DIFFERENTIATION OF COGNITIVE STATUS IN PATIENTS WITH CORONARY ARTERY DISEASE USING EEG CLUSTERIZATION BY DISCRETE OPTIMIZATION WITH A MINIMAX CRITERION

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Abstract. Cognitive status and EEG in the theta, alpha, and beta ranges were studied using cluster analysis by discrete optimization in patients with cardiovascular disease in the preoperative period of coronary artery bypass grafting. The cognitive status was measured by Mini-Mental State Examination (MMSE) scale, and an integral indicator of cognitive status (IICS) formed on the basis of complex testing the indices of visual-motor responses, attention, and memory. The new method of clustering the EEG power and the cognitive status made it possible to distinguish groups of patients differenced by cognitive reserves. The IICS better differentiates groups than MMSE. The factors of age and education were decisive only in specific groups. The clusters characterized by the most represented cognitive reserves according to the higher both MMSE and IICS indicators included less pronounced activation of the cortex according to more power of the theta, alpha, and less beta rhythm. Patients with supposedly minimal reserves are differed by a low level of cognitive status, as well as education level together with higher activation state of the cortex. The third type of clusters was distinguished by an unstable composition due to the variability of EEG indicators in it, mostly cortical activity at the alpha1 frequencies. The EEG neurophysiological approach, together with cognitive screening and proposed clustering analysis, could be helpful in understanding mechanisms of cognitive reserves and identify the risk factors of postoperative cognitive dysfunction in patients with brain cardiovascular damage.

Keywords: cognitive status, EEG, patients with coronary artery disease, clustering by discrete optimization, cognitive reserves.

List of Abbreviations

CVD – cardiovascular disease
EEG – electroencephalograhy
IICS – integral indicator of cognitive status
MCI – mild cognitive impairment
MMSE – Mini-Mental State Examination
POCD – postoperative cognitive dysfunction

Introduction

The compensatory significance of the education factor in the aging-associated development of cognitive dysfunctions is well known (e.g., Benson *et al.*, 2016; Glumac *et al.*, 2019). The results of our recent analysis of the content of publications presented in PubMed in the period 1990-2019 indicate the growing interest of researchers not only due to the education role as a compensatory brain reserve but also to EEG characteristics in different frequency ranges, especially in high-frequency beta ranges (Bakaev & Razumnikova, 2020). Mini-Mental State Examination (MMSE) scores are widely used to diagnose cerebral dysfunctions in the clinical setting. However, it is not a sensitive instrument and allows diagnosing only pronounced impairments of cognitive activity. Further work is needed to validate cognitive screening tools in the perioperative setting and to search for informative predictors of the cognitive status for assessing the overall frailty status in patients. For a more differentiated diagnosis of cognitive deficit that develops during cerebral ischemia due to cardiovascular disease and / or after a coronary bypass operation undertaken to treat such patients, an integral indicator of cognitive status (IICS) is used. IICS is formed on the basis of complex testing of the indices of visual-motor responses, attention, and memory and their subsequent normalization relative to the group of healthy people (Trubnikova *et al.*, 2017).

It has been shown that both age and low educational level are significant factors in reducing the cognitive status of patients with diagnosed coronary heart disease and surgical intervention for its treatment (Benson *et al.*, 2016; Glumac *et al.*, 2019; Gregory *et al.*, 2021; Kotekar *et al.*, 2018; Trubnikova *et al.*, 2017). Older patients with reduced preoperative cognitive functions are at risk of developing dementia within 5 years after cardiac surgery (Lingehall *et al.*, 2017). Postoperative cognitive dysfunction (POCD) has been found in a third of patients within a year after a surgery that limits their functional recovery and quality of life (Harrington *et al.*, 2011). Poor preoperative cognitive functions are a risk factor for POCD and play in predicting adverse events (Millar *et al.*, 2001; Newman *et al.*, 2001; O'Reilly-Shah *et al.*, 2019; Tarasova *et al.*, 2018; 2021). As the preoperative cognitive impairment is a leading risk factor for POCD their identifying is critical to create and implement the appropriate preventive strategies (Hasan *et al.*, 2020; Styra *et al.*, 2019). Therefore, further research using cognitive screening tools is necessary to identify cognitive dysfunctions, which can be intervened preemptively.

Different hypotheses are proposed to POCD understanding, such as excessive dopamine or reduced acetylcholine availability (i.e. neurotransmitter hypotheses) or ‘unmasking’ neurocognitive dysfunction due to surgical intervention in patients with underlying cerebrovascular disease or preclinical AD pathology (Mahanna-Gabrielli et al., 2019). EEG spectrum activity is sensitive to detect cardiovascular health and different impairments of cognitive functions (Musha *et al.*, 2013; Shibata *et al.*, 2017).

