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Emotional reactions in patients after frontal lobe stroke

Emocionalno reagovanje kod bolesnika nakon cerebrovaskularnog inzulta u čeonom režnju

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Abstract

Background/Aim. Emotional reactions have been documented after tumor lesions and the other damages of the brain. The aim of this paper was to examine the correlation between frontal lobe lesions and emotional reactions in patients with stroke. **Methods.** The research included 118 patients after stroke. Lesion localization was defined on computed axial tomography records, whereas the area and perimeter of lesion were measured by AutoCAD 2004 software. Examinations by means of the Hamilton Rating Scale for Anxiety and Depression (HRSA and HRSD) were carried out 11–40 days after stroke. Statistic data were processed by simple linear/nonlinear regression, Cox's and the generalized linear model. **Results.** A higher frequency of emotional reactions, i.e. anxiety, was determined in women after stroke ($p = 0.024$). A negative correlation between the lesion size and the intensity of anxiety manifestations was determined (Spearman's $r = -0.297$; $p = 0.001$). Anxiety was more frequent in patients with frontal lobe lesions in the dominant hemisphere (interaction: frontal lesion * hand dominant hemisphere, $p = 0.017$). Also, HRSD score values showed the tendency for lesser decline in case of greater frontal lobe lesions in relation to lesions of other regions of prosencephalon (interaction: frontal lesion * lesion area, $p = 0.001$). **Conclusion.** The results of this study indicate the correlation between evolutionary younger structures of the central nervous system and emotional reactions of man. Therefore, it is necessary to undertake proper early psychopharmacotherapy in the vulnerable group of patients.

Key words:
anxiety; depression; frontal lobe; stroke.

Apstrakt

Uvod/Cilj. Uočena je pojava emocionalnog reagovanja nakon lezija moždanih struktura kod tumora mozga, povreda glave i sl. Cilj našeg rada bio je ispitivanje povezanosti između lezija čeonog lobusa i emocionalnih reakcija kod bolesnika sa moždanim insultom. **Metode.** Istraživanjem je obuhvaćeno 118 osoba nakon cerebrovaskularnog inzulta. Lokalizacija lezije određivana je na aksijalnim nekontrasnim CT snimcima, a površina i obim lezije primenom AutoCAD 2004 digitalne planimetrije. Psihometrijsko ispitivanje pomoću Hamiltonove skale za anksioznost (HRSA) i depresiju (HRSD) izvođeno je 11–40 dana nakon insulta. Statistička analiza podataka vršena je prostom linearnom /nelinearnom regresijom, Cox-ovim hazardnim i generalizovanim linearnim modelom. **Rezultati**. Utvrđena je češća pojava emocionalnih reakcija, tj. anksioznosti, nakon cerebrovaskularnog insulta kod žena ($p = 0.024$). Utvrđena je negativna korelacija između veličine lezije i intenziteta anksioznog ispoljavanja (Spearman-ov $r = -0.297$; $p = 0.001$). Anksioznost je bila češća kod bolesnika sa lezijama čeonog lobusa dominantne hemisfere (interakcija: čeona lezija * motorno-dominantna hemisfera, $p = 0.017$). Takođe, vrednosti HRSD skorova pokazale su tendenciju manjeg opadanja u slučaju većih lezija čeonog lobusa u odnosu na lezije drugih regiona prosencefalona (interakcija: čeone lezije * površina lezije, $p = 0.001$). **Zaključak.** Rezultati našeg istraživanja ukazuju na povezanost između evoluciono mlađih struktura centralnog nervnog sistema i emotivnih reakcija čoveka. U tom smislu potrebno je preduzimanje odgovarajuće rane psihofarmakoterapije kod rizične grupe bolesnika.

Ključne reči:
anksioznost; depresija; mozak, čeoni režanj; mozak, infarkt.

Introduction

Emotional reactions have been documented after tumor lesions and the other damages of the brain [1]. The aim of this paper was to examine the significance of frontal lobe lesions for the control of emotional behaviour in patients with stroke. In our study we started from the hypothesis that frontal lobe lesions (contrary to the lesions of other regions of the

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forebrain) would cause statistically significant changes of emotional behaviour in patients with stroke.

Methods

Inclusion criteria of participants

The research included a total of 118 persons suffering from cerebrovascular stroke (of ischemic and hemorrhagic origin) who had no previously diagnosed psychiatric disorders: 59 male persons and 59 female persons at the age span 44–87 years. The patients were inquired at the Neurological Department of the Institute for Physical Medicine, Rehabilitation and Orthopaedic Surgery "Dr. Miroslav Zotović" Banja Luka. The study had two phases. In the first phase we assessed inclusion criteria, and in the second one we carried out psychological testing. The study included patients with first stroke and macroscopic lesions of prosencephalon on computed axial tomography (CAT) records. CAT records were done in the period of 72 h after stroke and psychometric examination 11–40 days after stroke. The exact day of psychometric testing for each patient was defined by means of the method of random selection. The patients were assessed once in the observed period.

