ISSN 0362-1197, Human Physiology, 2016, Vol. 42, No. 4, pp. 361–370. © Pleiades Publishing, Inc., 2016.
Original Russian Text © S.V. Kuptsova, M.V. Ivanova, A.G. Petrushevskiy, O.N. Fedina, L.A. Zhavoronkova, 2016, published in Fiziologiya Cheloveka, 2016, Vol. 42, No. 4, pp. 15–26.

Sex- and Age-related Characteristics of Brain Functioning during Task Switching (fMRI Study)

S. V. Kuptsova[a, b], M. V. Ivanova[c], A. G. Petrushevskiy[a], O. N. Fedina[a], and L. A. Zhavoronkova[b]

[a] *Center for Speech Pathology and Neurorehabilitation, Moscow, Russia*
[b] *Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, Moscow, Russia*
[c] *National Research University Higher School of Economics, Moscow, Russia*
e-mail: svoky@yandex.ru

Received October 12, 2015

Abstract—This study is focused on changes in the brain function throughout the adulthood in healthy men and women performing task switching (TS) in the visual modality. One hundred and forty healthy subjects aged 20 to 65 years (69 men) participated in the experiments. In the fMRI study, the subjects performed a test that required switching attention between two objectives (classifying figures according to their form or number). Using the voxel-based morphometry (VBM), we calculated the volumes of gray and white matter in the whole brain and in selected areas. The results showed that a common feature of different age and sex groups performing the TS was bilateral activation of the dorsolateral prefrontal areas, the inferior parietal lobes and the inferior occipital gyrus. We also found a transition from local to diffuse activation occurring with age. In young men (20 to 30 years of age) compared to women, a greater increase in the *BOLD* signal was found in the prefrontal areas bilaterally, the right parietal lobe and insula, and, in addition, bilateral activation in the supplementary motor area which were not observed in women. Older men and women (51 to 65 years) had no significant differences. The study of the *BOLD* signal correlations with age in women at the age from 20 to 40 and men from 20 to 55 years showed no significant changes. With further increase of age in both groups we found a consequent increase in the number of brain areas which are activated. The VBM analysis showed a significant decrease in the volume of gray, but not white, matter with age. No significant correlations between age-related changes in the gray matter volume (both in the whole brain and in the specific areas) and *BOLD* signal in this age group were detected.

Keywords: attention switching, task switching, executive functions, fMRI, age-related differences, sex-related differences

DOI: 10.1134/S0362119716040101

The ability to implement the goal-directed behaviors, as well as to control the activity, enables a person to deliberately organize their activities. Luria [1] singled out this ability as a separate functional unit of the brain, specifically, the unit of programming, regulation, and control of complex forms of activity. The term executive functions afterwards appeared in the Russian literature [2]. Miyake and Friedman [3] have identified three most frequently mentioned in the literature executive functions: shifting between tasks or mental sets, updating and monitoring of working memory representations, and inhibition of prepotent responses. Task switching (TS) [4], i.e., the ability to consciously and quickly switch attention between multiple tasks, operations, or mental sets [3, 5] are the most common in the studies of the executive functions.

Neuropsychological studies have shown an increase in perseverations, reduction in the number of correct answers, a decrease in response time, and an increase of the impact of interference on the executive functions with age [6]. The results of studies on age-related changes in cognitive functions and neuroanatomical substrate demonstrated a relationship between a decrease in the dorsolateral prefrontal areas and an increase in the number of errors in the performance of tasks on the executive functions [7]. In some studies on age-related changes of the morphological substrate of the brain, a significant decrease in the volume of gray matter, the surface and the thickness of the cortex with age have been shown [8–10]. However, in some studies, these differences tend to appear, but do not reach the level of significance [11]. According to Saveliev, the dynamics of age-related changes of the brain weight in healthy people depends on the sex and ethnicity of the person [12], which, apparently, could explain the difference in the obtained results. It could also be due to the different criteria for inclusion of subjects in the normal group (some authors included minor cerebrovascular changes and considered them

Table 1. The number of subjects in five-year age intervals depending on their sex ad age

Sex	Age								
	20–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65
Men	8	11	6	8	9	7	11	6	3
Women	10	10	10	6	8	7	8	9	3

as the normal age-related changes, others did not). EEG studies also revealed a change in the amplitude–time parameters of evoked potentials with age [13].

