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BOLD fMRI signal in stroke patients and its importance for prognosis in the subacute disease period – Preliminary report

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ABSTRACT

Functional magnetic resonance imaging (fMRI) allows for the assessment of neuronal activity through the blood-level-dependent signal. The purpose of study was to evaluate the pattern of brain activity in fMRI in patients with ischemic stroke and to assess the potential relationship between the activity pattern and the neurological/functional status.

Methods: The fMRI was performed in patients up to 4th day of stroke. All the patients were analyzed according to NIHSS on 1st day and mRankin scale on 14th day of stroke, followed by analyzing of fMRI signal.

Results: The study enrolled 13 patients at a mean age of 64.3 years. Eight (61.5%) showed cerebellar activation and 2 (15.38%)- insular activation. In those who scored 0–2 on mRankin scale, the most frequently observed activity was located in the regions: the M1, SMA and PMC in the stroke hemisphere and the cerebellum. In those cases, the non-stroke hemisphere was more frequently involved in the areas: the M1 and PMC. There was a tendency for a better prognosis in relation to age <65 years and activation of the SMA in the stroke hemisphere.

Conclusion: There are differences observed in the activation areas of the cerebral cortex both in the stroke and non-stroke hemispheres. More than half of the patients with hemispheric stroke but all with good outcome showed cerebellar activation. There is probable positive correlation between the BOLD-signal size, young age, activation of supplementary motor area in stroke hemisphere and good functional status of patients in the subacute period of stroke.

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1. Introduction

Functional magnetic resonance imaging (fMRI) allows for the assessment of neuronal activity. The method uses the phenomenon of increased blood flow in the activated areas of the cerebral cortex and variable magnetic properties of hemoglobin depending on its oxidation. Neurons show poor metabolic reserve and their metabolism depends on oxygen. During neuronal activity, both oxygen consumption and blood flow increase. That increase is associated with an increased supply of oxygen to the neuronal tissue in the form of oxyhemoglobin which is subsequently reduced to deoxyhemoglobin due to oxygen consumption. Change in the concentration ratio of oxyhemoglobin (diamagnetic) and deoxyhemoglobin (paramagnetic) results in the elevating of T_2^* and the signal increase in the T_2^*-weighted imaging, which is visualized in fMRI images. Essentially, fMRI imaging is to detect and measure the blood-oxygen-level-dependent contrast (BOLD) effect coordinated with oxygen consumption in brain structures. The strength of the BOLD effect depends on the change (increase) in blood flow and the degree of blood oxygenation within these brain structures that are active during mental or motor activities. The extent of the active cortical area and the number of stimulated neurons have a direct influence on changes in regional blood flow. That mechanism is named 'neurovascular coupling'.

Because the fMRI image results from hemodynamic changes, the technique provides information regarding brain function at the macrovascular level. The method is therefore particularly useful in finding the mechanisms of disturbed cerebral perfusion and tissue oxygenation during acute cerebral ischemia.

The purpose of this study was to evaluate the pattern of brain activity in fMRI in patients with first-in-life ischemic stroke and to assess the potential relationship between the cortical activity pattern and the neurological and functional status in patients during the acute disease period.

2. Methods

The prospective study conducted in December 2016–April 2017 enrolled 13 patients with first-in-life ischemic stroke diagnosed based on the WHO criteria and a present acute stroke lesion (in head CT and/or MRI) causing neurological symptoms [1]. The enrolled study participants were without speech disorders and were evaluated prior to stroke as 0–1 points on a modified Rankin Scale (mRS). During the given period, 216 patients with ischemic stroke were treated in the Department of Neurology. Initially, the criteria were met by 61 patients, 29 patients were enrolled in the study, and the results of 13 patients were included in the preparatory analysis presented in the preliminary report.

All the patients included in the study were analyzed according to:

- their age at the first-in-life stroke onset;
- the presence of comorbidities such as: atrial fibrillation (AF), arterial hypertension (AH), coronary heart disease (CHD), diabetes mellitus (DM) and lipid disorders (LD), >70% atherosclerotic carotid stenosis (ipsilaterally to the acute ischemic brain lesion) according to NASCET [2];
- their neurological status on the first day after stroke onset evaluated according to the National Institute of Health Stroke Scale (NIHSS) [3];
- the location of the stroke (total anterior cerebral infarct, TACI); partial anterior CI (PACI), lacunar CI (LACI) and posterior CI (POCI) [4];
- early therapeutic management in the acute stage of stroke (recombinant tissue plasminogen activator [iv rtPA], endovascular, antiplatelet treatment);
- their functional status at 14 days after stroke according to mRS [5].
- fMRI of the head up to 4th day of stroke