Due to a significant mixture of influences, patients in heavier, comorbid states (heart decompensation, unstable angina, *infarctus myocardii* in the previous year and the year of examination, infective diseases, malignant and chronic immunological diseases) were excluded. Also, the study included only patients with baseline National Institute of Health Stroke Scale (NIHSS) score at the moment of psychological testing $2 \leq X \leq 10$. A total score on NIHSS scale ranges between 0–42, where higher values reflect greater weight of cerebral infarction. NIHSS score of less than 10 includes patients with mild and adequately severe neurological deficit [2]. Among the patients with mild neurological deficit, those were included with whom "drift test" was positive on the same sided extremities (NIHSS = 1 + 1) or NIHSS score had the value of minimum 2 on one of the extremities. Exclusion criteria were also moderate and severe dysphasia since they complicate to a great extent carrying out of verbal neuropsychological tests which were used in our study. The study was approved by the Faculty of Medicine in Banja Luka Ethic Committee and the participants gave informed consent prior to their inclusion in the study.

Research instruments

Thes morphometric research included superacute (up to 24 h) and acute ischemic/hemorrhagic lesions (24 h up to 3 days). Sensitivity of CAT scanner in detection of early ischemic lesions is limited, and only one half of all strokes are visualized within 48 h after the stroke [3, 4]. Brain edema and the mass effect reach their maximum values usually 3 to 5 days after the stroke [4]. Given that in this case the pathological process spreads more and more into the healthy tissue, in our study morphological research was limited to lesions that appeared up to 72 h after the stroke. The measurement of the area of hemorrhagic lesions (in 13 patients) included the zone of cytotoxic edema too.

Localization of lesions with clearly stated damages of specific morphoanatomic structures [5, 6] was defined on non-contrast CAT records (5 mm layer thickness) on the surface of the biggest lesion cross section. Cerebral lesions were classified into the following categories: frontal lobe/other forebrain segments damages; striate body damages (yes/no); limbic lobe, i.e. medial and basolateral limbic cortex, adjacent white matter, limbic nuclei damages (yes/no), and interbrain damages (thalamus and/or hypothalamus) (yes/no). The aforementioned lobe categories have included both cortical and subcortical lesions. To define deep frontal lesions, the border of the frontal lobe at the level of insular cortex and parainsular structure sections was the orthogonal line drawn through the front end of sulcus *circularis insulae* on the axis of *neuraxis* (mediosagittal plane), thus comprising precaudate structures. Mixed lesions that caught the adjacent lobes were included into frontal lesions (25 of total 35 frontal lesions were mixed). The area and perimeter of lesions were measured by AutoCAD digital planimetry (Figure 1) with previous transformation of CAT records into the digital format by means of a digital camera with resolution 8 Mpx. AutoCAD 2004 for PC Windows (developed by Autodesk, Inc. San Rafael, California, USA; see *http://usa.autodesk.com/autocad/*) belongs to programme package groups meant for drawing, projecting and other forms of computer application in engineering practice. This programme package can be used for measuring surfaces which have irregular geometric forms, such as the structures of central nervous system [7].

Fig. 1 – AutoCAD digital morphometry. Frontoparietal cerebrovascular lesion affecting the right *gyrus frontalis superior*, right *gyrus precentralis* and deep anterior groove segment of *gyrus postcentralis*. Area: 966,29 mm², perimeter: 16,577 cm.

Psychometric tests

The following psychometric tests were used to test disorders in psychic functions: the Hamilton Rating Scale for Anxiety (HRSA), 14 items [8]; values 0–13 are in the normal range

(without anxiety), 14–17 indicate mild anxiety and 18–24 moderate anxiety, whereas values ≥ 25 indicate severe anxiety; the Hamilton Rating Scale for Depression (HRSD), 17 scored items [9]; values 0–7 are normal, 8–13 indicate mild depression, 14–18 moderate depression, 19–22 severe depression, whereas values ≥ 23 indicate very severe depression; a questionnaire for qualitative evaluation of object relations in etiopathogenesis of post-stroke behavioural and emotional disturbances [10].

For the purpose of an orientation insight into childhood quality of object relations (up to the age of 18) of patients affected by cerebrovascular stroke, the following parameters were tested: patient's primary family profile compared to its integrity: divorces, death of a parent; continuous separation of the patient from his/her mother: death of mother during childbirth, custody of a child given to father after divorce, the adopted child, woman immature for the role of a mother gives her child to someone else; discontinuous separation of mother from the patient: prolonged hospitalization of mother due to mental illness, prolonged hospitalisation of mother due to somatic illness, parental substitutes – "weekend" mother, which was justified with housing and economic reasons. The patients who presented one or more positive answers were classified into category: detachment from parents = yes, which was used for further statistical analysis. We used the Handedness Questionnaire to evaluate the dominance of brain hemisphere in sensory-motor functions [11, 12].

Statistic analyses

The size of focal lesion was brought in connection with the intensity of emotional manifestations by applying following mathematical/statistical models: Pearson's coefficient of linear correlation (basic assumptions of the linear model: normality, homoscedasticity were tested) [13], simple nonlinear regression as well as Spearman's rank correlation. Besides classical parameters such as odds ratio (OR) and relative risk (RR) we also used Kaplan-Meier's and Cox's hazard model, and Generalized Linear Model. To reduce variability, one examiner, i.e. the first author, carried out all HRSA and HRSD psychometric testing. Statistic analyses were performed using SPSS version 20.0 for Windows. Statistic conclusions were derived on the basis of 2-tailed *p* values and the level of significance $p < 0.05$.