In many studies of age-related features of higher mental functions, special attention is given to children and the elderly age due to the conspicuous rapid changes in these groups, and few of them address changes and reorganization of higher mental functions in adults. This is most likely to be caused by the fact that changes are not that obvious in adulthood, and this age is considered to be a relatively stable period. Age-related changes in the TS in adult people and their distinctive features in men and women are not fully studied. Such knowledge would give the most complete picture of this process and would help to understand how this function changes with age, and the timing of certain age-related reorganizations in the brain when performing tasks of this type.

There are a number of age period classifications which include the adult age. These classifications are based on various principles of distinguishing the age periods, and therefore differ from each other. For example, Bunak's classification is based on morphological and anthropological features and related structural and functional changes [14]. Erikson based the classification on the stages of psychosocial development of the person [15]. Ananiev used the principle of heterochrony of the psychophysiological development and distinguished macroperiods based on the behavioral experimental data obtained in the studies of memory, thinking, and attention [14]. One of the most comprehensive and popular classifications suggested by Bromley is based on various principles (age, social status, physiological changes, etc.), and human life is considered to consist of several cycles [14]. These are only a few examples of age periodization of individual human development. Most of these systems are similar and often contain the same period names with similar age ranges. Since there are many different age classifications developed by experts in various fields and there is no single concept of age periodization, in our opinion, the best option would be to consider the entire continuum of age-related changes from the younger to the older adult age without division into groups according to various principles.

Thus, the purpose of this study was to analyze the dynamics of functional and structural changes in the brain of subjects of different ages and sexes during the test on switching visual attention between tasks.

METHODS

The study enrolled 172 subjects at the age of 20 to 70 years. All subjects completed questionnaires to evaluate the presence of neurological and psychiatric conditions. The presence (or absence) of organic brain damage was determined in the T_1 and T_2 weighted images. To increase the validity of data, the threshold of correct answers was set at the level of 75% in the fMRI task. Handedness was defined using the Annette test [16]. Subjects also underwent neuropsychological testing (D-KEFS Trail Making Test for assessing the executive functions [17] and subtests of Wechsler Memory Scale to assess the auditory and visual memory [18]). Data from subjects with organic brain lesions (23 subjects), with the number of correct answers less than 75% (6 subjects), left-handed subjects (2 subjects), and taking psychotropic drugs at the time of the study (1 subject) were excluded from the analysis of the results. The final sample of 140 right-handed subjects at the age from 20 to 65 years included 69 men (mean age, 41.02 ± 12.20 years) and 71 women (mean age, 40.63 ± 12.90 years). Of these subjects, 11% had secondary education; 11.5%, incomplete higher education; 66%, higher education; and 11.5% had an academic degree. The samples did not differ significantly in age or educational level. The numbers of subjects of each sex in five-year age groups are shown in Table 1.

In compliance of the Helsinki Declaration, all subjects gave their written informed consent to participate in the experiment, data processing, and publication of the results.

The test for TS in the visual modality for the fMRI study consisted of two blocks: an experimental (subjects needed to switch attention between two objectives) and a control (which did not require switching the attention and just requested to follow the instructions on the screen). An example of a task is described in our previous article [20].

In the experimental block, a subject had to evaluate presented geometric figures by the form or number. On the black background screen, white geometric figures were presented consecutively (one or two figures at a time); each of them was preceded by an cue image defining the method of estimating the figure. Cue images were an empty square and two empty circles. If the subject saw the "empty square", he or she had to estimate whether the following figure matched the "square" shape, focusing on the external shape of the figure (if this was a square, the subject had to click the right mouse button; if not, click the left). If the image "two empty circles" appeared, subject had to assess the match with the number "two" (if there were two figures, the subject had to click the right button; if there was one figure, the left one). The figures were presented in a pseudo-random order.

