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Functional rearrangement of the primary and secondary motor cortex in patients with primary tumors of the central nervous system located in the region of the central sulcus depending on the histopathological type and the size of tumor: Examination by means of functional magnetic resonance imaging

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Summary

Background: The aim of this study was to analyze the reorganization of the centers of the motor cortex in patients with primary neuroepithelial tumors of the central nervous system (CNS) located in the region of the central sulcus in relation to the histopathological type and the size of tumor, as determined by means of functional magnetic resonance imaging (fMRI).

Material/Methods: The fMRI was performed prior to the surgical treatment of patients with tumors located in the region of the central sulcus (WHO stage I and II, n=15; WHO stage III and IV, n=25). The analysis included a record of the activity in the areas of the primary motor cortex (M1) and the secondary motor cortex: the premotor cortex (PMA) and the accessory motor area (SMA). The results were correlated with the histopathological type of the tumor and its size expressed in cm^3.

Results: The frequency of activation of the motor center was higher in the group of patients who had less aggressive tumors, such as low-grade glioma (LGG), as well as in tumors of lower volume, and this was true both for the hemisphere where the tumor was located and in the contralateral one. Mean values of t-statistics of activation intensity, mean numbers of activated clusters, and their ranges were lower in all analyzed motor areas of LGG tumors. The values of t-statistics and activation areas were higher in the case of small tumors located in ipsilateral centers, and in large tumors located in contralateral centers, aside from the SMA area where the values of t-statistics were equal for both groups. The contralateral SMA area was characterized by the highest stability of all examined centers of secondary motor cortex.

No significant association ($p>0.05$) was observed between the absolute value of the mean registered activity (t-statistics) and the size of examined areas (number of clusters) when the groups were stratified with regards to the analyzed parameters.

Conclusions: The presence of a neoplastic lesion, its histopathological type and finally its size modulate the functional reorganization of the motor centers as suggested by the differences in the frequency of the neural center activation in the analyzed groups.

Processes of functional rearrangement are more pronounced and more precisely defined in patients with less aggressive and/or smaller tumors.

The contralateral accessory area is the most frequently activated center in all analyzed groups irrespective of the grade and size of the tumor.

Key words: **neuroplasticity • motor cortex • functional magnetic resonance imaging • glioma**

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Background

The clinical approach to the treatment of neuroepithelial primary brain tumors located in functionally important cortical centers, also referred to as eloquent brain areas, has undergone considerable changes in the recent decade. The development of modern diagnostic imaging techniques, namely functional magnetic resonance imaging (fMRI), new neurophysiological methods, including intraoperative monitoring techniques of somatosensoric evoked potentials (SEP) and motor evoked potentials (MEP), and the resulting better understanding of the process of functional rearrangement of the central nervous system (CNS) enabled the development of novel standards of therapy [1,2]. Understanding the role of clinically important cortical centers and their reciprocal complex relationships corresponds directly to the quality of life and function after surgery [3]. The key role of the surgical approach is not limited to increasing the survival time; in fact, the primary focus pertains to the patient's quality of life [4,5]. Thus, the principal goal of the therapy, consisting of a maximal gross total surgical resection of tumors located in the region of the central sulcus, cannot be achieved in every case due to potential neurological deficits that are not accepted by patients. One should not forget a crucial fact, namely that neural centers, including regions associated with sensory and motor function, undergo continuous reorganization during postnatal life of man [6]. The rearrangement of primary and secondary motor cortex centers in response to the presence of a neoplastic lesion has not yet been extensively analyzed in the literature.

The aim of this study was to identify potential patterns of functional reorganization of the brain in patients with primary neuroepithelial tumors of the motor cortex. We also analyzed a potential relationship between these patterns and the size and histopathological types of neoplastic lesions.

Material and Methods

The protocol of this study was approved by the Bioethical Committee of the Medical University of Lodz (decision no. RNN/123/09/KE). There were 40 patients included in the study, with primary neuroepithelial brain tumors located in the region of the central sulcus, treated at the Department of Neurosurgery, University Clinical Hospital No. 1 in Lodz, between 2009 and 2011. The patients were enrolled in the study after having given their written informed consent, based on the following inclusion criteria: 1) lesion located within a radius of 10 mm from the central sulcus; the location was determined based on morphological images acquired prior to fMRI, 2) no history of neurosurgeries, and no other organic CNS pathologies, 3) neurological status enabling standardization of the procedure, i.e. paresis of the upper limb performing a task not greater than 3 points in Lovett scale, 4) good cooperation with the patient during the examination confirmed during the neuropsychological qualification.