Results

The frontal lobe was affected in 35 (29.7%) of the cases, corpus striatum in 33, limbic lobe in 19, and interbrain (thalamus and/or hypothalamus) in 15 of the cases. The mean value of HRSA score on the examined sample of patients was 7.39 (SD = 4.741, n = 118). Anxiety on the same sample (HRSA positive, i.e. score > 13) was found in 17.8% of the patients and anxiety comorbid with depression (HRSD score > 7) in 11.0% of the cases. The statistical parameter values (Figure 2, Table 1) were obtained by using regression analysis of HRSA score values of all patients (anxious and not anxious) and the area of the biggest cross-section of cerebrovascular lesions.

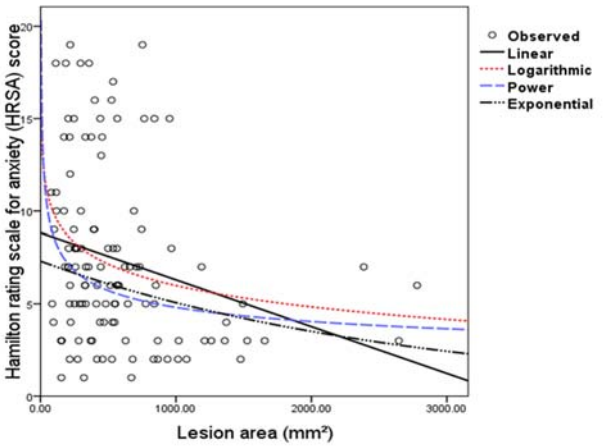

Fig. 2 – Regression analysis between the largest cross-section area of cerebrovascular lesion and the level intensity of anxiety in patients with stroke. X-axis shows values of the area of cerebrovascular lesions (in mm²) measured through the largest cross-section, while Y-axis shows the observed Hamilton Rating Scale for Anxiety (HRSA) score values of patients included in the study. Using the method of least squares the line and curves (logarithmic, power, and exponential) which best fit the observed data are plotted.

A statistically significant linear correlation between the area of the biggest cross-section of cerebrovascular lesions and the intensity of manifestations of anxiety (HRSA scores) ($p = 0.005$) was established by means of regression analysis and

Table 1

Coefficient of determination (R^2) of the largest cross-section area of cerebrovascular lesions and the intensity level of anxiety manifestations [Hamilton Rating Scale for Anxiety (HRSA) score values]

	R^2	F	df1	df2	*p*	Regression constant	Regression coefficient b1
Linear	0.066	8.168	1	116	0.005	8.831	-0.003
Logarithmic	0.068	8.411	1	116	0.004	17.521	-1.669
Power	0.070	8.727	1	116	0.004	27.150	-0.251
Exponential	0.063	7.850	1	116	0.006	7.308	-0.0004

Dependent variable: HRSA score.
The independent variable is lesion area (mm²).
Linear -0.00253 * x + 8.8314.
Power $27.149 * x^{-0.2506}$.

the coefficient of determination (R^2). Due to violation of the basic assumptions of the linear model: normality (Shapiro-Wilk, $p < 0.001$) and homoscedasticity, we examined the Spearman's rank correlation coefficient. A negative correlation between the size of cerebrovascular lesions and the intensity of manifestations of anxiety in the patients with stroke was obtained (Spearman's r = -0.297, $p = 0.001$). Exclusion of high leverage values and values with a high Cook's distance from the regression model did not change the direction of Pearson's r or statistical significance, and the rank correlation coefficient was: Spearman r = -0.294 ($p = 0.001$).

The odds ratio (OR) and relative risk (RR) of dependence of the occurrence of anxiety on variables of interest are shown in Table 2. Kaplan-Meier analysis showed a higher hazard of the occurrence of anxiety in female persons (Log Rank, $p = 0.024$) (Figure 3).

Table 3 shows Cox's regression analysis of the occurrence of anxiety depending on the degree of affection of the frontal lobe. It was established by means of Cox's analysis that the occurrence of anxiety depends on patient's gender. A higher risk for female persons was ascertained ($p = 0.033$). On the other hand, dependence of the occurrence of anxiety on frontal lobe affection was not obtained ($p = 0.277$). By inserting the same independent variables that were used in Table 3 (except for the frontal lobe variable) into Cox's model, we found that the risk of the occurrence of anxiety due to corpus striatum affection was 50.7% lower, but this difference was not statistically significant ($p = 0.223$).

The results of the Generalized Linear Model of the dependence of the intensity of anxiety manifestations (HRSA scores) on frontal lobe affection in the dominant hemisphere are shown in Table 4 and Figure 4.

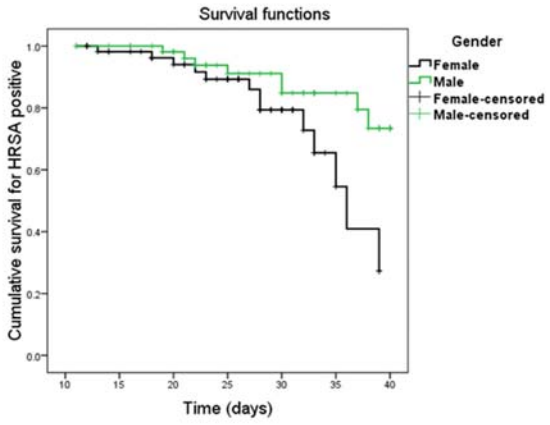

Fig. 3 – Kaplan-Meier hazard analysis of anxiety manifestations in patients with stroke depending on the patients gender. "Survival functions" is the common name for presented functions, since the initial tests were used to assess the risk of death from specific disease. The lower the curve of an event (in our example the occurrence of anxiety) for the modality of tested characteristics (gender of respondents), the higher the risk.
HRSA – Hamilton Rating Scale for Anxiety.

