

# Comparison of Brain Activation According to fMRI Data in Patient with Depression (After Acute Coronary Syndrome and Somatically Healthy) and Healthy Volunteers

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## Abstract

**Objective:** The present study is devoted to the study of brain activation using fMRI in patients with depression (after acute coronary syndrome and somatically healthy) and in healthy volunteers.

**Method:** The study enrolled a total of 51 patients: 11 with depression after acute coronary syndrome, 16 with primary depressive episode and recurrent depression without prior coronary event, and 24 with ACS without depression. The groups were matched by sex and age. The emotional information processing was evaluated with the Pennsylvania Test of Emotion Recognition. All patients underwent fMRI at the time of this test. The data processing was performed with SPM12 and xjView applications.

**Results:** During the processing of emotional information in the depressed patients after ACS, specific activation zones in the frontal cortex ( $P < 0.001$ ), right fusiform gyrus ( $P < 0.001$ ), and right insular lobe were identified ( $P = 0.017$ ). In the patients with primary depressive episode and recurrent depression without ACS, certain zones of activation were identified in frontal cortex ( $P < 0.001$ ;  $0.001$ ), left fusiform gyrus ( $P < 0.001$ ), occipital cortex ( $P < 0.001$ ). In the patients who had ACS, without depression, some zones of activation were specified in the right middle occipital gyrus ( $P < 0.001$ ), the right superior frontal gyrus ( $P = 0.088$ ), and the putamen projection on the right ( $P < 0.001$ ) and on the left ( $P = 0.009$ ), as well as the left insular lobe ( $P = 0.015$ ).

**Conclusion:** The pathogenesis of depression is significantly associated with the peculiarities of processing emotionally significant information, regardless of the conditions under which it develops.

**Key words:** *Acute Coronary Syndrome; Depression; fMRI; Brain; Neurophysiology*

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One of the leading causes of death worldwide is heart disease, primarily myocardial infarction – caused by coronary arteries atherosclerosis. The many causing factors of clinical atherosclerosis include dyslipoproteinemia, increased lipoprotein (a) levels, diabetes mellitus, obesity, tobacco smoking, arterial hypertension, and a systemic inflammatory disease (e.g., rheumatoid arthritis). Episodes of myocardial ischemia and primarily acute coronary syndrome (ACS) are significant depression risk factors (1).

According to generalized data, depression is diagnosed in 20-35% after ACS (depending on the type of questionnaire used) (2). M. Yuan *et al.* found these risk factors for depression after ACS to be most important: history of depression, history of antidepressant use, widowhood or housewife status, and presence of congestive heart failure (3).

Early and precise diagnosis of depression in this group requires routine systematic screening, as depression is often unrecognized or misdiagnosed outside of psychiatric healthcare settings (4). Depression affects not only the emotional state of the patient, but it is also a pathological process that affects the main neurohumoral, immunological and vegetative processes of the whole organism (5). Delayed diagnosis of depression results in a negative impact on the prognosis and course of cardiovascular diseases. A large-scale meta-analysis showed that depression after ACS was associated with the higher risk of rehospitalization, more frequent relapse of ACS, and increased mortality. In this regard, the negative impact of depression on ACS seems to be undeniable (6). The issues of early diagnosis of depression become especially important due to the fact that a recent meta-analysis indicated a decrease in the frequency of recurrence of myocardial infarction after successful antidepressant treatment (OR 0.45, 95% CI 0.25-0.81) (7).

Magnetic resonance imaging (MRI) is the leading method for the diagnosis of brain diseases. The recent technological advances have enabled the investigation of the structural and functional state of the brain resulting in new insights into the brain neurobiology. A new approach and the ability to visualize cognitive processes emerged following the introduction of functional magnetic resonance imaging (fMRI). This method enables the location of various cognitive impairments in the cortex. These techniques can be useful for the disease differential diagnosis and course monitoring, and the treatment efficacy evaluation (8, 9). Numerous studies on depressed patients have revealed significant activity changes in brain regions both related to the cerebral hemispheres (frontal, temporal lobes, hippocampus) and to deeper structures such as the amygdala and thalamus (10). However, no fMRI studies have been conducted on the changes in the areas of brain activation in depressive patients who had ACS. At the same time, one of the most promising paradigms for assessing brain activation is

tasks related to the perception of emotionally significant stimuli, for example, various facial expressions (11, 12). In this regard, we undertook the present study aiming at studying brain activation in patients with depression after ACS using fMRI and a face recognition paradigm.