The fMRI was performed using the GE Optima 450W magnetic resonance scanner, 1.5T (63.86 MHz), 16-channel head coil with mirror. The stimulus was delivered with the use of NordicNeuroLab software (Bergen, Norway) compatible with resonance imaging and a back-projection screen. Before starting the imaging, patients were trained to perform a task: pianist's motion, i.e. alternating finger movements. MRI included the following anatomical sequences: inversion T2-weighted sequence: FLAIR (fluid-attenuated inversion recovery, slice thickness = 5 mm, spacing = 0.5 mm, TR = 7500 ms, TE = 108 ms, auto refocus flip angle = 160°, bandwidth = 31.25 kHz, matrix = 320 (frequency) × 192 (phase), NEX = 2, Freq. FOV = 24 cm), T1-weighted high-resolution sequence: 3D BRAVO (brain volume imaging, slice thickness = 2 mm, TR = 8.5 ms, TE = 3.3 ms, flip angle = 12°, bandwidth = 31.25 kHz, matrix = 256 (frequency) × 256 (phase), NEX = 1, Freq. FOV = 24 cm, Phase FOV = 1.0), DWI (diffusion weighted imaging sequence, slice thickness = 5 mm, TR = 5980 ms, TE = 97.9 ms, bandwidth = 250 kHz, matrix = 128 (frequency) × 128 (phase), NEX for T2 = 1, *b*-values 1000 s/mm^2, diffusion direction = 3, Freq. FOV = 24 cm, Phase FOV = 1.0). The DWI aimed at finding the size and site of stroke lesion at the time of fMRI. Subsequently, the functional sequence was started along with the motion performed with the paretic limb. The fMRI sequence parameters were as follows: slice thickness = 4 mm, TR = 3000 ms, TE = 35 ms, flip angle = 90°, bandwidth = 250 kHz, matrix = 96 (frequency) × 96 (phase), NEX = 1, Freq. FOV = 24 cm, Phase FOV = 1.0. The task was performed in accordance with the established paradigm and its implementation was constantly monitored by the personnel operating the MRI scanner. If the patient failed to perform the task correctly, the fMRI sequence was repeated. The paradigm consisted of five resting blocks and four active blocks, each block taking 30 s, and the entire sequence took 4 min and 30 s.

The fMRI analysis was performed using SPM 12 (Welcome Trust Centre for Neuroimaging, Institute of Neurology, University College London, UK). The preprocessing stage included: motion correction (realign), co-registering (coregister) to match the fMRI scans with the anatomical scans, spatial normalization (normalize) of the fMRI and anatomical scans in relation to the reference standard of brain scan (standard brains from the Montreal Neurological Institute: MNI-space templates) and finally, spatial smoothing of fMRI images using

the Gaussian smoothing kernel = 4 mm FWHM (Full Width at Half Maximum) in *X*, *Y* and *Z* directions to obtain images of a higher SNR while maintaining the appropriate resolution. The data was then subjected to statistical analysis with the use of the General Linear Model (GLM). It included a following steps: first – specification of the GLM design matrix by specified various timing parameters, fMRI scans and conditions (a vector of onset times, event durations, orthogonalize modulations), filtering (high-pass filter with cutoff of 128 s), masking threshold (defaults value of 0.8) and serial correlations using an autoregressive AR(1) model. Then estimation of GLM parameters using ReML (Restricted Maximum Likelihood) and interrogation of results using contrast vectors to produce Statistical Parametric Maps (SPMs). The statistical significance threshold of p value (FWE) < 0.05 was provided [6]. The activation areas resulting from the statistical analysis were applied to anatomical images (BRAVO). Identification of anatomical location of active areas was based on visual assessment of obtained images, determination of coordinates in MNI space for each maximum and value of *T*- and *Z*- statistic and by using the e-Anatomy atlas of human anatomy (IMAIOS).

Analysis was made using a single and multi-factorial method of nonlinear estimation – logistic regression (STATISTICA 5.0PL) to identify independent factors for post-stroke disability at 14 days following stroke. $p < 0.05$ was considered statistically significant. The significance of the following parameters was analyzed: age < and ≥65 years, sex, presence of atrial fibrillation (AF), arterial hypertension (AH), coronary heart disease (CHD), diabetes mellitus (DM) and lipid disorders (LD), >70% atherosclerotic carotid stenosis (ipsilaterally to the ischemic brain lesion), activation of individual areas of the primary and secondary motor cortices. We have adopted the dichotomy of age (< and ≥65 years) used in many studies, also cited in this paper.