Prior to the surgical treatment, an fMRI was performed in all patients using a 1.5 T magnetic resonance scanner (Siemens, Avanto). Morphological, three-dimensional T1-weighted sequences were obtained according to the following protocol: FOV=256×256 mm, matrix=512×512, TR=8.8 ms, TE=4.8 ms, TA=5′07. Each volume acquired contained 160 slices, 1 mm thick. The functional examination included echoplanar imaging (EPI) sequences: TR=3000 ms, TE=50 ms, FOV=1680×1680 mm, matrix 64×64, thirty-eight slices, 3 mm thick; 100 volumes were acquired with TA=5′11. All patients were properly instructed approximately 30 minutes prior to the

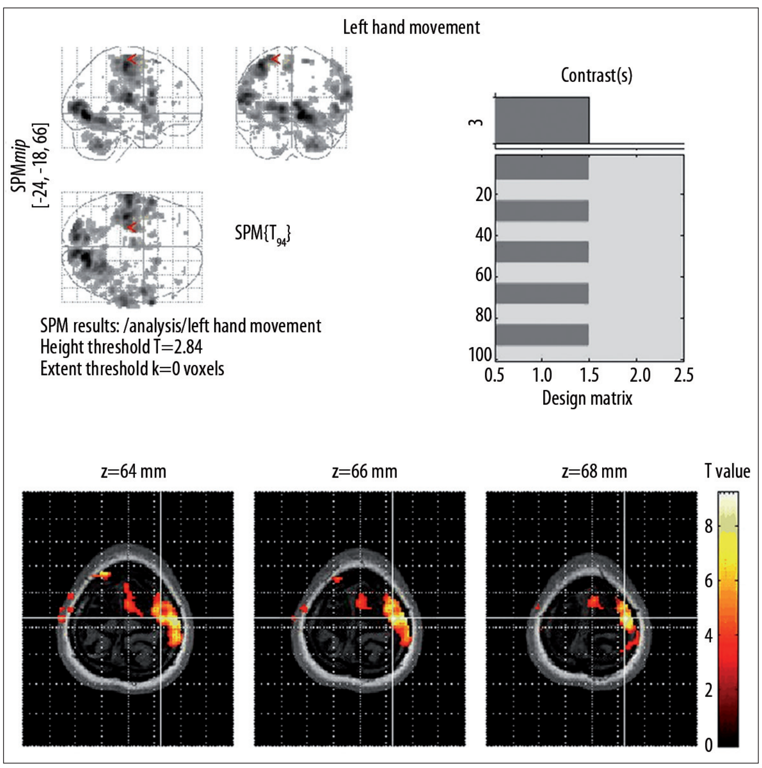

Figure 1. Ttransverse cross-section showing motor activity in a patient with a tumor located in the region of the central sulcus prepared using Matlab software with SPM2 statistical overlay.

performance of a functional task. The analyzed paradigm included clenching and opening the fist of the upper limb located contralaterally to pathological lesion.

The examination included 5 blocks, 10 acquisitions each, with an ABABABABAB stimulation pattern, where A corresponded to resting (control) period, and B – to stimulation period.

Statistical calculations were carried out using the Matlab software with Statistical Parametric Mapping 2 package (*http: //www.fil.ion.ucl.ac.uk/spm/*; Figure 1). The analysis included spatial smoothing (filter – kernel FWHM=5 mm), a general linear model (GLM,) and corrected statistical thresholds taking into account the FDR correction. The data was analyzed using $p=0.05$ as a statistical significance threshold.

Based on the histopathological examination results, the patients were retrospectively assigned into two groups. The first group included patients with less aggressive primary malignancies of neuroepithelial origin (low-grade glioma, LGG), corresponding to WHO stages I and II. This group comprised of 15 individuals (13 women and 2 men, median age 44 years, range 23–75 years). The second group was composed of patients with highly aggressive primary neuroepithelial malignancies (high-grade glioma, HGG), WHO stage III and IV. This group included 25 patients (4 women and 21 men, median age 57 years, range 17–75 years). The distribution of the tumors with regard to histopathological type is presented in Table 1.

All participants were right-handed. Among patients in group I, 13 individuals had a lesion located in the area of the primary motor cortex and the secondary premotor cortex of the left cerebral hemisphere, in one patient there was a lesion located in the analogous area of the right hemisphere, and one individual had a lesion limited to the primary cortex of the right hemisphere. Within group II, 16 patients had their lesion located in the area of the primary motor cortex and the secondary premotor cortex of the left cerebral hemisphere, four patients had lesions located in the analogous area of the right hemisphere, and five patients had lesions limited to the primary motor cortex of the left hemisphere.

The activities of the following areas of the primary and secondary motor cortex, identified on the basis of the rules of anatomy and atlases of radiologic anatomy, were analyzed: (M1a) – the area of the precentral gyrus of the hemisphere ipsilateral to the neoplastic process (Brodmann 4), (M1u) – the area of the precentral gyrus of the hemisphere contralateral to the neoplastic process, (PMAa) – premotor cortex of the hemisphere involved with the neoplastic process located in the lateral segment of Brodmann's area 6 (premotor cortex area), (PMAu) – premotor cortex of the hemisphere not involved with the neoplastic process, (SMAa) – accessory motor area located in the superior medial region of Brodmann's area 6 in the hemisphere involved with the neoplastic process.

The second stage involved the measurement of the analyzed tumor volume, as determined with the Vector Vision

Table 1. Distribution of tumors with regard to their histopathological type.