The aim of the present study was to use neuroimaging data features of the brain activity in tasks with emotional stimuli in patients with newly diagnosed depression after ACS, as compared to the features of brain activation in depressive patients who have not undergone ACS and patients after ACS without comorbid depression.

## Materials and Methods

The study was carried out at the Department of Emergency Cardiology of the Myasnikov Institute of Clinical Cardiology, and consulted by a psychiatrist of the Psychotherapeutic Department of the University Clinical Hospital No. 3 of Sechenov University. The study included patients with a depressive episode after a newly diagnosed ACS. The sample of cardiac patients did not include patients with previous episodes of depression or mania. Another sample included depressive patients without cardiac pathologies, recruited among the patients of the Psychotherapeutic Department of the University Clinical Hospital No. 3 of Sechenov University. Patients with general contraindications for MRI, a history of brain trauma, other neurological diseases, or a previous ACS were excluded. MRI- detected structural brain pathologies and depression as part of bipolar affective disorder were also reasons for exclusion from the study. The depression was diagnosed with clinical-psychopathological and psychometric methods based on the analysis of anamnestic information and the mental status of the patient. The depression diagnosis involved the ICD-10 (ICD-10 formal diagnostic criteria require the presence of depressive symptoms for at least 2 weeks. In this regard, after discharge, the patients reached via phone to confirm the persistence of their depressive symptoms.) criteria for a depressive episode. For a formalized assessment of the severity of depression, the Montgomery-Asberg Depression Scale (MADRS) was used, which was completed by a psychiatrist after a detailed mental status assessment. This questionnaire was used because of its well-established high sensitivity and specificity (13). To reliably exclude the bipolar disorder, we employed the bipolarity index, a statistical tool that enables formal assessment of the bipolar disorder risk based on an analysis of the patient's history and status. Based on the available psychometric tests, the patients were excluded from the study if the index value was > 50 points out of 100 (14).

All the subjects underwent standard and functional magnetic resonance imaging on a tomograph with a magnetic induction of 1.5 T. The patients were tested for the emotional information processing with the Pennsylvania Emotion Recognition Test. The choice of this test was associated with accumulating data such that

it allows for identifying the features of the emotionally significant stimuli in depressive patients compared with the controls, both when this test is used independently (10, 15) and as part of the fMRI procedure (12).

The participants were presented with alternating images of 24 faces with different expressions - joyful, sad, and without emotional expression (10). Data processing was made with SPM12 running in MATLAB (r2014b) and xjView applications. fMRI scans were pre-processed using a protocol consisting of slice-time correction, realignment and reslicing, co-registration of the fMRI data to the corresponding anatomical scans, unified segmentation, and normalization of anatomical and functional data to MNI space, and spatial smoothing (12).

Sociodemographic and clinical data were analyzed with SPSS Statistics v23. We used the Kolmogorov-Smirnov test to assess the distribution of variables. We applied a t-test to compare quantitative variables and a chi-square test for qualitative variables, both with a statistical significance set at  $P < 0.05$ . A t-test for independent samples was also used to compare brain activation between groups, and a t-test for dependent samples was utilized to compare changes in activation during treatment. Regional activation was considered significant

at a cluster-level threshold (t-value)  $\geq 2.8$  with  $P < 0.05$  corrected to control the whole-brain family-wise error rate (FWE) (12).

A prerequisite for the inclusion of patients in the study was the signing of their voluntary informed consent. Approval committee opinion of Miasnikov Clinical Cardiology Institute is No. 262, dated 30.11.2020.

#### Ethical Consideration

All patients signed the informed consent form to participate in this study. Ethics committee review board license number is 1103/2021.

#### Results

The study involved 51 patients of both sexes: 35 patients after ACS (11 depressed and 24 non-depressed). They were examined 5-10 days after the onset of ACS. 16 patients with primary depressive episode and recurrent depression without prior coronary event constituted a third group. The analysis of standard MRI images of the brain in five patients with ACS revealed areas of acute cerebrovascular event; these patients were not included in the analysis (Table 1). Table 1 shows the sociodemographic and clinical parameters of samples.