3. Results

The study enrolled 13 patients (F/M: 8/5) at a mean age of 64.3 (61–88) years. The clinical characteristics of the patients are shown in Table 1.

Areas of the most frequent activity of the stroke hemisphere (SH) during the motion performed by the hand opposite to the location of the stroke lesion were as follows: the motor cortex (M1), supplementary motor area (SMA), premotor cortex (PMC); those for the non-stroke hemisphere (nSH) activation were: the M1 and PMC. The pattern of brain activation in individual patients is shown in Table 2.

Eight (61.5%) patients showed cerebellar activation and 2 patients (15.38%) showed insular activation.

In those who scored 0–2 on mRankin scale on the 14th day following stroke, the most frequently observed activity was located in at least three areas, most often in the following regions: the M1, SMA and PMC in the SH and the cerebellum. In those cases, the nSH was more frequently involved in the following areas: the M1 and PMC.

No independent prognostic factors for good outcome (mRS 0–2) were found based on the analysis of the activation pattern for the cerebral structures; however, there was a tendency for a better prognosis in relation to these 2 parameters: age <65 years ($p = 0.22$) and activation of the SMA in the SH ($p = 0.29$).

Exemplary fMRI (patient no 3) is shown in Fig. 1.

Table 1 – Patient characteristics.

Age	71.1 ± 10.7 [53–88]
Sex F/M	8/5
Stroke type PACI TACI LACI	*n* (%) 7 (53.8) 5 (38.4) 1 (7.6)
Arterial hypertension	12 (92.30)
Diabetes	4 (30.7)
Atrial fibrillation	3 (23.0)
Lipid disorders	9 (69.2)
Ultra-acute phase therapy rt-PA Antiplatelet	*n* (%) 3 (23.0) 1 (7.6)
Thrombectomy	8 (61.5)
NIHSS	2 [0–17] IQR 3
mRS	3 [0–4] IQR 2

PACI, parietal anterior cerebral ischemia; TACI, total anterior cerebral ischemia; LACI, lacunar cerebral ischemia; rt-PA, recombinant tissue plasminogen activator; NIHSS, National Institute of Health Stroke Scale; mRS, modified Rankin Scale.

4. Discussion

Improvement in the neurological state patients with ischemic stroke is possible even in the chronic period of disease, which shows the importance of the compensatory mechanisms not only related to reperfusion. A favorable prognostic factor which affects the acute stage of stroke is, among others, the short time from neural tissue ischemia to total reperfusion. This parameter indicates improvement of neurological status in the first days of stroke. However, it is still possible in the next stage of the condition, which is probably due to compensatory reorganization of the cerebral cortex in response to ischemic injury. Hakimelahi et al. showed poor correlation between infarct volume and the time post stroke, indicating that there are some additional factors, stronger than time, to determine the extent of cerebral infarct [7]. The processes of most importance are probably the ones which occur in the neural network, and the reorganization and emergence of new synapses. The fMRI enables us to study the network distributed in the brain (functional connectivity, FC) in resting state (resting-state fMRI) and during the performance of a motor or cognitive task, that is the 'paradigms' (task-based fMRI). The motor cortex is located in the frontal lobe, right in front of the central sulcus (Rolandic fissure) and is divided into three mutually connected areas: the primary motor cortex (MI), supplementary motor area (SMA) and premotor cortex (PM). The SMA and PM make up the secondary

Table 2 – Selected clinical parameters and brain structure activation pattern (motion of paretic upper limb).

Patient	Sex	Age	Stroke location	NIHSS	mRankin	Activation in stroke cortex	Activation in non-stroke cortex	Activation in other areas
1	M	76	LH	2	3	M1, SMA, PMC,	PMC, OF, SMC	CB
2	F	69	RH	5	3	SMA, AG, SMC	PMC	CB
3	M	61	LH	2	0	M1, AG, SMA, PMC, SMC	M1, PMC, SMC	CB
4	M	67	RH	5	1	M1, PMC, SMA	M1, PMC, SMC	CB
5	F	82	LH	17	3	SMA, PMC, SMC	–	I
6	F	69	LH	2	3	M1, SMA	M1, PMC, SMC	
7	M	66	RH	7	4	M1, PMC	M1, PMC	
8	F	88	LH	10	4	M1, SMA, PMC, SMC	SMA	I
9	M	62	RH	4	3	M1, SMA, PMC	M1	CB
10	F	88	LH	2	3	M1, PMC	M1, PMC	
11	F	53	LH	0	0	M1, SMA, PMC	–	CB
12	F	78	LH	1	1	M1, V2, SMA, PMC, SMC	V2	CB
13	F	65	LH	1	1	M1, SMA, PMC, SMC	M1, SMA, PMC, SMC	CB