It was shown that vascular lesions in MCI induce an increase of slow delta and theta frequency EEG power, whereas cholinergic deafferentation and or corticocortical disconnection are associated with a significant reduction in alpha and beta power (Sheorajpanday *et al.*, 2013; Shibata *et al.*, 2017). An increase in the theta oscillations is considered a predictor of postoperative cortical dysfunction (Tarasova *et al.*, 2016; Trubnikova *et al.*, 2017). The lateral specificity of the theta oscillations changes, i.e. a greater power of the left hemispheric rhythm, characterizes the dynamics of the development of persistent POCD (Tarasova *et al.*, 2018). Other predictors of POCD development at the stages of early or late postoperative examination may be changes in biopotentials in the alpha and beta ranges (Tarasova, *et al.*, 2018; 2021).

Therefore, the aim of this work was to identify the most informative markers of the preoperative cognitive status of patients for differentiation of cognitive reserves using neuropsychological indicators, such as MMSE and IICS, as well as a power of low- and high-frequency rhythms of EEG in the left and right hemispheres.

Materials and Methods

The study involved 114 male patients admitted to the clinic for coronary bypass surgery, the average age was 55.9 ± 5.3 years. All of them gave informed consent; the study complies with the Declaration of Helsinki and was approved by the ethics committee of the State Research Institute for Complex Issues of Cardiovascular Diseases.

The exclusion criteria from the study were: the patient's age over 70 years, stenosis of the carotid arteries 50% or more, the presence of severe rhythm disturbances, chronic heart failure (CHF) stage II B, diabetes mellitus, chronic obstructive pulmonary diseases, oncopathology, diseases of the central nervous system, brain trauma, episodes of cerebrovascular accident, the number of points on the MMSE scale is less than 24 and / or less than 11 points on the Frontal Assessment Battery scale, the number of points on the Beck scale is more than 8.

EEG of patients was recorded in resting-state with eyes closed in 62 sites using a cap with built-in Ag / AgCl electrodes (QuikCap, NeuroSoft Inc., USA), a Neuvo multichannel amplifier (Compumedics, USA) and programs “Scan 4.5”. After removing the artifacts, the EEG power was computed using a fast Fourier transformation and averaged over all channels in the right and left hemispheres for each subject. For cluster analysis of the EEG data, we focused on the power indices of the theta (4–6 Hz), alpha (8–10 Hz) and beta (20–30 Hz) rhythms.

To assess the cognitive status of patients, along with MMSE, IICP was used, formed based on a set of parameters obtained during registration of sensory-motor response and characteristics of attention and memory using the psychophysiological hardware-software complex “Status PF” (Trubnikova et al., 2017).

To analyse the power of theta, alpha and beta rhythms in the left and right hemispheres, together with the MMSE and IICS indicators, we used the previously developed clustering algorithm based on discrete optimization with a minimax criterion (Mezenrsev & Estraykh, 2018; Mezentsev et al., 2019).

Statistical processing of the data in the clusters has been done with a standard set of statistical programs (Statistica13.0).

Results

As a result of the calculations performed, three clusters were identified in each frequency bands, and the quantitative composition of patients in them did not differ significantly (see Table 1). To analyse the power of rhythms in the clusters, we used one-way ANOVAs for the CLUSTER variable (3). Its results for the EEG power in the left and right hemispheres for three EEG frequency ranges are shown in Table 1.

According to the data presented in Table 1, at the theta frequency, a more pronounced differentiation of power indices by the clusters is characteristic of the right hemisphere, and at the beta frequency, for the left. In the alpha range, for the left hemispheric activity, one cluster with high values of the alpha rhythm is formed, whereas the power indicators are lower in the other two clusters. For the right hemispheric, there is a cluster with low alpha power values, which differs from the other two with a higher alpha level (see Table 1).

No significant differences in the EEG between the clusters were found only for the right hemispheric beta rhythm. Consequently, the main variables underlying clustering, in this case, can be considered cognitive indicators. To clarify their specificity in the formed clusters: not only for beta but also for other considered frequencies of biopotentials, as well as the effects of the factors AGE and EDUCATION, the Kruskall-Wallis ANOVA method was used.

As a result of the AGE analysis, only when comparing clusters formed with the inclusion of the right hemispheric theta rhythm, a tendency to age differences was noted ($H = 4.09$, $p = 0.13$) with lower values in the first cluster (Cluster 1ϴRH) than in the third (Cluster 3ϴRH) (55.0 and 59.0 years, correspondently).