**Table 1. General Sociodemographic and Clinical Characteristics of Study Groups**

Parameters	The Patients with Depression after ACS (n = 11)	The Patients with Depression without ACS (n = 16)	The Patients without Depression after ACS (n = 24)	P-Value
Sex (%)				
Male	(36.4) 4	(12.5) 2	(70.8) 17	0.015
Female	(63.6) 7	(87.5) 14	(29.2) 7	
Age (year)				
ACS	55.7 ± 11.6	37.9 ± 12.5	55.4 ± 9.8	
ST Elevation Myocardial Infarction n (%)	11 (100)	–	17 (70.8)	0.65
Non-ST Elevation Myocardial Infarction n (%)	–	–	5 (20.8)	0.092
Unstable Angina	–	–	2 (8.3)	
Mean MADRS Score	20.2 ± 3.5	26.3 ± 4.4	5 ± 1.4	0.001

Depression after ACS was registered in 11 patients (32.5%) (see Table 1). No patients with bipolar spectrum disorders were identified, while 11 patients were diagnosed with mild depression and 2 with moderate depression. All patients in this group had a depressive episode for the first time in their lives. The mean MADRS score in the patients diagnosed with depression was  $21.1 \pm 3.9$  suggesting mild depression. An analysis of the syndromic structure of the identified depressions revealed

a predominance of anxious depressions (9 observations out of 13, 69%), which is in line with the previous data on the clinical structure of depressive disorders manifesting in cardiovascular pathology (16, 17). Patients with depression without previous ACS had mean MADRS score  $26.3 \pm 4.4$ . This group was also dominated by patients with a primary depressive episode (12 patients, 75%), and 4 patients (25%) were diagnosed with recurrent depressive disorder. In the latter, the number of

depressive episodes in history ranged from 1 to 3. In turn, the symptoms of depression such as anhedonia, cognitive dysfunction, and suicidal ideation were observed in only two patients in this sample.

The group analysis of fMRI findings in the depressed ACS patients revealed a change in the activity of brain neurons following the demonstration of positive and negative paradigms (Table 2). The demonstration of the

neutral paradigm resulted in no changes in the neuronal activation zones.

Table 2 shows the statistical data of clusters and peaks of cortical activation in response to the study task in post-ACS patients with depression. J - joyful emotions, S - sad emotions. Here and further the t-test for independent samples with the family-wise error rate (FWE) correction was used for the analyses (18).

**Table 2. Statistical Data of Clusters and Peaks of Cortical Activation in Response to the Study Task in Post-Acute Coronary Syndrome Patients with Depression. J (Joyful Emotions), S (Sad Emotions)**

Cluster location	Emotions	Volume	t-value	P (FEW corrected)	MNI coordinates
Left middle frontal gyrus, BA 46	S	2237	6.42	< 0.001	-48; 22; 26
Left superior frontal gyrus, BA 10	S	382	5.83	< 0.001	-2; 50; -12
Right fusiform gyrus BA 37	S	771	8.7	< 0.001	-2; 50; -12
Right insular lobe	J	41	5.42	0.017	32; -8; 22

The group analysis of fMRI findings in this group revealed a change in the activity of brain neurons following the demonstration of sad faces in the left middle frontal gyrus, Brodmann area (BA) 46 (Figure 1 1A-1C), the left superior frontal gyrus, BA 10 (Figure 1 2A-2C), the right fusiform gyrus, and BA 37 (Figure 1 3A-3C). The demonstration of joyful faces revealed an activation zone in the right insular lobe (Figure 1 4A-4C).

Figure 1 (1A-1C) shows the activation of the frontal cortex (left middle frontal gyrus, BA 46) in patients with depression after ACS; (2A-2C) shows the activation of the frontal cortex (left superior frontal gyrus, BA 10) in

patients with depression after ACS; (3A-3C) shows the activation of the right fusiform gyrus in the patients with depression after ACS; (4A-4C) shows the activation of the right insular lobe in patients with depression after a coronary event.