Histopathological diagnosis	Number	Percent
Astrocytoma pilocyticum WHO I	1	2.5%
Astrocytoma fibrillare WHO II	14	35.0%
Oligoastrocytoma anaplasticum WHO III	2	5.0%
Astrocytoma anaplasticum WHO III	3	7.5%
Glioblastoma WHO IV	20	50.0%
Total	40	100.0%

(Brain Lab) neuronavigation system and Brainlab© I plan 2.6 neuronavigation software. After performing the analysis and determining the average volume of the neoplastic lesions in the study population, we divided the patients into two groups based on a 40-cm^3 cut-off volume. Group III ($V<40$ cm^3) included 23 patients: 7 with LGG and 16 with HGG, mean volume $V_{mean}=22.91\pm10.21$ cm^3, median Me=22.54. Group IV ($V>40$ cm^3) was comprised of 17 patients: 8 with LGG and 9 with HGG, mean volume $V_{mean}=59.61\pm19.97$ cm^3, median Me=50.128.

Results

The analysis of the histopathological type of neoplastic lesion revealed that all of the examined centers of the primary and secondary motor cortices were activated more frequently in the group of less aggressive tumors.

Aside from the primary motor cortex – contralateral to the upper limb performing the task, the most frequently activated motor centers included:

a. in the group of LGG malignancies: SMAa and contralateral PMAa, both characterized by the same frequency of activation,
b. in the group of HGG malignancies: SMAa followed by contralateral PMAa.

The most pronounced intergroup difference in the frequency of induced activation pertained to PMAa, and the least pronounced one – to SMAa.

Mean values of t-statistics of activation intensity in the group with less aggressive malignancies were lower than in those with highly aggressive tumors in all examined areas, except for the contralateral M1a, where they were equal.

In group I, the mean number of activated clusters in all motor areas was lower, corresponding to a smaller area of activation. The most pronounced difference in the number of clusters referred to M1u and PMAu.

In the group of patients with less aggressive tumors, the range of intensity values and activation area values of all examined centers was narrower. Detailed data for patients with group I and II tumors is presented in Table 2.

Box-and-whisker Figures 2 and 3 illustrate the distribution of t-statistic values and the number of clusters in selected

Table 2. Cumulative presentation of the motor areas analyzed in groups I and II, taking into account the histopathological type of the neoplastic lesion.

	Group I				Group II				Mann-Whitney U test p<0.05	
Variable	**%N**	**Tm**	**km**	**SD**	**%N**	**Tm**	**km**	**SD**	**p-level**	**Z**
(M1a) T	100%	10.8		3.43	92%	10.61		4.27	0.89	0.13
(M1a) k			291.13	114.44			302.74	124.65	0.67	–0.43
(PMAa) T	73%	6.49		1.6	32%	7.81		4.24	0.68	–0.41
(PMAa) k			138.45	84.02			180.5	166.75	0.56	–0.58
(SMAa) T	73%	5.61		1.38	64%	6.71		2.72	0.29	–1.06
(SMAa) k			146.64	108.1			191.56	151.85	0.57	–0.57
(M1u) T	26%	5.42		1.25	12%	7.92		4.86	0.48	–0.71
(M1u) k			165.25	116.2			271.33	224.96	0.72	–0.35
(PMAu) T	26%	6.26		1.99	16%	7.19		3.86	0.951	0.01
(PMAu) k			115.1	71.84			219.25	194.09	0.56	–0.58

T_m – mean value of t-statistics; k_m – mean number of clusters; %N – percent of predicted activity; SD – standard deviation; Z – Z coefficient; p – coefficient of significance.