M, motor cortex; SMA, supplementary motor area; PMC, premotor cortex; CB, cerebellum; AG, angular gyrus; V2, secondary visual cortex; OF, orbitofrontal area; I, insula; SMC, sensorimotor cortex; LH, left hemisphere; RH, right hemisphere.

motor cortex (MII). MII has strong connections to the cerebellum and basal nuclei. The activation area of the cortex in task-based fMRI in patients with ischemic brain injury is wider than in healthy volunteers. The differences are most prominent in the area of the right brain hemisphere [8–12]. Similar observations were made on the basis of comparative imaging between the patients with Alzheimer's disease and healthy subjects. [13] The results of these studies suggest that neurological deficits are compensated for by engaging larger areas of the cerebral cortex. In this study, we evaluated neuronal activity in response to hand motion in patients with hemispheric stroke. The fMRI results indicate a somewhat differentiated model of cortex activation in the ipsilateral and contralateral hemispheres of the brain. We reported the activation of cerebellar structures in 60% of the patients. As the patients enrolled had no prior brain damage, we can assume that we had an opportunity to observe changes in the cerebral cortex in response to acute ischemia.

The organization of the motor cortex is plastic and changes with learning and damage. It is possible that this process is different for brain damage of varying etiology, although similar patterns of cortical activity were demonstrated in patients with brain injury and multiple sclerosis [14]. We did not observe a relationship between the severity of neurological condition on the first day and the location, number or size of the activated areas in the cerebral cortex. However, the results of this study indicate that the size of activation was related to the functional status on the 14th day of the disease. Patients with extensive activation of the cortex in the SH involving the primary and secondary cortices obtained functional independence, unlike those patients whose activation was limited to the primary cortex or additionally involved one zone of the secondary cortex. Few authors have reported the activation of anterior premotor pathways in patients with an extensive post-stroke motor deficit [15]. Others have shown that increased activity in fMRI in the areas of supplementary motor cortex, lateral premotor cortex and superior parietal cortex on the first days of stroke was associated with improved functional patient status [16]. In this study, we observed better prognostic tendencies in patients under 65 years of age and those with SMA activation in the SH; however, these had no statistical significance. Same authors have shown that the extent of cortical activation changes with time from the onset of cerebral stroke [17]. The assessment of BOLD-activity dynamics in patients with stroke indicates that cortical activity decrease is most noticeable in the right hemisphere of the brain [8]. Even if it was partly due to habituation, the changes were different than in healthy subjects. The relationship between anti-spastic therapy and cortical activity reduction has been demonstrated [8]. Intentional movements are improved with rehabilitation, and cortical representation of the trained sequence in fMRI is greater than in the control sequence.

When analyzing fMRI results, one must consider the factors that may affect neurovascular coupling efficiency. Age-related differences in motor and visual cortex activation were observed [18,19]. Post-traumatic gliosis, atrophic lesions, neurotransmitter system disorders, chronic neural tissue ischemia, compensatory vasodilatation of cerebral arteries in patients with carotid artery stenosis, changes in reactivity of cerebral arteries, chronic diseases (arterial hypertension, diabetes) and medications may also have some impact. The above factors may affect the BOLD-signal by altering the decrease in cerebral blood flow (CBF) and neurovascular coupling. Few fMRI studies have investigated the effects of medications on BOLD [20–22]. It appears that the clinical state of stroke patients not only results in ischemic damage to certain brain structures located in the supply of a stenosis or occluded artery but additionally related to a neuronal network that exceeds the anatomical limits of vascular bed. Modification of FC function in future may provide additional therapeutic support in patients with cerebral stroke.

Recent research has demonstrated the importance of global changes to the functional organization of the brain network in patients with stroke. Advanced imaging allows us to identify patients with stroke and to determine the size of ischemic and potentially salvageable focus, all of which yield crucial information for proper stroke management. fMRI can be a valuable supplement to the methods important for predicting the post-stroke state of patients. A more valuable assessment