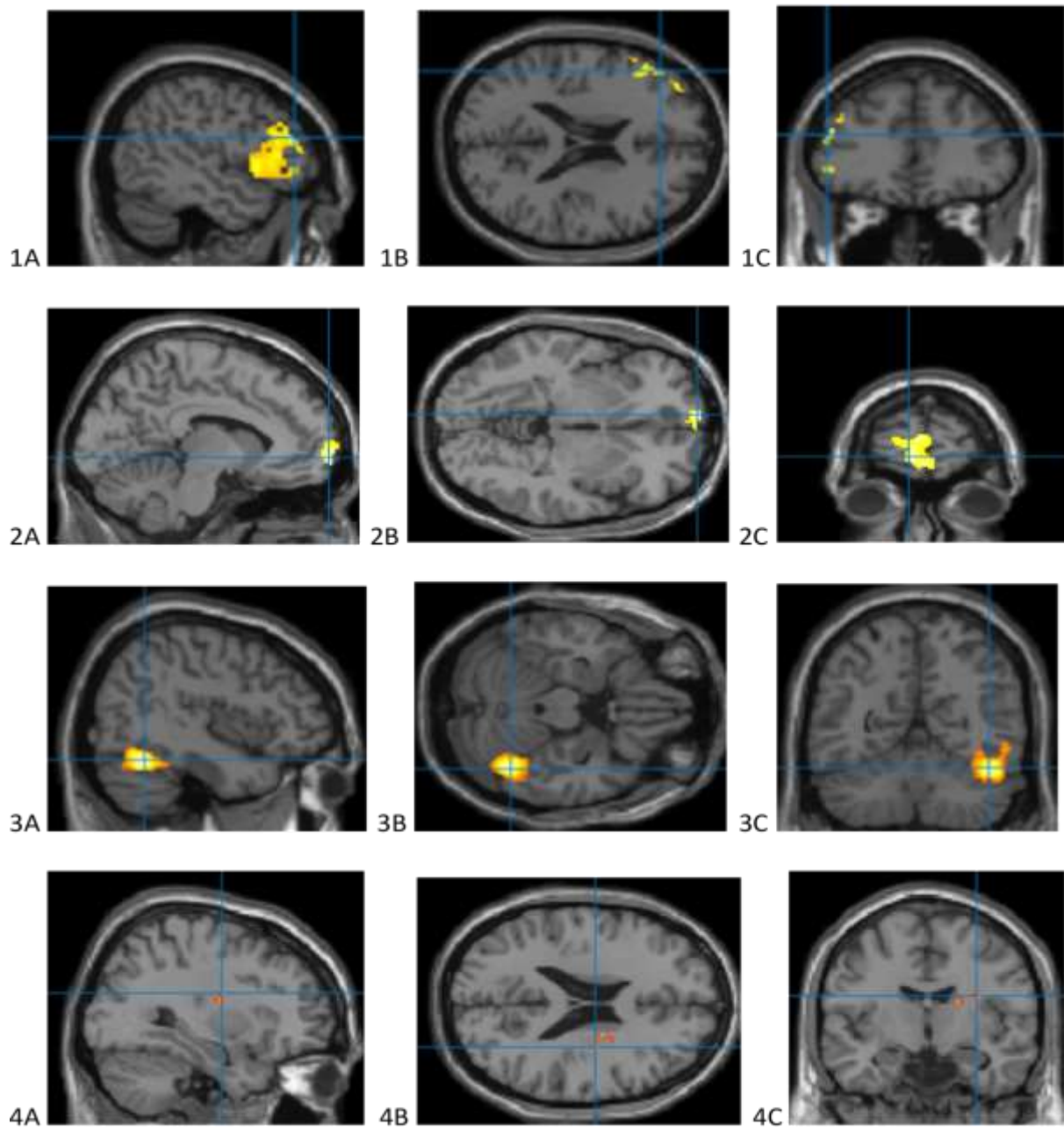
The group analysis of fMRI findings in the patients with depression without ACS revealed a change in the activity of brain neurons following the demonstration of positive, negative, and neutral paradigms (Table 3). Table 3 shows the statistical data of clusters and peaks of cortical activation in response to the study task in patients with depression without a previous coronary event.

**Table 3. Statistical Data of Clusters and Peaks of Cortical Activation in Response to the Study Task in Patients with Depression without a Previous Coronary Event. J - Joyful Emotions, N - Neutral Emotions.**

Cluster location	Emotions	Volume	t-value	P (FEW corrected)	MNI coordinates
Left middle frontal gyrus, BA 46	N	1457	6.24	< 0.001	-48; 38; 20
Right inferior frontal gyrus, BA 46	N	632	8.83	0.001	50; 40; 4
Right middle frontal gyrus	S	2064	10.89	< 0.001	54; 20; 30
Right inferior frontal gyrus	J	2368	8.91	< 0.001	46; 22; 8
Left fusiform gyrus BA 37	N	2001	10.59	< 0.001	-40; -70; -18
Right inferior occipital gyrus	S	3095	16.45	< 0.001	40; -70; -16
Right occipital cortex, BA 17	J	4282	13.27	< 0.001	18; -96; -4
Left middle occipital gyrus, Cuneus	J	2017	10.8	< 0.001	-24; -92; 6

In the patients with depression without a previous coronary event, the demonstration of neutral faces resulted in the following zones of activation in the frontal cortex (Figures 2 1A-1C and 2A-2C), left fusiform gyrus,

BA 37 (Figure 2 4A-4C). The demonstration of sad faces revealed an activation zone in the frontal cortex (Figure 2 3A-3C).