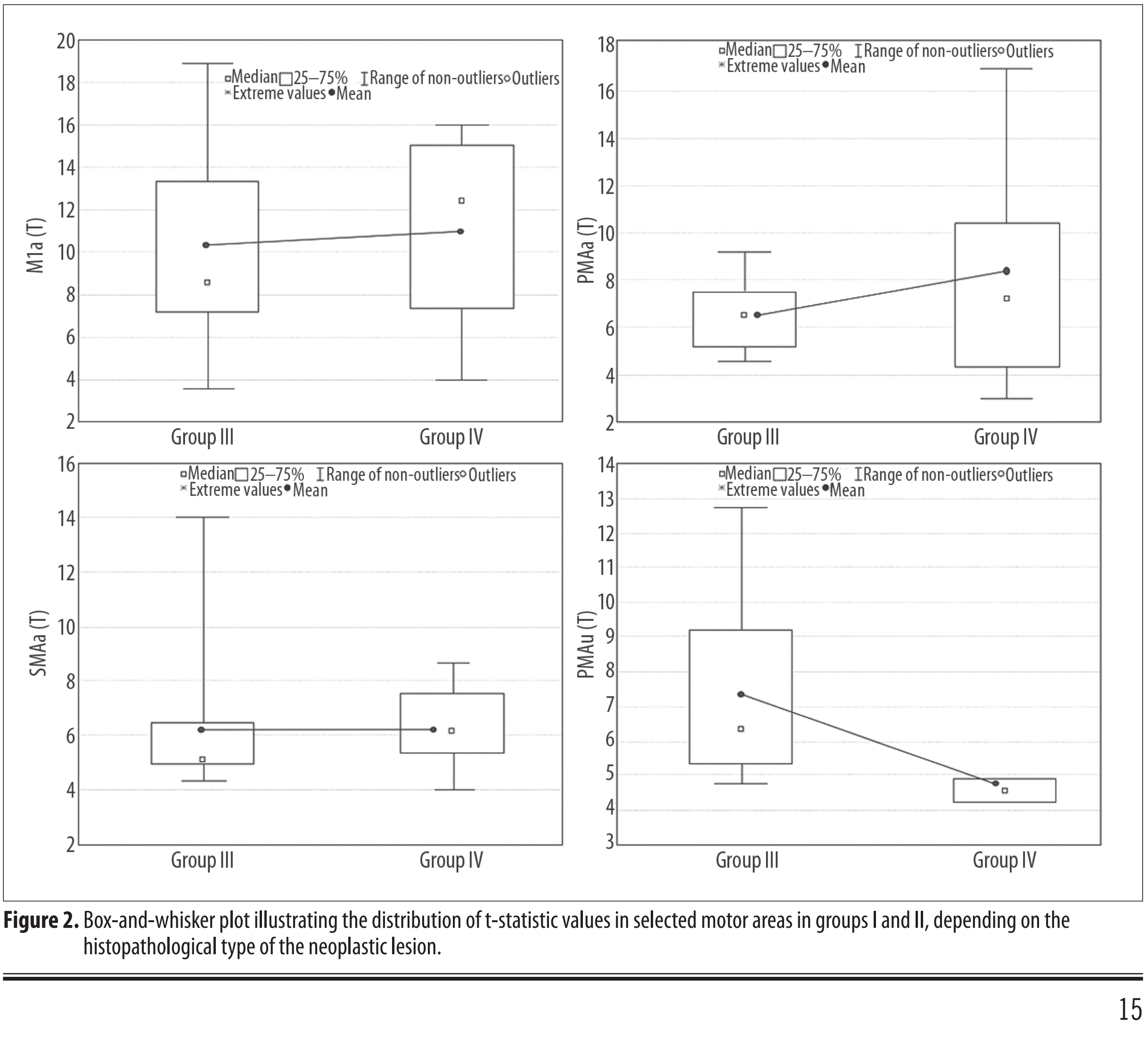

Figure 2. Box-and-whisker plot illustrating the distribution of t-statistic values in selected motor areas in groups I and II, depending on the histopathological type of the neoplastic lesion.