Table 2

Odds ratio and relative risk of anxiety occurrence in patients with stroke

Variable	Odds ratio (OR)	Relative risk (RR)	Fisher's exact test (2-sided)
Gender (female / male)	1.802	1.625	0.336
Detachment from parents (e.g. death of parent or divorce before age 18) (yes / no)	1.853	1.628	0.328
Hand-dominant hemisphere (yes / no)	2.163	1.903	0.153
Frontal lobe / Other forebrain segments	1.595	1.459	0.430
Striated body (yes / no)	0.552	0.606	0.425
Limbic lobe (limbic cortex, adjacent white matter, limbic nuclei) (yes / no)	0.844	0.868	0.999
Diencephalon (yes / no)	0.680	0.723	0.999
Hemorrhagic lesion (yes / no)	1.450	1.346	0.700

Table 3

Cox's regression analysis of anxiety occurrence in patients with stroke – affected frontal lobe

	Regression coefficient b	SE	df	*p*	Hazard ratio e^b (HR)	95.0% CI for HR	
						lower	upper
Gender (female / male)	1.008	0.474	1	0.033	2.739	1.082	6.932
Detachment from parents (yes / no)	0.183	0.577	1	0.751	1.201	0.387	3.725
Lesion area (mm^2)	-0.00065	0.001	1	0.377	0.9993	0.998	1.001
Hand dominant hemisphere (yes / no)	0.579	0.492	1	0.239	1.784	0.681	4.676
Frontal lobe (yes / no)	0.566	0.521	1	0.277	1.762	0.635	4.889

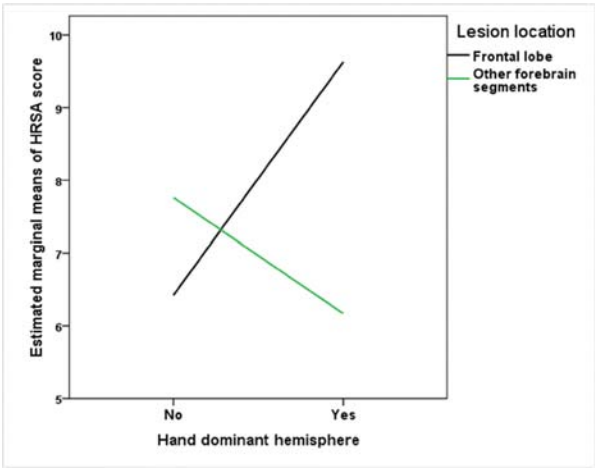

Fig. 4 – Estimated marginal means of Hamilton Rating Scale for Anxiety (HRSA) score. Figure shows estimated marginal means of HRSA score in case of simple or combined affectedness of the frontal lobe and hand dominant hemisphere. Simultaneous lesion of the frontal lobe and hand dominant hemisphere abruptly amplifies the value of HRSA score (p = 0.017).

The results of the Generalized Linear Model of dependence of the intensity of depression manifestations (HRSD scores) on frontal lobe affection and the size of cerebrovascular lesions are shown in Table 5 and Figure 5.

By applying the Generalized Linear Model we established that greater frontal lobe lesions (in relation to lesions of other regions of the forebrain) are associated with a smaller decrease in the intensity of manifestations of depression (p = 0.001). In case of damages of other regions of the forebrain, the regression coefficient was b = -0.000650, whereas in case of damage of the frontal lobe the regression coefficient increases and has the value b = 0.000463 (Table 5). Using the formula ln(Y) = 1.9369 - 0.000650 · [lesion area (mm²)] + 0.000463 · [lesion area (mm²) · frontal lobe (No = 0; Yes = 1)] in case of the lesion size of 218.72 mm² and damage of the other regions of prosencephalon, the predicted value of the mean of response of HRSD score was: $Y = e^{1.794732}$, that is, 6.018 (Euler's number, e = 2.71828), while in case of frontal lobe damage by the same lesion size the HRSD score is somewhat higher: $Y = e^{1.895999}$, that is, 6.659. An insight into the effect of the interaction frontal lobe * lesion area is gained by comparing the previously obtained values with HRSD score for greater lesions. For the lesion size of 1211.52 mm², HRSD score was Y = 3.156 due to damage of the other regions of prosencephalon, whereas in the case of frontal lobe it amounts to Y = 5.531, which is proportionally much greater than in the previous case 75.3% : 10.7% (Figure 5).