**Figure 1. fMRI. 1A – Sagittal Projection, 1B – Coronal Projection, 1C – Frontal Projection. The Crosshair Points to the Zone of Activation in the Left Middle Frontal Gyrus, BA 46 in the Patients with Depression after ACS. 2A – Sagittal Projection, 2B – Coronal Projection, 2C – Frontal Projection. The Crosshairs Indicate the Area of Activation in the Left Superior Frontal Gyrus, BA 10 in the Patients with Depression after ACS. 3A – Sagittal Projection, 3B – Coronal Projection, 3C – Frontal Projection. The Crosshairs Indicate the Zone of Activation in the Right Fusiform Gyrus in the Patients with Depression after ACS. 4A – Sagittal Projection, 4B – Coronal Projection, 4C – Frontal Projection. The Crosshairs Indicate the Zone of Activation in the Right Insular Lobe in the Patients with Depression after ACS.**

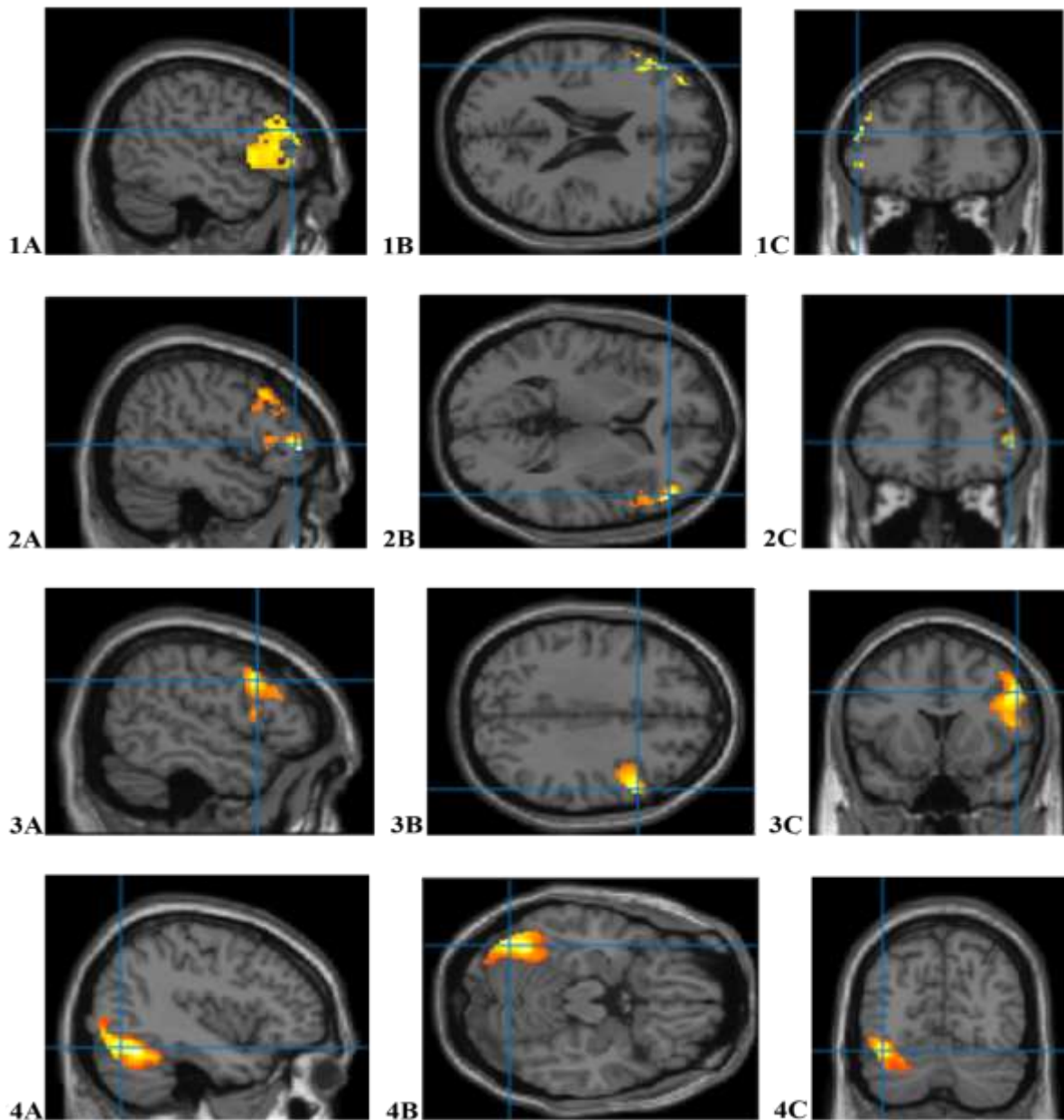


Figure 2. fMRI. 1A – sagittal projection, 1B – coronal projection, 1C – frontal projection. The crosshairs indicate the zone of activation in the left middle frontal gyrus, BA 46 in the patients with depression without ACS. 2A – Sagittal Projection, 2B – Coronal Projection, 2C – Frontal Projection. The Crosshairs Indicate the Zone of Activation in the Right Inferior Frontal Gyrus, BA 46 in the Patients with Depression without ACS. 3A – Sagittal Projection, 3B – Coronal Projection, 3C – Frontal Projection. The Crosshairs Indicate the Zone of Activation in the Right Middle Frontal Gyrus in the Patients with Depression without ACS. 4A – Sagittal Projection, 4B – Coronal Projection, 4C – Frontal Projection. The Crosshairs Indicate the Zone of Activation in the Left Fusiform Gyrus, BA 37 in the Patients with Depression without ACS.

Figure 2 1A-1C shows the activation of the frontal cortex (left middle frontal gyrus, BA 46) in patients with depression without cardiovascular diseases.

