shows a particular mechanism underlying such interaction that is associated with the presence of common fragment in the VWM and DCP

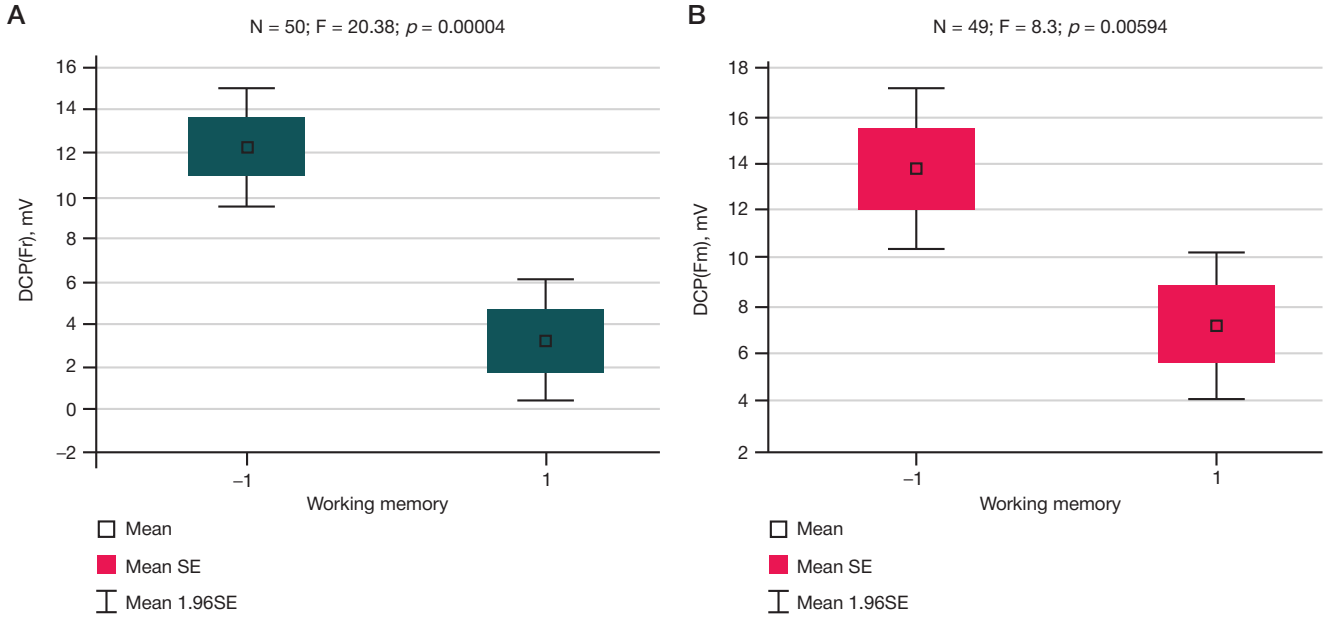

Fig. 2. DCP recorded with the frontal lead in two groups of patients with CCI having low (–1) and high (1) VWM values reported in the resting state **(A)** and when performing the Luria test **(B)**. Statistical characteristics of differences are shown at the top of the figure. DCP values in mV are along the vertical axis. F — Fisher's exact test; N — number of subjects; *p* — significance level

Table. Significance of differences in two VWM groups of patients with CCI for various DCP leads

DCP leads	Significance of differences in DCP in two groups (*p*)
F (Frontal)	0.000041
C (Central)	0.015256
O (Occipital)	0.007895
Td (Right temporal	0.010093
Ts (Left temporal)	0.085361

neural networks. Apparently, this VWM fragment consists of neurons synergistic with the infra-slow electrical activity generation processes. Other fragments of the VWM network and DCP are generated by the non-overlapping neural network fragments. In the active wakefulness state, for example, during execution of the tasks, the resting-state neural networks cease to execute old tasks, while the anatomically close fragments of these networks and most likely the same networks possessing multimodal neurons switch to solving other problems that meet the new conditions [16]. Furthermore, the VWM capacity can be predicted based on the resting-state networks [25]. A similar pattern was observed in our studies, when the differences of infra-slow activity at rest and during execution of a cognitive task corresponded to the differences in VWM of patients with CCI. This can be exemplified by the fact that two groups of subjects demonstrate stable, unchanging differences in the infra-slow activity characteristics in the resting wakefulness state and during execution of cognitive tasks. Since the ratio of DCP (Fig. 2) in the resting state and during execution of tasks in two groups of patients was almost the same, it can be assumed that the ratio of activated (functioning) neurons remains the same in both groups in these two states.

The use of resting state fMRI opens new avenues for identification of biomarkers; for this it is enough to assess overlapping of two resting-state neural networks. The first resting-state network is the network of the main process (in this paper it is the VWM neural network), while the second neural network is the network of biomarker itself, i.e. of specific synchronized group of neurons responsible not only for genesis of the main process, but also for the specific type of electrical processes that can be recorded by non-invasive methods. This approach to the use of resting state fMRI eliminates the main question of biomarker specificity, since specificity is determined by overlapping between the VWM network and another neural network, functioning of which can be recorded by a convenient method, for example by non-invasive electrophysiological method, like in this situation.