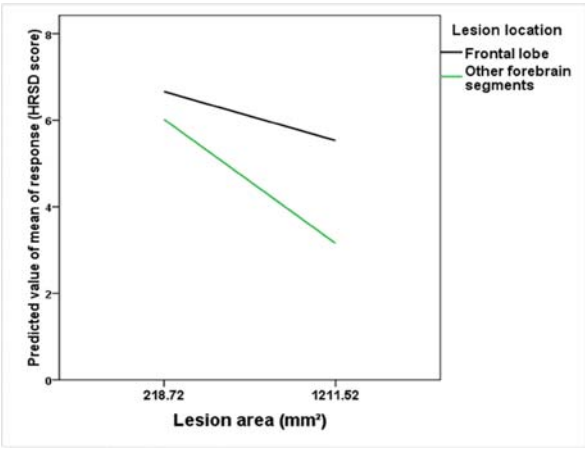

Fig. 5 – Interaction: frontal lobe * lesion area. The figure portrays significantly lesser decrease of Hamilton Rating Scale for Depression (HRSD) score when the frontal lobe is affected.

Table 4

Generalized linear model of dependence between anxiety manifestations [Hamilton Rating Scale for Anxiety (HRSA) scores] and frontal dominant lobe lesions

Parameter	Tests of model effects Generalized linear model: gamma with log link robust estimator		
	Wald chi-square	df	*p*
Intercept	833.110	1	< 0.001
Lesion area (mm²)	12.787	1	< 0.001
Frontal lobe * Hand dominant hemisphere	10.186	3	0.017

Dependent variable: HRSA score.
Model: intercept, lesion area (mm²), frontal lobe *hand dominant hemisphere.

Table 5

Generalized linear model of dependence between depressive manifestations [Hamilton Rating Scale for Depression (HRSD) scores] and the size of frontal lesions

Parameter	Regression coefficient b	SE	95% Wald confidence interval		Hypothesis test		
			Lower	Upper	Wald chi-square	df	*p*
Intercept	1.9369	0.075170	1.7896	2.0843	663.959	1	< 0.001
Lesion area (mm²)	-0.000650	0.000120	-0.000886	-0.000415	29.317	1	< 0.001
[Frontal lobe = Yes] *Lesion area (mm²)	0.000463	0.000134	0.000201	0.000726	11.969	1	0.001
[Frontal lobe = No] *Lesion area (mm²)	0*						

***Set to zero because this parameter is redundant.**

In the example dependence analysis of the intensity of depression symptoms on the size of lesions and affection of the frontal lobe (Table 5), we point out to authors that the value of correlation of the assessed parameters: lesion area with frontal lobe (Yes) * lesion area was 0.622. By using the general linear model with a transformed fourth root dependent (HRSD score) and an independent (lesion area) variable in order to satisfy the assumptions of the model (normality and homogeneity of variances), the observed power of the lesion area parameter was 0.967, while the observed power of the parameter frontal lobe (Yes) * lesion area amounted to an acceptable 0.790. By using linear regression with the stated transformed fourth root variables, collinearity between independent variables (lesion area and frontal lobe (Yes) * lesion area), that is, variance inflation factor was: VIF = 1.163, whereas the Condition Index = 12.634. The general linear model and multiple linear regression with transformed variables confirmed the results of the generalized linear model.

Discussion

Incidence of anxiety in patients with stroke

The frequency of anxiety in patients with cerebrovascular accident to a great extent depends on the design of the study, that is, the time of observing the patients as well as the psychometric tests used thereby. De Wit et al. [14] established the prevalence of anxiety two months after stroke in 25% of patients. This prevalence was 22% four and six months after the occurrence of stroke. Similarly, Aström [15] found the generalized anxiety disorder (GAD) in the early stages after stroke (the first three months) in 28% of the patients. Leppävuori et al. [16] describe the frequency of GAD three to four months after stroke of 20.6%. Observed over a longer period (3–5 years after stroke), the frequency of anxiety disorder does not differ significantly, amounting to about 20% [17].

By contrast to the mentioned studies, we stress that in our research we investigated the frequency of anxiety according to the HRSA criteria, and not the diagnostics of anxiety disorder (for instance, according to ICD-10 or DSM-IV). The frequency of anxiety 11–40 days after the occurrence of stroke amounted to 17.8%. We explain the differences in the frequency of anxiety in our research (17.8%) in relation to the one found in other studies [14, 15] (25% and 28%, respectively) in terms of different design of those studies, that is, later observation period (2–3 months after stroke), diagnosing anxiety by means of other measurement scales (for example, by using "Hospital Anxiety Scale"), as well as the presence of poorer somatic state of patients in our study due to a shorter period of recovery after stroke. A relatively low frequency of anxiety in our study is explained by the characteristics of HRSA that attaches greater significance to somatic equivalents of emotions, but also to the specific milieu our study was done in, which improves patients' psychosomatic state (patient health care involving rehabilitation Z50). There also arises the question of the validity of the study methodology in the acute phase of stroke (the first three months), given that the presence of anxiety symptoms is necessary to last as long as six months for diagnosing the generalized anxiety disorder by DSM-IV criteria [15].