2A-2C shows the activation of the frontal cortex (right inferior frontal gyrus, BA 46) in patients with depression without cardiovascular diseases.

3A-3C shows the activation of the frontal cortex (right middle frontal gyrus) in patients with depression without cardiovascular diseases.

4A-4C shows the activation of the left fusiform gyrus, BA 37 in patients with depression without cardiovascular diseases.

The group analysis of fMRI findings in the patients without depression after ACS revealed a change in the activity of brain neurons following the demonstration of neutral and negative paradigms (Table 4).

The demonstration of the joyful paradigm resulted in no changes in the neuronal activation zones.

Table 4 shows the statistical data of clusters and peaks of cortical activation in response to the study task in post-ACS patients without depression.

**Table 4. Statistical Data of Clusters and Peaks of Cortical Activation in Response to the Study Task in Post-ACS Patients without Depression. N - Neutral Emotions, S - Sad Emotions.**

Cluster location	Emotions	Volume	t-value	P (FEW corrected)	MNI coordinates
Right middle occipital gyrus, BA 18	N	741	8.37	< 0.001	42; -82; 4
Right superior frontal gyrus	N	90	8.35	0.088	50; 24; 20
Putamen on the left	S	132	12.95	0.009	-28; -20; 10
Putamen on the right	S	258	8.11	< 0.001	24; 4; 10
Left insular lobe	S	118	6.68	0.015	-26; 18; 12

In the patients with ACS without further depression, the demonstration of neutral faces activated the right middle occipital gyrus, BA 18 (Figure 3 1A-1C) and the right superior frontal gyrus (Figure 3 2A-2C). The demonstration of sad faces resulted in the following zones of neuronal activation: in the projection of the putamen in both hemispheres (Figures 3 3A-3C and 4A-4C) and the insular lobe on the left (Figure 3 5A-5C).

Figure 3 1A-1C shows the activation of the right occipital lobe in patients without depression after coronary event.