CONCLUSIONS

Working memory is a fundamental function responsible for temporary storage and processing of information that is necessary to solve various cognitive problems. The working memory biomarkers can help understand individual differences in cognitive ability, as well as improve the diagnosis and treatment of cognitive impairment. The fact that working memory was considered in terms of the neurovascular unit functioning resulted in the fact that the dynamics of infra-slow potentials as

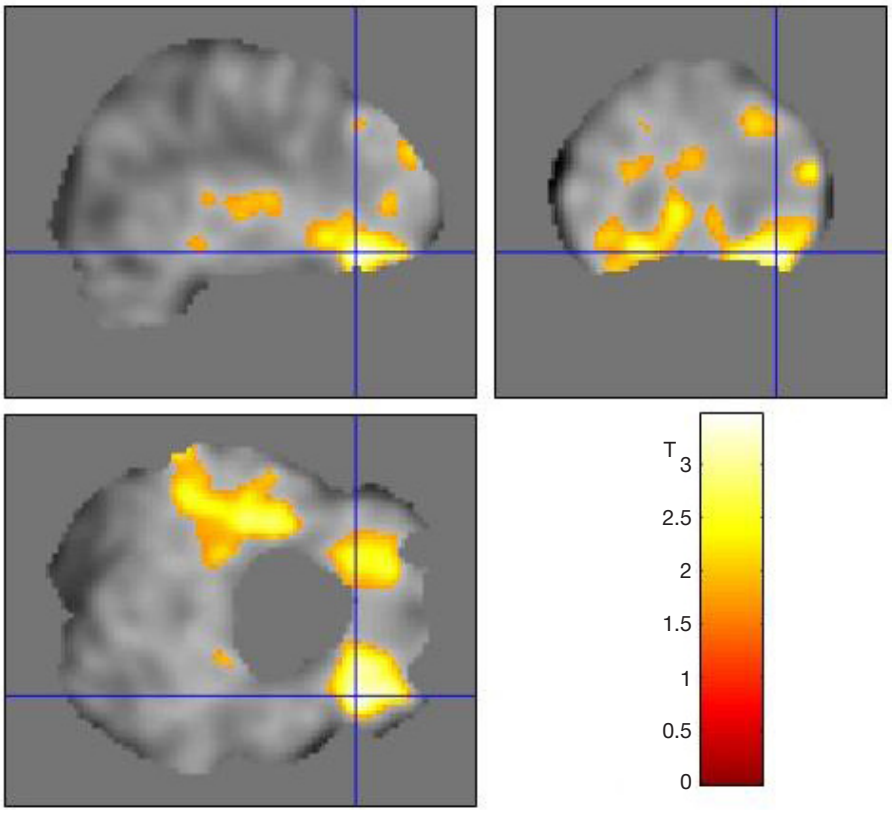

Fig. 3. Brain regions corresponding to the activated voxel difference in CCI patients with low and high DCP in the frontal region. The activated voxels in the right and left lateral fronto-orbital gyri (28 36 –16) and (–28 36 –16), as well as in the left superior temporal gyrus (–40 –17 –7) are highlighted in Fig. 3. Other designations are the same, as in Fig. 1

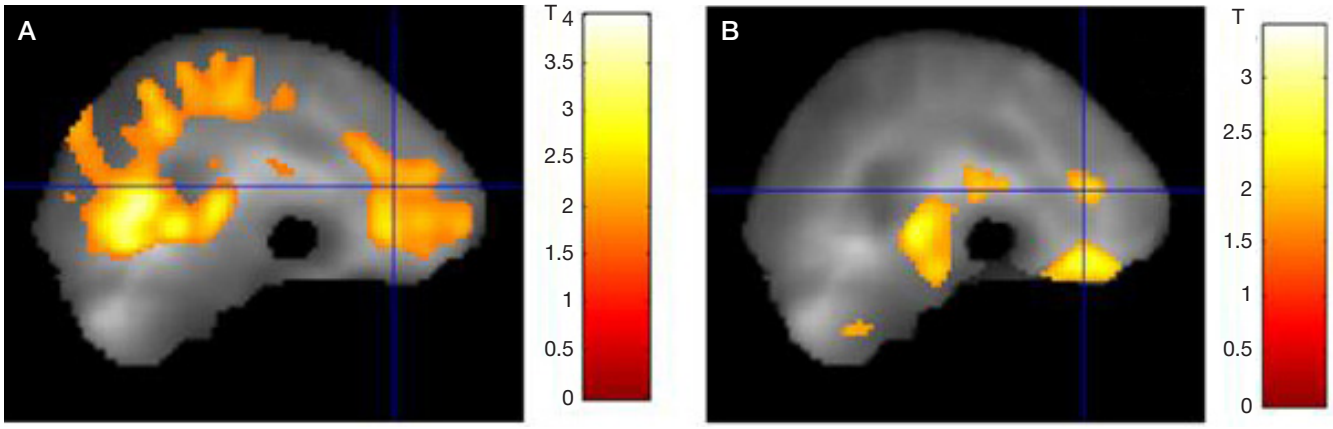

Fig. 4. Brain regions corresponding to the working memory overlap with the areas that generate infra-slow activity. Intersection of the coordinate axes corresponds to the MNI coordinates –28 32 18 — middle frontal gyrus, to the DMN networks and Salience Network. The activated voxel difference in patients with good and worse working memory **(A)** and with low and high DCPs recorded in the frontal lead of infra-slow potentials **(B)** is observed in these regions. This area is marked with the coordinate axes intersection on both figures, A and B

possible working memory biomarkers was studied. The resting state fMRI studies revealed brain regions and networks involved in the working memory functioning. Some of these overlap with the brain regions generating infra-slow activity that can be recorded with the frontal lead. Such infra-slow potentials can be considered as the VWM biomarkers due to overlapping of the brain regions involved in the working memory processes and generation of infra-slow electrical activity.

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