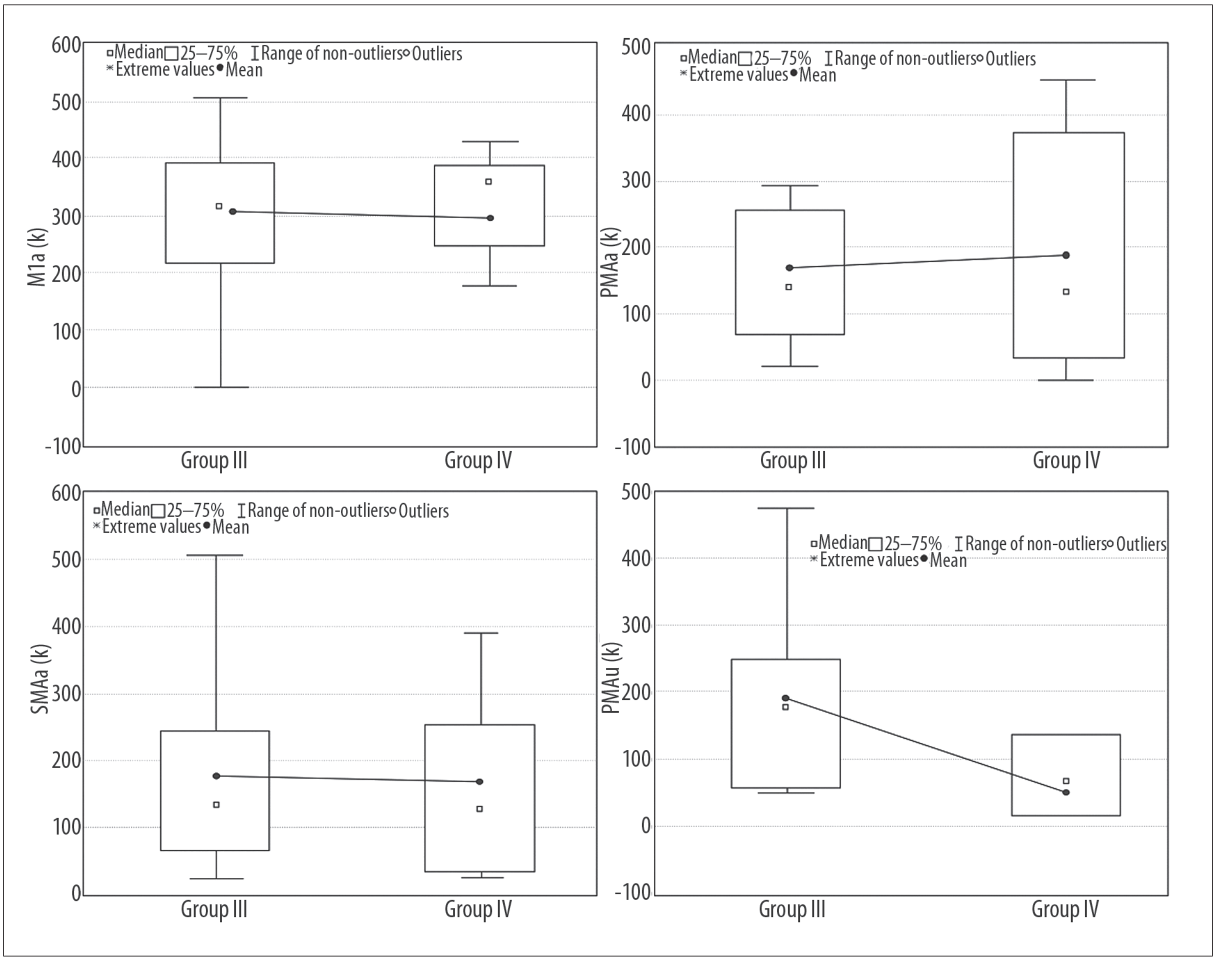

Figure 3. Box-and-whisker plot illustrating the distribution of the cluster number in selected motor areas in groups I and II, depending on the histopathological type of the neoplastic lesion.

motor areas in group I and II according to the histopathological type of the neoplastic lesion.

The analysis regarding the neoplastic lesion volume revealed that in the group of tumors with a smaller volume (group III), all centers of the motor cortex other than M1u located ipsilaterally to the upper limb performing the task were activated more frequently than in group IV. Aside from M1a, the most frequently activated centers of small and large tumors included SMAa, followed by PMAa. The most pronounced difference in the frequency of induced activation pertained to PMAa, and the least pronounced to M1u.

The values of t-statistics were greater in the case of small tumors located in ipsilateral centers, and in large tumors located in contralateral centers, aside from the accessory motor area where the values of t-statistics were equal for both groups.

No tendencies were observed regarding the differences in the size of activation areas in small and larger tumors.

The range of activation intensity values for contralateral centers in the group of small tumors and for ipsilateral centers in the group of large tumors was the same or narrower. The range of activation area in the group of larger tumors was always narrower, except regarding the PMAa area. The detailed data for tumors of group III and IV is presented in Table 3.

Box-and-whisker Figures 4 and 5 illustrate the distribution of t-statistic values and the number of clusters in the selected motor areas in group III and IV depending on the volume of the neoplastic lesion.

Due to the nature of examined variables and the lack of their normal distribution (both in case of the histopathological type and tumor volume), the statistical analysis of the data was based on the non-parametric Mann-Whitney U test. The statistical significance was assumed at $p<0.05$. The values of t-statistics and the number of clusters did not significantly differ between the groups when stratified with regards to analyzed variables. Based on the analyzed data, one can observe certain tendencies: in the case of SMAa, the results of the analysis referring to the tumor histopathological type suggested that a greater aggressiveness of the malignancy was associated with higher values of t-statistics in this center.

Discussion

"Plasticity" is a term currently understood as an ability for structural and functional modifications to take place

Table 3. Cumulative presentation of the motor areas analyzed in groups III and IV, taking into account the volume of the neoplastic lesion.

	Group III (V<40 cm3)				Group IV (V>40 cm3)				Mann-Whitney U testp<0.05	
Variable	**%N**	**Tm**	**km**	**SD**	**%N**	**Tm**	**km**	**SD**	**p-level**	**Z**
(M1a) T	100%	10.15		3.93	88%	11.50		3.86	0.32	0.01
(M1a) k			302.65	113.33			291.26	131.63	0.90	0.04
(PMAa) T	56%	6.50		1.40	35%	8.21		4.97	0.72	0.35
(PMAa) k			154.60	96.19			189.33	183.55	0.95	0.05
(SMAa) T	74%	6.29		2.71	59%	6.20		1.48	0.40	0.82
(SMAa) k			182.35	146.30			157.80	120.00	0.68	–0.40
(M1u) T	17%	6.91		4.50	18%	5.92		0.30	0.90	0.05
(M1u) k			205.00	228.28			218.30	46.75	0.72	0.35
(PMAu) T	26%	7.44		3.02	12%	4.56		0.50	0.09	–1.66
(PMAu) k			196.83	155.95			78.00	86.26	0.18	–1.33

T_m – mean value of t-statistics; k_m – mean number of clusters; %N – percent of predicted activity; SD – standard deviation; Z – Z coefficient; p – coefficient of significance.