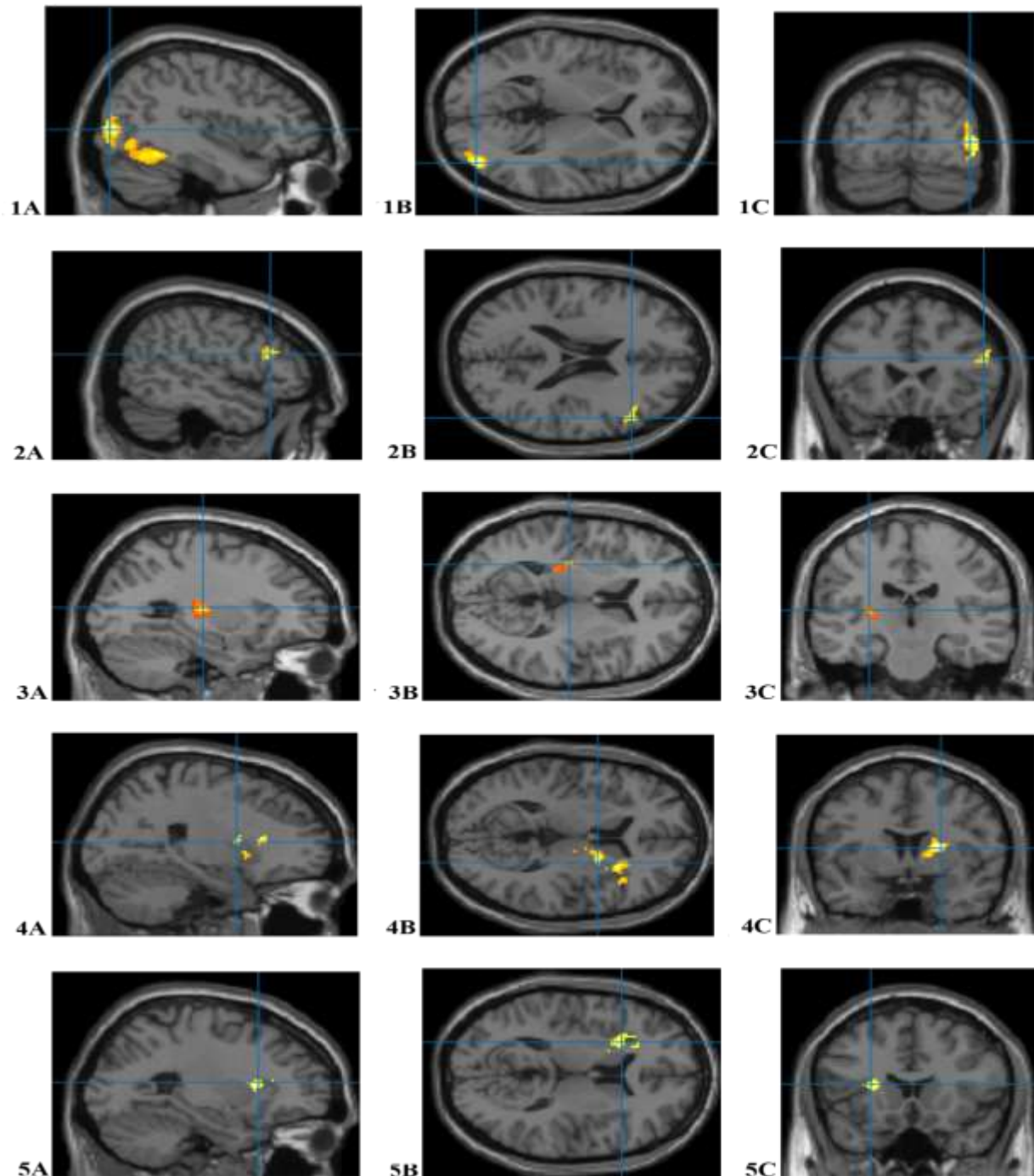
2A-2C shows the activation of the right superior frontal gyrus in patients without depression after coronary event.

3A-3C shows the activation of the left putamen in patients without depression after coronary event.

4A-4C shows the activation of the right putamen in patients without depression after coronary event.

5A-5C shows the activation of the insular lobe on the left in patients without depression after coronary event.

When comparing patients from the group with depression after ACS and patients from the group with depression without previous cardiac pathology, no statistically significant differences were found. However, some trends should be noted. Demonstration of neutral emotions led to more intense activation of the frontal cortex in patients without prior ACS, while in patients with depression after a coronary event, zones of changes in neuronal activity in the frontal cortex were revealed when demonstrating sad faces. The area of face recognition in the fusiform gyrus on the left when showing neutral faces was found in patients with depression without previous cardiac pathology, while in patients with depression after ACS, an activation area was found in the right fusiform gyrus when showing sad faces.