Correlation analysis of the AGE and EEG power indicators revealed their significant relations in Cluster 2ϴRH (with an average age of 57.6 years): negative – with the left hemispheric theta and positive – with the left hemispheric beta (Rs = –0.34 and 0.33, respectively, at $p = 0.03$; in a two-sided comparison, $p = 0.003$). It should be noted that a significant negative relationship between age and the amplitude of biopotentials in the general sample was observed only at theta frequency, regardless of hemispheric specialization (Rs = –0.23, $p = 0.01$), but not at the beta frequency (Rs = = 0.080 at $p => 0.3$).

For the EDUCATION variable, differences between the clusters were found for the left hemispheric alpha rhythm (H = 7.90, p = 0.02) with a higher level in the third cluster (Cluster 3αLH). Moreover, the general sample was characterized by a positive relationship between the EDUCATION indicator and the power of the right hemispheric beta rhythm (Rs = 0.21, $p = 0.02$).

When analyzing the indicators of cognitive status, significant effects associated with different cluster affiliations are shown in Table 2.

The MMSE and IICP indicators in the general sample have a positive, albeit low correlation (Rs = 0.30 at $p = 0.001$); therefore, when analyzing the differences in the identified clusters, the ratio of these two indicators in them is unidirectional, but not always equally significant. As can be seen from the data presented in Table 2, the IICS allows differentiating groups to a greater extent; therefore, we will dwell on the description of the intergroup comparison of this indicator.

In the theta range, in the first cluster, characterized by high power values, a higher IICS level is also noted regardless of laterality. Differences between the other two groups turn out to be significant only when clustering with the inclusion of left-hemispheric but not right-hemispheric theta (Table 2). Consequently, the application of the developed clustering method makes it possible to distinguish different groups of patients depending on IICS and the level of hemispheric activation from the general sample.

All mean normalized indices averaged over a group of CVD patients in three obtained clusters are shown in Figure 1. Fig. 1A presents the results in Cluster 1ϴRH as the age-related effect was found while clustering the right-hemispheric theta data.

The similar effect for IICS was observed in the alpha range (Table 2, Fig. 1 B), but independent of age, and associated with the higher level of education in Cluster 3αLH. Patients included in Cluster 2αLH were characterized by low values of both theta and alpha rhythm, and the minimum IICS values (Fig. 1, Tables 1 and 2). Also, the MMSE score in this cluster

Table 1

Lateralized power indices in the theta, alpha and beta bands in three formed clusters

Cluster	Left hemisphere					Right hemisphere				
	$F_{2,119}$	p	η	n	M	$F_{2,119}$	p	η	n	M
Theta										
1	3.64	0.03	0.06	37	0.21*	15,25	0.00001	0.20	36	0.28*#
2				42	0.12				**41**	**0.13***
3				43	0.10*				45	0.05#
Alpha										
1	30.86	0.00001	0.34	41	0.69*#	24,18	0.00001	0.29	37	0.57*
2				44	0.23*				42	0.12*#
3				**37**	**0.21#**				43	0.54#
Beta										
1	6.08	0.003	0.09	40	-0.56*	0.11	0.90	0.002	44	-0.51
2				40	-0.59#				42	-0.53
3				42	-0.43*#				36	-0.51

Note. M is the power of biopotentials in the corresponding frequency range, n is the number of patients in clusters; * and # show significant differences in power values between the clusters ($0.0001 < p < 0.05$ with Bonferroni correction).

Table 2

Significant effects of comparing cognitive indicators in the three identified clusters

Cluster	Left hemisphere			Right hemisphere			Index of cognitive status
	H	**p**	**MMSE/ IICS**	**H**	**p**	**MMSE/ IICS**	
Theta							
1	41,07	0.00001	28	32,0	0.0001	28	MMSE
2			26*			26*	
3			28			28	
1	57,69	0.00001	0.68*	52,66	0.00001	0.68*	IICS
2			0.39*#			0.40	
3			0.46#			0.44	

End of Table 2

Cluster	Left hemisphere			Right hemisphere			Index of cognitive status
	H	p	MMSE/ IICS	H	p	MMSE/ IICS	
Alpha							
1	12,38	0.002	28	16,91	0.0002	28	MMSE
2			27*			28	
3			28			27*	
1	17,31	0.0002	0.56*	32,02	0.00001	0.65*	IICS
2			0.41*#			0.42	
3			0.52#			0.44	
Beta							
1	64,90	0.00001	26*	25,96	0.00001	27*	MMSE
2			28			28	
3			28			28	
1	40,07	0.00001	0.42	42,04	0.00001	0.40#	IICS
2			0.66*			0.59*	
3			0.43			0.51#	