Correlation analysis between intensity of anxiety manifestations and the size of cerebrovascular lesions

Interestingly, the literature on this subject is scarce. Sharpe et al. [17] exclude the connection between the size of lesion and the intensity of anxiety, but this study was done with patients three to five years after stroke. On the other hand, we examined this connection in the subacute phase, that is, 11–40 days after stroke. In our study the linear determination coefficient for the area of the biggest cross-section of cerebrovascular lesions and the intensity of anxiety manifestations (HRSA scores) was $R^2 = 0.066$ ($p = 0.005$). Due to a significant deviation of the basic assumption of the linear model – normality of the observed HRSA score values, as well as because of the presence of more severe heteroscedasticity (at lower values of the lesion area), the rank correlation coefficient was calculated. Spearman's coefficient was $r = -0.297$ ($p = 0.001$). A negative correlation between the lesion size and the intensity of anxiety manifestation was confirmed in this way. We explained a lower intensity of anxiety manifestations in patients with a greater area of cerebrovascular lesions by the activation of repair mechanisms due to poorer somatic state of patients in the subacute phase of stroke. From the viewpoint of evolutionary psychology and works of some researchers, depression-withdrawal has a defence character with the aim of saving organism energy [18]. In a similar way, greater lesions of the brain might also activate defence mechanisms associated with stopping the anxiety and energy saving. A high frequency of mild anxiety in our study (71.4% of the total anxiety) speaks in favour of this. One of the reasons for the indifference of patients with greater strokes, which is in accordance with the James-Lange theory of emotions, is the malfunctioning of peripheral sensitive/proprioceptive innervations (due to neurological deficits) that act as the antecedent of emotions. Although this concept was abandoned in favour of the Papez-MacLean theory of emotions, Damasio [19] explains the emergence of consciousness by means of these peripheral mechanisms. In an earlier research, we used these mechanisms to explain a lower intensity of depression manifestations (HRSD scores) due to greater cerebrovascular lesions of the brain (Spearman's $r = -0.263$, $p = 0.004$) [20].

Gender and anxiety in patients with stroke

The results anxiety dependence on gender differ in the literature. Schultz et al. [21] describe a higher frequency of anxiety and vulnerability of female and younger persons, whereas De Wit et al. [14] deny these differences. In our study, the risk for female persons (OR) was 1.802 times higher in relation to male persons, but this difference was not statistically significant ($p = 0.336$). However, a statistically important risk for women was determined by using the Kaplan-Meier model (Log Rank, $p = 0.024$) (Figure 3).

Side of hemispheric lesion and anxiety occurrence in patients with stroke

Results are contradictory with respect to the affected side of hemisphere. Aström [15] and Castellanos-Pinedo at al. [22] point to a higher frequency of anxiety disorder in persons with right-hemisphere lesions, whereas Williams [23] stress the affection of the left hemisphere. Schramke et al. [24] indentify a more pronounced distress in patients with left-sided lesions by using the Beck Anxiety Inventory. In our study we evaluated the dependence of anxiety occurrence on the damage of the motor-dominant hemisphere because of a greater operating-functional deficit of patients (affected dominant hand) which could have an impact on the occurrence of anxiety. A higher risk due to the affection of the dominant hemisphere was found, but it was not statistically significant (OR = 2.163, $p = 0.153$).

Morpho-anatomical localization of lesions and anxiety occurrence in patients with stroke

Sharpe et al. [17] exclude the connection between the localization of lesions and the intensity of anxiety. On the other hand, Tang et al. [25] suggest that right frontal acute infarcts may play a role in the development of post-stroke anxiety symptoms (OR = 4.44, $p = 0.002$). Robinson and Starkstein [26] associate the connection of major depression and the generalized anxiety disorder with cortical lesions, and isolated depression with subcortical lesions. Knutson et al. [27] in patients with penetrating brain injuries indicate anxiety to lesions of limbic areas and temporal lobe. When it comes to the affection of the prosencephalon structures in our study, the risk of the occurrence of anxiety is higher with the frontal lobe damage (OR = 1.595), while being lower in the case of corpus striatum and lobus limbicus (corpus striatum: OR = 0.552; lobus limbicus: OR = 0.844), but these differences are not statistically significant ($p > 0.05$). Although not statistically significant (Cox's model), the affection of basal ganglia is associated with 50.7% lower hazard of anxiety occurrence, which does not speak in favour of the thesis that the lesions of these anatomical structures are the cause of native emotional disorders in Parkinson's and Huntington's disease. The tendency of the development of anxiety due to the affection of the frontal lobe in the dominant hemisphere (Table 3) indicates the importance of cognitive functions in the etiopathogenesis of anxiety disorders, for instance, mistakes in making conclusions, anticipation and similar. A small number of positive cases of anxiety in our study represents one of the deficiencies of the risk parameters (OR and HR), which has an impact on the values of inferential statistics. In order to compensate for this and substantially increase the quantity of information as well as the examined sample (to n = 118), we processed data by means of the generalized linear model. Due to the earlier stated properties of empirical values of HRSA score, we used a subclass of the model: gamma with log link – robust estimator. This model showed a dependence and higher intensity of manifestations of anxiety due to frontal lobe lesions in the dominant hemisphere ($p = 0.017$) (Table 4, Figure 4). However, it is necessary to stress that the simple summation effect, was not determined in this case, but an interaction i.e. boosting effect of the frontal lobe and hand dominant hemisphere damages on the occurrence of anxiety manifestations. This effect is similar, for example, to the boosting effect of alcohol and benzodiazepines on the respiratory depression. We should also bear in mind that the persons with lesions in the dominant hemisphere suffer and anticipate a greater neurological operating-functional deficit given that the dominant hand is affected, which makes it the case that the stated interaction is not necessarily a consequence of the lateralization of the functions of the frontal lobe in the cerebral hemispheres. That cognitive functions play an important part in etiology of anxiety speaks in favour of the study [28] which associates deterioration of anxiety with better mentality. On the other hand, Starkstein and Tranel [29] stress that damage of ventromedial prefrontal cortex diminishes anxiety and thought concern for the future. Therefore, we recommend that impact of frontal lobe lesions on anxiety should be further investigated.