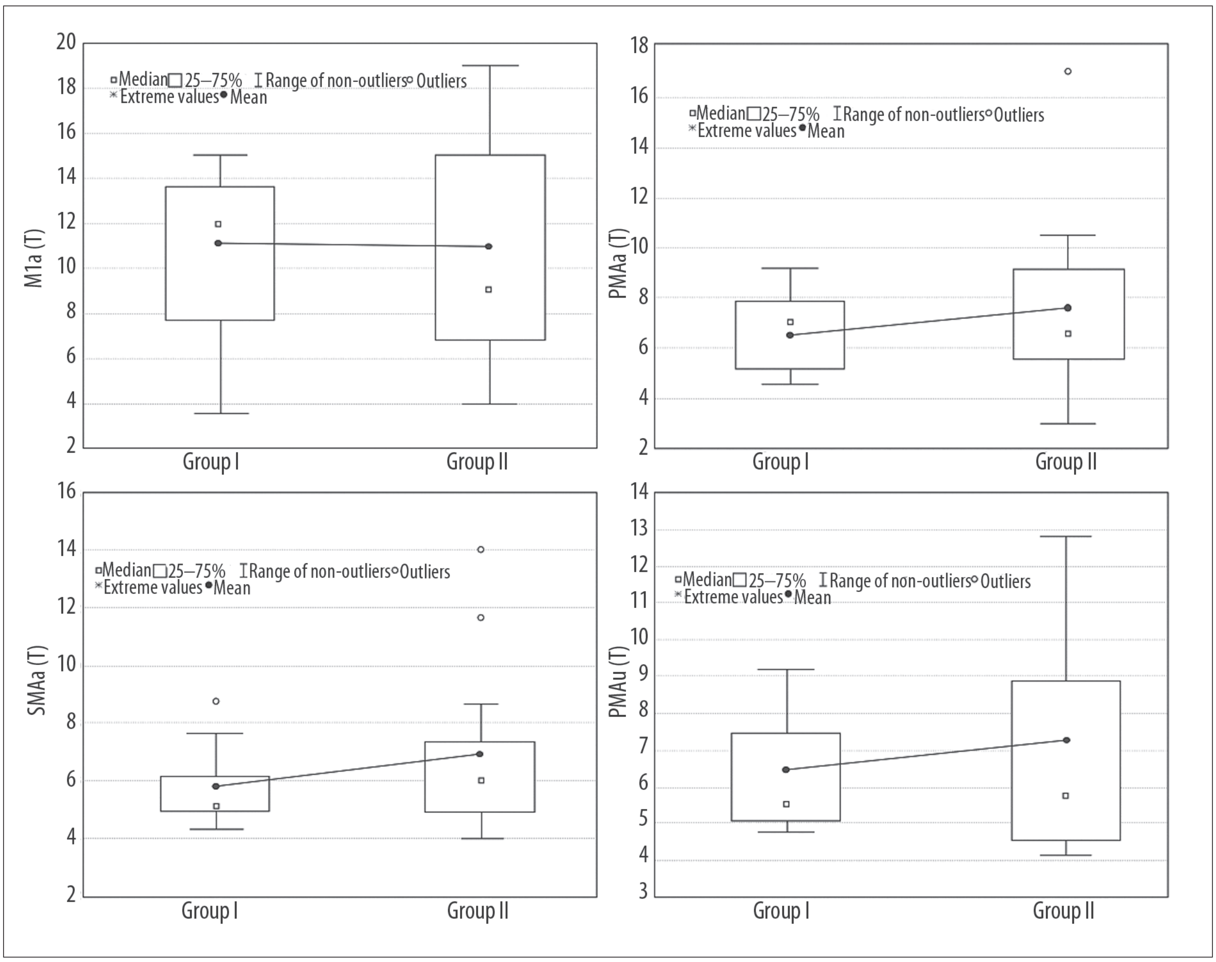

Figure 4. Box-and-whisker plot illustrating the distribution of the t-statistic values in selected motor areas in groups III and IV, depending on the volume of the neoplastic lesion.