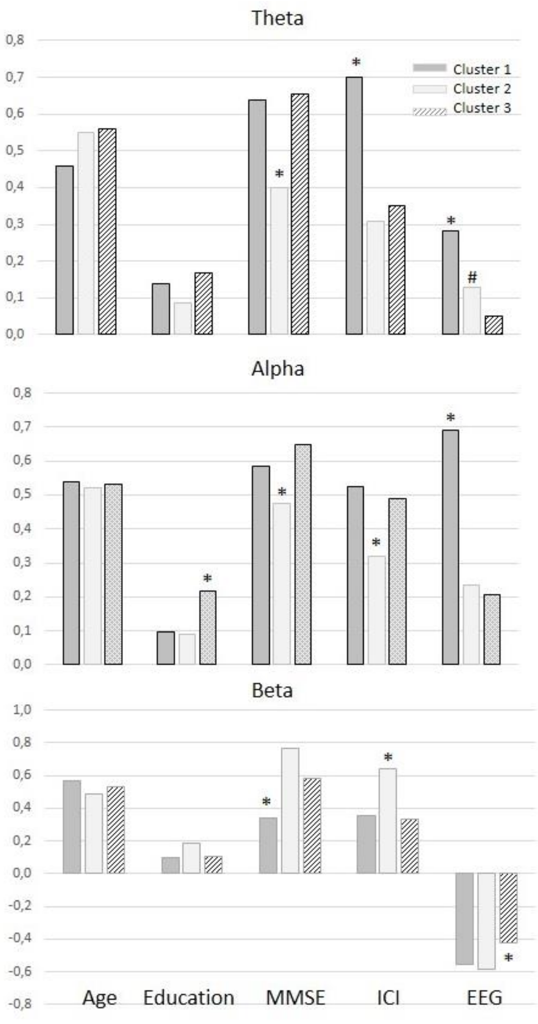

Fig. 1. Changes in socio-demographic, cognitive, and EEG parameters in the clusters
Note: * – the values are significantly different ($p < 0.05$)

was significantly lower than that in other clusters obtained analyzing the alpha and theta rhythms.

Considering this result and the positive correlation between IICS and the power of these rhythms in the general sample ($0.21 < Rs < 0.25$ with $0.006 < p < 0.03$ for left hemispheric theta and alpha and right hemispheric alpha), we can conclude that a relatively high IICS level in patients with CVD is collocated with maintaining high values of the power of low-frequency EEG oscillations.

In the beta range, the highest IICS values were obtained for Cluster 2βLH (Fig. 1 C). However, intergroup differences are more differentiated during clustering taking into account the right hemispheric beta rhythm (Table 2). Checking the composition of the clusters revealed that the majority of patients from the Cluster 1ϴRH and Cluster 2ϴRH (Fig.1 A) were respectively represented in the Cluster 1αLH and Cluster 2αLH (Fig.1 B), whereas the subjects from Cluster 3ϴRH were redistributed to all three alpha clusters but respectively were presented in the Cluster βLH (Fig. 1 C). Along with this, the composition of the Cluster 1ϴRH and Cluster 2ϴRH changed to Cluster 2βLH and Cluster 1βLH.

Thus, the use of clustering by optimal discretization made it possible to distinguish the clusters, differing in the cognitive reserves of patients with CVD. The clusters characterized by the most represented cognitive reserves according to the higher both MMSE (28 scores) and IICS (0.66 scores) indicators included less pronounced activation of the cortex (according to more power of the theta, alpha, and less beta rhythm). The factors of age and education were decisive only in specific groups. Patients with supposedly minimal reserves are differed by a low level of cognitive status (26 for MMSE and 0.40 for IICS), as well as education level together with a higher activation state of the cortex. The third type of clusters was distinguished by an unstable composition due to the variability of EEG indicators in it.

At the frequencies of the alpha and beta ranges, the activation state of the left hemisphere is more informative to differentiation of cognitive status of the CVD patients, and in the theta range, the right hemisphere.

Discussion

Using clustering by discrete optimization with a minimax criterion, three groups in the CVD patients were distinguished by analysis of the power of theta, alpha1, beta2 rhythms, IICS, and MMSE. We demonstrated that IICS presents the cognitive index with a greater resolution to discriminate patients in a higher-risk pool or cognitive reserves. This result is in line with the opinion that other screening tests are used for the detection of MCI among patients but not the MMSE scale (Ciesielska *et al.*, 2016).