Frontal lobe lesions and depression

Some authors mention left anterior lesions, that is, lesions of the cerebral hemispheres that are closer to the frontal pole in the etiopathogenesis of post-stroke depressive disorders [30–35]. Tham et al. [36] have highlighted pathology of white matter in prefrontal brain region. On the other hand, other authors [37–39] exclude the connection between post-stroke depressions and left anterior lesions of the hemispheres, whereas Finset et al. [40] make connection between depression and deep retrorolandic lesions. We ascertained in our study that the greater frontal lobe lesions (in relation to lesions of other regions of the forebrain) are associated with a smaller decrease in the intensity of depression manifestations ($p = 0.001$) (Table 5, Figure 5). We had not noticed this in the previous study [20] given that we had not used the generalized linear model. The interaction frontal lesion * lesion area in the case of depression and the interaction frontal lesion * hand dominant hemisphere in the case of anxiety are precisely what proves the working hypothesis.

The frontal lobe is the seat of evolutionary younger and higher cortical functions: abstract thinking, judgement and attention [1]. Even though some authors [41] point out that humans and large primates have an equal size of the frontal cortex as the common characteristic, they do not exclude evolutionary upgrade and a higher degree of interconnectivity between the frontal areas in humans. In this sense, the frontal lobe damage and its connection with emotional disorders (depression and anxiety) which was confirmed in our study indicate the significance of evolutionary younger central nervous system structures and their relation to regulation of emotional behaviour in man.

Strength and limitations of study

As a limitation of our study we state the small number of positive cases of anxiety (HRSA positive), which makes it the case that the odds ratio (OR) and Cox's model analysis results are not definitive. In the example of the analysis of the dependence of the intensity of depression symptoms on the lesion size and the affection of the frontal lobe, we rec-

ommend increasing the sample due to a relatively high correlation of the assessed parameters, in order to ensure reproducibility of significant results.

The applicability of our study is limited to the population of patients in the subacute phase of stroke (11–40 days), given that poorer somatic state had a significant impact on the results. The advantages would be seen in a detailed statistical analysis in which a greater number of statistical models were used, and thereby in disclosure of hidden interactions that prove the dependence of emotional disorders in man on the lesions of specific brain regions.

Conclusion

Frontal lobe lesions are associated with changes in the emotional behaviour of patients with stroke. The results of this study indicate the significance of phylogenetically/evolutionary younger structures of the central nervous system for the regulation of emotional behaviour of man. Therefore, it is necessary to undertake proper early psycho/pharmacotherapy in the vulnerable group of patients.