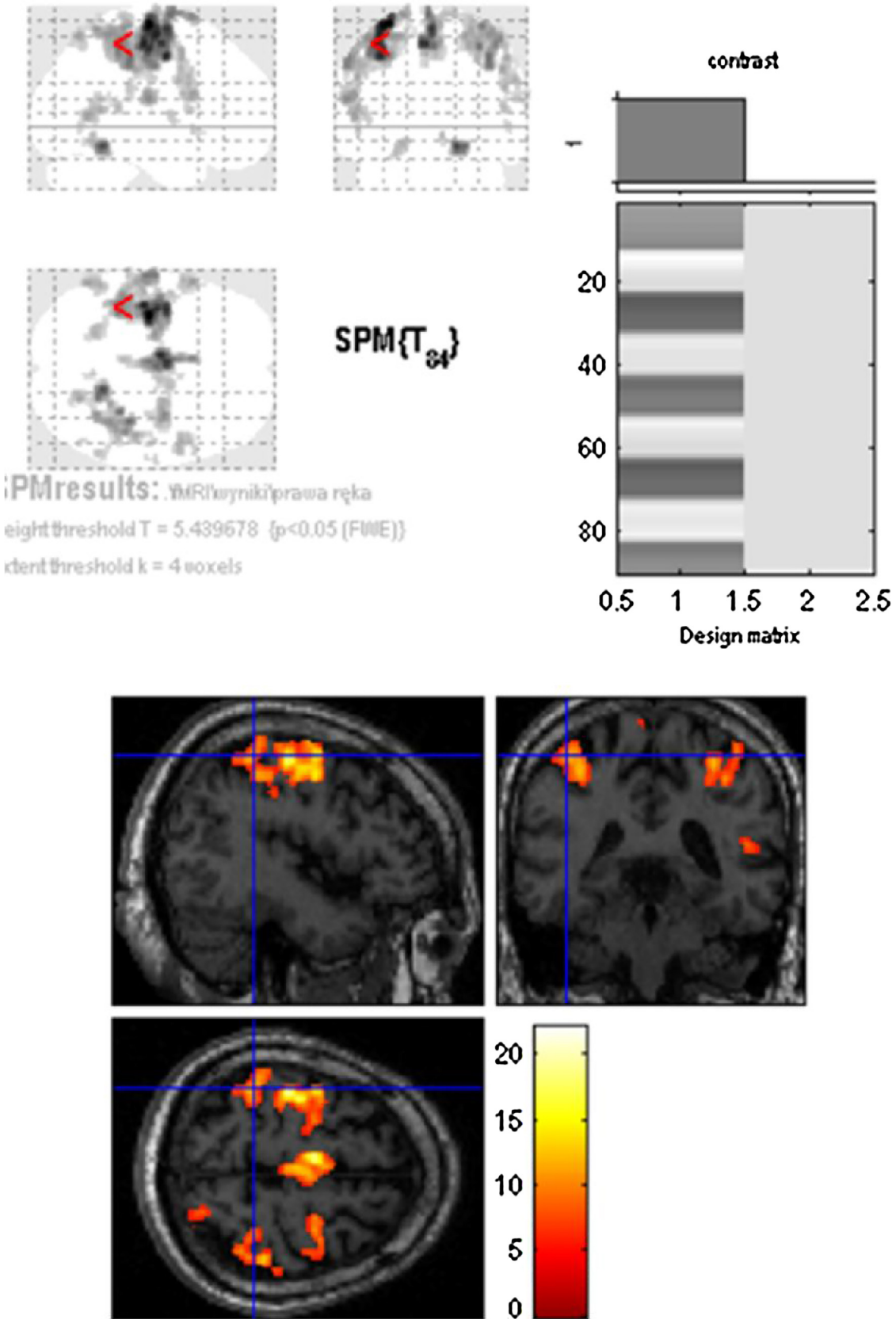

Fig. 1 – Exemplary of fMRI in left-hemisphere stroke patient.
SPM{Z} representing regions during the motion of paretic hand (right site). The activation areas were applied to glass brain and anatomical images BRAVO. All clusters are significant at $p < 0.05$, corrected for multiple comparisons across the whole brain.

here, and the focus of future research, is the evaluation of the dynamics of cortical activation changes in the acute period of disease, and not just a single evaluation of cortical activation maps.

Study limitations: small number of patients at the present stage of the study.

5. Conclusion

There are differences observed in the activation areas of the cerebral cortex both in the stroke and non-stroke hemispheres of the brain in stroke patients.

More than half of the patients with hemispheric stroke but all with good outcome showed cerebellar activation.

There was no clear correlation between the cortical activation pattern and the neurological status on the first day of stroke.

There is probable positive correlation between the size of BOLD-signal in fMRI, young age, activation of supplementary motor area in stroke hemisphere and good functional status of patients in the acute period of stroke.

Conflict of interest

None declared.

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None declared.

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