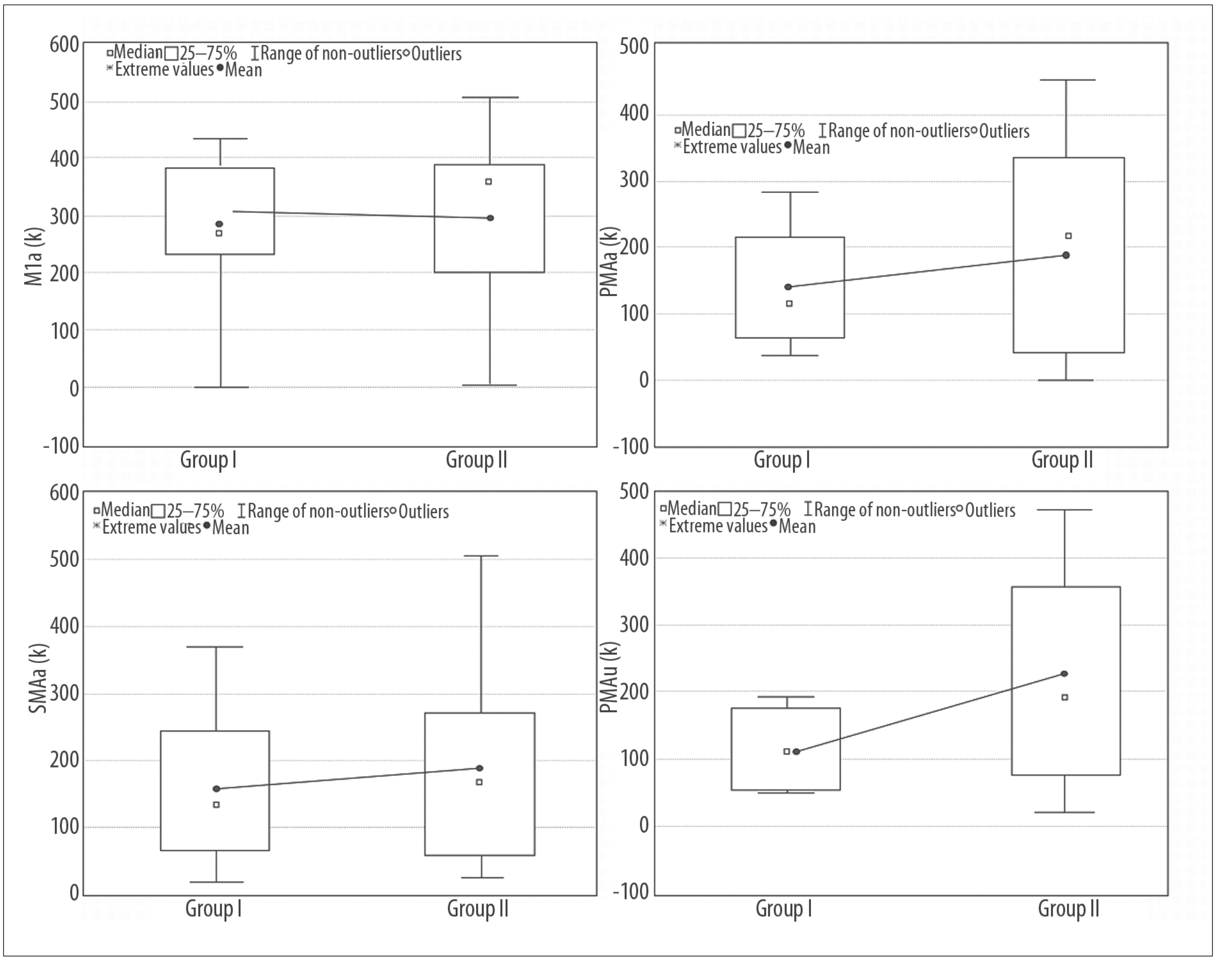

Figure 5. Box-and-whisker plot illustrating the distribution of the cluster number in selected motor areas in groups III and IV, depending on the volume of the neoplastic lesion.

within the neuronal network in response to both an external environmental stimulus and an internal one arising from an array of CNS complex processes. The term has been gaining importance since the rebuttal of the theory of neurogenesis completion within the embryonic period. Since the early 1990s, the presence of neuronal stem cells in the central nervous system has been evidenced. They are capable of differentiating into functionally mature, specialized neurons, which are inextricably associated with the process of brain plasticity [7]. Recent studies center around the identification of factors determining the processes of CNS reorganization, and utilization of this evidence in everyday clinical practice.

Currently, an array of factors is postulated to influence the survival time of patients with neoplastic lesions: structure, character, and growth rate of tumor, its variable biology, and the risk of anaplastic transformation [4,5]. Consequently, it is likely that parameters such as the histopathological type of malignancy and its size can have a significant impact on the process of functionally important center rearrangement, i.e. that of centers whose injury leads to profound, persistent neurological deficit.

The results of our study confirm previous findings documented in the literature, according to which simple motor paradigms in patients with neoplastic processes ongoing in the region of the central sulcus involve both primary and secondary motor centers [8]. In a population of healthy volunteers, simple paradigms revealed an activation solely in regard to primary motor cortex.

This finding constitutes a proof of ongoing rearrangement and reciprocal association between various motor centers, which take place in the presence of a neoplastic lesion. In the authors' opinion, in spite of the lack of statistically significant relationships between the mean values of activity (t-statistics) in a given motor area and the number of clusters in various centers in all analyzed groups, some tendencies should be noted. Despite the restrictive inclusion criteria of this study and the standardization of the procedure, homogenous group selection in terms of tumor location and size could only constitute an approximation. Thus, it is more clinically than statistically significant to determine the presence or absence of an activity in a given motor area.

In our study, the primary and secondary motor centers were activated more frequently in the group of patients with slow-growing highly-differentiated glioma (LGG) than in those with HGG, both in the hemisphere involved with neoplastic process and in the contralateral hemisphere.

According to the evaluation pattern of neural center reorganization in the group of LGG tumors that was proposed by Alkadhi et al, this observation can be explained by a slower and less aggressive rate of the tumor growth [8–10]. For instance, in fibrillar astrocytoma, a gain of tumor mass amounts to approximately 4 mm per year [11]. This slow growth rate provides a sufficient time frame for the development of new activities within already existing neuronal networks, in areas still unaffected by the neoplastic process, frequently prior to the manifestation of the first clinical signs of the disease [5,12]. This is particularly important in patients with LGG brain tumors, in whom the average survival time amounts to approximately 7–10 years [6,11].