Significant increased IICS score in one cluster and moderate or severe cognitive dysfunctions in two other groups differenced by EEG patterns are showed. Brain activity in the theta range is more informative for the differentiation of the cognitive status indices. Lower IICS (this cluster included about a third of patients) is associated with a significant decrease in both theta and alpha power as well as an increase in beta oscillations, i.e. increased desynchronization cortical networks on low frequencies but synchronization of high-frequency neuronal oscillations.

This result is not congruent with other data indicate on EEG slowing measured in the elderly participants at rest condition (Babiloni *et al.*, 2016; Choi *et al.*, 2019) and an opinion that vascular lesions in MCI associated with an increase of the theta power (Mahanna-Gabrielli *et al.*, 2019). It is possible that high cortical activation is due to emotional preoperative stress in patients. Indeed, increased beta responses together with greater α-band suppression have been related to greater personal distress (Woodruff *et al.*, 2011).

Current literature suggests that power changes in the alpha and beta frequency bands could be indicative of network-specific deterioration in aging and neurodegenerative diseases (i.e. Buzsaki *et al.*, 2012; Choi *et al.*, 2020; Scally *et al.*, 2018). However, total consistency in diagnosis of the cognitive impairment and EEG measures is lacked (Cohan *et al.*, 2019; Koelewijn *et al.*, 2017; Lejko *et al.*, 2020). The combined use of different EEG parameters and cognitive scales is recommended to improve the detection of differences between pathological and healthy brain aging (Ishii *et al.*, 2017).

The present study identified that such well known CVD-related factors of cognitive dysfunctions as AGE and EDUCATION are significant not in all cases. The influence of the AGE factor is most reflected in the activity of the cortex at the theta range, but this effect is not uniform depending on the power level in the right and left hemispheres. Our data are in line with the opinion that advanced age has been considered as an independent risk factor in the development of POCD (Kotekar *et al.*, 2018). This factor acquires a negative role if it is accompanied by significant age-related changes in the patterns of brain activation.

For representatives of Cluster 3 αLH, higher education can be considered as a compensatory reserve that allows maintaining a relatively high IICS at low values of the power of alpha oscillations. So, the negative role of the age and education factors while POCD development may be compensated by brain activity reserves which reflected in the right hemispheric low frequency cortical oscillations.

Although current EEG literature is heterogeneous in the role of high and low oscillations in neural communication, coherent evidence is emerging that these oscillations play a role in inter-network coupling processes in the brain. This reciprocity between activation and inhibitory mechanisms in the brain (high- and low-frequency oscillations) creates different pathways that award multi-directional relationships between the age-related cognitive decline and using created cognitive reserves in the VCD patients. As preventive and supportive strategies, while collaboration between surgeons and neuropsychologists, cognitive training may be recommended for patients before surgery as well as after hospital stay.

The use of a new method of clustering the EEG power and the cognitive status of patients made it possible to distinguish special groups of patients: (i) characterized by high IICS values, regardless of their age or education, and (ii) lower IICS. Distinctive features of these clusters turned out to be different brain activation according to the power of the theta, alpha, and beta oscillations. Improvements of the clustering method are necessary for cognitive screening and EEG to be more widely applied for detecting MCI risk or cognitive reserves in CVD patients. Further studies are needed to confirm our observations.

The quantitative clustering method of EEG and indices of cognitive functions may provide new information that would increase the understanding of the pathophysiology of VCI. Different EEG frequency components may have their role in the characterization of cerebral activities (Musha *et al.*, 2013) be used in detecting vascular cognitive impaired patients (Shibata *et al.*, 2014). Furthermore, this may allow better differentiation of the VCD patients in the preoperative period.

In the present study, we investigated mean EEG power in the left and right hemispheres. A more detailed regional analysis of the EEG rhythmicity could highlight closer relations among specific cerebral oscillatory activity associated with cognitive reserves or critical cognitive dysfunctions due to cardiovascular damages.

Conclusions

The cluster analysis by discrete optimization with a minimax criterion confirmed good reliability in detecting differenced groups of the VCD patients in the preoperative period of coronary artery bypass grafting. Three groups were distinguished while analyzing the power of theta, alpha1, and beta2 rhythms and the indices of cognitive status. The integrated indicator of cognitive status better differentiates groups than MMSE. The composition of the clusters changes depending on the patterns of left and right hemispheric cortical activity at the theta, alpha1, and beta2 frequencies. The EEG neurophysiological approach, together with cognitive screening and proposed clustering analysis, could be helpful in understanding cognitive reserves in patients with brain cardiovascular damage. This tool can help identify

EEG and cognitive markers of POCD in CVD patients and functional prognoses of different surgery and therapy methods.

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