**Figure 3. fMRI. 1A – Sagittal Projection, 1B – Coronal Projection, 1C – Frontal Projection. The Crosshairs Indicate an Area of Activation in the Right Occipital Lobe in non-Depressed Patients after ACS. 2A – Sagittal Projection, 2B – Coronal Projection, 2C – Frontal Projection. The Crosshairs Indicate an Area of Activation in the Right Superior Frontal Gyrus, in non-Depressed Patients after ACS. 3A – Sagittal Projection, 3B – Coronal Projection, 3C – Frontal Projection. The Crosshairs Indicate the Zone of Activation in the Projection of the Putamen on the Left in Patients without Depression after ACS. 4A – Sagittal Projection, 4B – Coronal Projection, 4C – Frontal Projection. The Crosshairs Indicate the Zone of Activation in the Projection of the Putamen on the Right in the Patients without Depression after ACS. 5A – Sagittal Projection, 5B – Coronal Projection, 5C – Frontal Projection. The Crosshairs Indicate the Zone of Activation in the Projection of the Insular Lobe on the Left in the Patients without Depression after ACS.**



**Discussion**

To the best of our knowledge, the study is the first to demonstrate fMRI brain functional changes in the patients with a depression after ACS. The results of the study are generally consistent with previous studies that have been performed on depressed patients without comorbid cardiac pathology.

Thus, according to existing research, the prefrontal cortex plays a leading role in the processing of emotionally significant information. For example, the prefrontal cortex is involved in the cognitive evaluation of stimuli during the emotional tasks processing (19). Activation of the left medial frontal gyrus, the right inferior frontal gyrus, the bilateral precentral gyrus, and the bilateral middle frontal gyrus is the typical response to negative emotional stimuli in patients with depression (19).

In addition to obtaining formal information about age, race and gender, facial expression analysis allows for recognizing a person's emotions, as well as quickly personalizing a face and relating it to a specific person (20). Kanwisher *et al.* for the first time demonstrated the fusiform gyrus involvement in the facial perception. During fMRI, the researchers demonstrated images of people's faces and images of various objects to the patients. A high intensity BOLD-signal (Blood oxygenation level dependent) was revealed in the projection of the fusiform gyrus following facial demonstration compared with demonstration of other objects (21).

In this regard, the insular lobe seems to be extremely important, which reveals a connection both with the cerebral cortex and with the limbic system (22). This brain structure is involved in a range of high-order cognitive functions, including emotional cognitions such as empathy (23). The neuroimaging data demonstrated that insular dysfunction significantly contributes to changes in the functional capabilities of the patients with depression (24, 25).

In a recent study, subjects were shown the faces of people to whom they were indifferent, as well as the faces of those they disliked. When viewing images with a negative pattern, the subjects demonstrated activity in the subcortical regions of the brain (specifically putamen and insular lobe). In this regard, a hypothesis was put forward about the possible involvement of putamen in the formation of such negative emotions as anger and disgust (26).

At the same time, no statistically significant differences were found to differentiate patients with depression after ACS from somatically healthy patients with depression. Depressed patients after ACS according to the fMRI profile turned out to be significantly more similar to younger patients without clinically significant cardiovascular diseases than to those comparable in age and disease. This similarity further emphasizes the significance of our approach, which is quite sensitive to the presence of depression in the patient. Moreover, these results confirm the multietiological nature of depression

and allow for considering ACS as a nonspecific, albeit extremely significant, risk factor (27).

At the same time, some differences were identified at the level of statistically insignificant trends. Most interesting is the more intense activation of the right fusiform cortex in depressed ACS patients. As a hypothesis, we can assume that its greater activation is associated with the psychological characteristics of hospital stay after ACS and reflect the stressful effect of a cardiovascular catastrophe. However, the data available to us do not allow us to confirm this assumption.

**Limitation**

Most of the patients had a ST-segment elevation ACS. Therefore, the results of this study cannot be fully generalized to all patients after ACS. All subjects had a relatively low severity of depression, which makes it impossible to apply the results to patients with various severities of depressions.

**Conclusion**

Our results confirm the pathogenic significance of disturbances in the processing of emotionally significant information in unipolar depression. We identified the changes in the neuronal activation zones in the depressed patients after ACS. Postinfarction depression is quite widespread in patients; however, in most cases, depression remains undiagnosed, and therefore insufficiently treated. Developing new strategies to improve diagnostic approaches for depression after ACS requires a deep understanding of the mechanisms that affect prognosis, as well as knowledge of the care currently provided.

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**Conflict of Interest**

None.

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