The process of functional reorganization is not that frequently observed in the group of patients with poorly differentiated tumors (HGG), where our study revealed a lower frequency of activation in all centers of both examined hemispheres. The areas of activation were larger in this group, and both the calculated values of t-statistics and the numbers of clusters were characterized by higher variability. We interpret these findings as follows: a less pronounced activation of the reorganization processes when compared to the LGG group, a less precise activation of the plasticity mechanisms, and a transfer of the function onto supporting and accessory centers [13].

Undoubtedly, the results of this study could be modulated to a certain degree by various factors associated with the histopathological type of tumor. Some of these factors influence the processes of cerebral perfusion in the surroundings of the tumor, thus modulating the BOLD signal constituting a basis for fMRI [14–17]. Nonetheless, the effects of these factors are only limited to the centers located in the hemisphere ipsilateral to the neoplastic process. They can modulate the values of t-statistics and the number of clusters, leading to the lack of statistical significance; however, they do not influence the frequency of the neural center activation. We did not reveal a predominance of centers located in the ipsilateral hemisphere in any of the analyzed groups.

Furthermore, the results of this study suggest a greater activity of motor centers in patients with tumors of lower volume, both in the hemisphere ipsilateral to the neoplastic process and in the contralateral hemisphere, which can be explained by a smaller mass effect, smaller area of peritumoral edema, and a less pronounced decrease in the perfusion coefficient. Aside from this aforementioned relationship, we did not observe any other significant associations between the parameters studied in patients from groups III and IV. Therefore, the histopathological type of tumor seems to have a stronger impact on the processes of functional rearrangement when compared to the effect of the neoplastic lesion volume.

Another important finding pertains to the high frequency of the SMAa area activation in all studied groups. It was the second most frequently activated motor area after the contralateral primary motor cortex, irrespective of the grade and size of the neoplastic lesion. In groups I and III, i.e. in the case of less advanced neoplastic processes, the differences in the activation frequency of SMAa and PMAa areas were less pronounced. In groups II and IV, where the neoplastic processes were characterized by a higher aggressiveness, more pronounced differences were documented in favor of the SMAa area.

From a physiological viewpoint, the accessory motor cortex is responsible for planification of the motor pattern, preparing the gait, as well as coordinating and determining the timing of the motor reaction. Its activation requires solely to imagine the movement. The results of the recently published studies suggest that the involvement of the SMAa area is greater in the case of HGG tumors, not only with regard to the principal role of this region, but also in supporting the M1a area in performing more complex motor tasks [18,19,20,21,22,23]. The accessory motor area seems to be the most stable motor area with regard to the frequency of activation.

Based on the results of more detailed spatial analyses of the frequency distribution of induced activities, one can hypothesize that the process of functional rearrangement generally occurs more frequently and efficiently in the contralateral hemisphere. In all studied groups, the contralateral PMAa area in relation to the limb performing the task, was activated more frequently. This could result from a higher number of active connections between the centers of the same hemisphere, possibly promoting this particular pattern of neuronal rearrangement, as well as from the local effects of the neoplastic lesion itself [17,19]. The frequency of the PMAu area activation was lower in centers of the ipsilateral hemisphere. Additionally, in groups I, II, and III, the PMAu area of ipsilateral hemisphere was activated more frequently than M1u, suggesting a higher susceptibility of the contralateral secondary cortex to rearrangements.

For a practicing clinician, the determination of reorganization patterns of the motor centers can have a considerable prognostic role with regard to a potential deficit resulting from surgical treatment. According to the current literature, the risk of such deficits pertaining to limbs can be estimated at approximately 50% in the case of tumor resection located less than 1 cm from a functionally important area. A distance of 2 cm from the tumor is in turn considered a safe margin, and thus one should be familiarized with the true distribution of the neural centers [1,14,15]. Obviously, only an injury to the primary motor cortex is reflected by persistent neurological deficit. In contrast, an intervention within the centers of the secondary motor cortex is usually reflected by transient disorders of the CNS function with an individualized morphology. This plausibly reflects a different susceptibility of the primary and secondary cortex to the processes of functional modification, particularly with regard to the histopathological type of neoplastic lesion.

Conclusions

1. The mobilization of supportive and accessory centers occurs more frequently in patients with less aggressive malignancies as well as in those with smaller tumors, both in the hemisphere involved with neoplastic process and in the contralateral one.

2. Processes of functional reorganization are more pronounced and more precisely defined in patients with less aggressive and/or smaller tumors.
3. In clinical practice, the determination of a location of a contralateral accessory area becomes of vital importance, since this area is the most frequently activated center in all analyzed groups, irrespective of the grade and size of the tumor.
4. The histopathological type of the tumor, rather than the volume of the neoplastic lesion, seems to be the most important determinant in the process of functional rearrangement.

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