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REFERENCES

1. *Kalicanin P.* Psychiatry. Belgrade: Draslar Partner; 2002. (Serbian)
2. *Brott T, Adams HP, Olinger CP, Marler JR, Barsan WG, Biller J,* et al. Measurements of acute cerebral infarction: a clinical examination scale. Stroke 1989; 20(7): 864−70.
3. *Daffner RH.* Clinical radiology. Baltimore (USA): Williams and Wilkins; 1993.
4. *Rumbaugh CL, Wang AM, Tsai FY.* Cerebrovascular disease: Imaging and interventional treatment options. New York: Igaku-Shoin Medical Publishers; 1995.
5. *Heimer L.* The human brain and spinal cord: functional neuroanatomy and dissection guide. New York: Springer-Verlag; 1995.
6. *Marinkovic S, Milisavljevic M, Kostic V.* The functional and topographical neuroanatomy. 2nd ed. Belgrade: Nauka; 1998. (Serbian)
7. *Spasojevic G, Stojanovic Z, Suscevic D, Malobabic S.* Sexual dimorphism of the human corpus callosum-digital morphometric study. Vojnosanit Pregl 2006; 11(63): 933−8. (Serbian)
8. *Hamilton M.* The assessment of anxiety states by rating. Br J Med Psychol 1959; 32(1): 50−5.
9. *Hamilton M.* A rating scale for depression. J Neurol Neurosurg Psychiatr 1960; 23: 56−62.
10. *Sandic M.* Dyadic relation reflection on the war-related posttraumatic stress disorder. Banja Luka: Grafoinval; 2000. (Serbian)
11. *Coren S.* The left-hander syndrome: The causes and consequences of left-handedness. New York: Vintage; 1993.
12. *Porac C, Coren S.* Lateral preferences and human behavior. New York: Springer-Verlag; 1981.
13. *Lovric M, Komic J, Stevic S.* Statistical analysis: methods and application. Banja Luka: Faculty of Economics; 2006. (Serbian)
14. *de Wit L, Putman K, Baert I, Lincoln NB, Angst F, Beyens H,* et al. Anxiety and depression in the first six months after stroke. A longitudinal multicentre study. Disabil Rehabil 2008; 30(24): 1858−66.
15. *Aström M.* Generalized anxiety disorder in stroke patients. A 3-year longitudinal study. Stroke 1996; 27(2): 270−5.
16. *Leppävuori A, Pohjasvaara T, Vataja R, Kaste M, Erkinjuntti T.* Generalized anxiety disorders three to four months after ischemic stroke. Cerebrovasc Dis 2003; 16(3): 257−64.
17. *Sharpe M, Hawton K, House A, Molyneux A, Sandercock P, Bamford J,* et al. Mood disorders in long-term survivors of stroke: associations with brain lesion location and volume. Psychol Med 1990; 20(4): 815−28.
18. *Engel G.* Psychological development in health and disease. Philadelphia: Saunders; 1962.
19. *Damasio A.* The feeling of what happens: Body and emotion in the making of consciousness. New York: Harvest Books; 2000.
20. *Stojanovic Z, Vukadinovic Stojanovic S.* Correlation analysis between depressive manifestations and morphological lesion characteristics in patients with stroke. Sanamed 2014; 9(1): 31−40.
21. *Schultz SK, Castillo CS, Kosier JT, Robinson RG.* Generalized anxiety and depression. Assessment over 2 years after stroke. Am J Geriatr Psychiatry 1997; 5(3): 229−37.
22. *Castellanos-Pinedo F, Hernández-Pérez JM, Zurdo M, Rodríguez-Fúnez B, Hernández-Bayo JM, García-Fernández C,* et al. Influence of premorbid psychopathology and lesion location on affective and behavioral disorders after ischemic stroke. J Neuropsychiatry Clin Neurosci 2011; 23(3): 340−7.
23. *Williams AM.* Self-report of indifference and anxiety among persons with right hemisphere stroke. Res Nurs Health 1992; 15(5): 343−7.
24. *Schramke CJ, Stowe RM, Ratcliff G, Goldstein G, Condray R.* Post-stroke depression and anxiety: different assessment methods result in variations in incidence and severity estimates. J Clin Exp Neuropsychol 1998; 20(5): 723−37.
25. *Tang WK, Chen Y, Lu J, Liang H, Chu WC, Tong MV,* et al. Frontal infarcts and anxiety in stroke. Stroke 2012; 43(5): 1426−8.
26. *Robinson RG, Starkstein SE.* Current research in affective disorders following stroke. J Neuropsychiatry Clin Neurosci 1990; 2(1): 1−14.
27. *Knutson KM, Rakowsky ST, Solomon J, Krueger F, Raymont V, Tierney MC,* et al. Injured brain regions associated with anxiety in Vietnam veterans. Neuropsychologia 2013; 51(4): 686−94.
28. *Ku H, Chen C, Yang Y, Hu C, Wu D, Chen C,* et al. Association between cerebral lesions and emotional changes in acute ischemic stroke patients. J Nerv Ment Dis 2013; 201(5): 400−6.
29. *Starkstein SE, Tranel D.* Neurological and psychiatric aspects of emotion. Handb Clin Neurol 2012; 106: 53−74.
30. *Aström M, Adolfsson R, Asplund K.* Major depression in stroke patients. A 3-year longitudinal study. Stroke 1993; 24(7): 976−82.

31. *Lipsey JR, Robinson RG, Pearlson GD, Rao K, Price TR.* Mood change following bilateral hemisphere brain injury. Br J Psychiatry 1983; 143: 266−73.
32. *Robinson RG, Kubos KL, Starr LB, Rao K, Price TR.* Mood disorders in stroke patients. Importance of location of lesion. Brain 1984; 107(Pt 1): 81−93.
33. *Robinson RG, Lipsey JR, Bolla-Wilson K, Bolduc PL, Pearlson GD, Rao K*, et al. Mood disorders in left-handed stroke patients. Am J Psychiatry 1985; 142(12): 1424−9.
34. *Starkstein SE, Robinson RG, Price TR.* Comparison of cortical and subcortical lesions in the production of poststroke mood disorders. Brain 1987; 110(Pt 4): 1045−59.
35. *Kucharska-Pietura K, Hunca-Bednarska A.* Emotional behavior in schizophrenia and one-sided brain damage. Cerebral hemispheric asymmetry. Part I. Psychiatr Pol 2002; 36(3): 421−34.
36. *Tham MW, Woon PS, Sum MY, Lee T, Sim K.* White matter abnormalities in major depression: evidence from post-mortem, neuroimaging and genetic studies. J Affect Disord 2011; 132(1−2): 26−36.
37. *Sharpe M, Hawton K, House A, Molyneux A, Sandercock P, Bamford J,* et al. Mood disorders in long-term survivors of stroke: associations with brain lesion location and volume. Psychol Med 1990; 20(4): 815−28.
38. *Aben I, Lodder J, Honig A, Lousberg R, Boreas A, Verhey F.* Focal or generalized vascular brain damage and vulnerability to depression after stroke: a 1-year prospective follow-up study. Int Psychogeriatr 2006; 18(1): 19−35.
39. *House A, Dennis M, Warlow C, Hawton K, Molyneux A.* Mood disorders after stroke and their relation to lesion location. A CT scan study. Brain 1990; 113(Pt 4): 1113-29.
40. *Finset A, Goffeng L, Landrø NI, Haakonsen M.* Depressed mood and intra-hemispheric location of lesion in right hemisphere stroke patients. Scand J Rehabil Med 1989; 21(1): 1−6.
41. *Semendeferi K, Lu A, Schenker N, Damasio H.* Humans and great apes share a large frontal cortex. Nat Neurosci 2002; 5(3): 272−6.

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