Under the control condition, a subject was presented with a triangle with an acute angle pointing to the right or to the left. The subject was asked to press the button on the side of the angle was pointing. A cross was shown between the triangles.

Before each experimental block subjects saw the instruction "sorting" on the screen, before the control block, "direction." Instructions were presented for 2000 ms and followed by a black screen (for 1000 ms) and the test block. Time of presentation of each figure was 4000 ms, the image-instruction in the experimental series, and crosses between the triangles in the control blocks were presented for 1000 ms. Each block consisted of six figures. The experimental blocks consisted of three switches from one task to another. The duration of each block was 30 s. The blocks were presented in pseudo-random ordering, eight blocks of each type, and one more training experimental block at the beginning of the task, which was not included in further analysis. The number of clicks on the left and the right button by the left hand was the same under the experimental and control conditions. To carry out further clinical studies at the Center for Speech Pathology and Neurorehabilitation, where this task was developed, the subjects were asked to use the left hand (right button corresponds to the index finger, and the left one, to the middle). Most patients of the Center have language and speech disorders and often have right-sided paresis. More detailed description of the task is provided in our previous papers [19, 20].

Prior to the main experiment, all subjects performed a similar short task as computer training. After a correct performing, subjects were asked to perform a similar task inside a MRI scanner.

The task for fMRI studies was shown for the subjects automatically using the E-Prime 1.0 software. During the task performing, the response times to stimuli, as well as the number of correct and incorrect answers were recorded. The regions of brain activation during performing this type of tasks, the difference in activation in both men and women at the younger adult age, and correlation of *BOLD* signal with the widely used neuropsychological tests for TS (Delis-Kaplan) are described in detail in our previous study [20].

The fMRI scanning was conducted using a MAGNETOM Avanto 1.5T system (Siemens). The T1 MP-RAGE sequence (TR, 1900 ms; TE, 2.91 ms; slice thickness, 1 mm; 176 slices; FoV, 250 mm; reconstruction matrix, 256 × 256; voxel size, 1 × 1 × 1 mm) was used to obtain the sagittal anatomical image. The EPI sequence was used to register the BOLD signal in fMRI (TR, 3000 ms; TE, 50 ms; 35 slices; FoV, 192 mm; matrix, 64 × 64; voxel size, 3 × 3 × 3 mm). The fMRI study included 241 measurements.

The data were analyzed using the *SPM*8 software (http://www.fil.ion.ucl.ac.uk/spm/) based on Matlab R2012b (MathWorks, Natick, MA, United States) individually and at the group level. Sections were oriented parallel to the plane of the anterior and posterior brain commissures. Prior to second level statistical analyses, the images were realigned, coregistered, segmented, and normalized to the stereotactic template of the Montreal Neurological Institute (MNI-template). Normalized images were smoothed with an Gaussian kernel of 8 mm FWHM. Individual activation maps were constructed using the general linear model. Group maps were produced from the data of individual subject maps using a random effect model. To construct activation maps in different groups, the one-sample *t* test was used. To compare groups, the two-sample *t* test was used. All activation clusters obtained were represented in the *MNI* coordinates. For the analysis of group activation maps separately for each group, the statistical thresholds were set at voxel levels $p < 0.001$ (*unc.*) with the corrected threshold of the significance of cluster-level *p* (*FWE-corr*) < 0.001. The comparison of groups was carried out with voxel threshold corresponding to $p < 0.001$ (*unc.*) with the corrected threshold of significance of cluster-level *p* (*FWE-corr*) < 0.01. To obtain the data on the spatial location and volume of activated regions, the SPM anatomy toolbox, version 1.8 was used [21]. To distinguish cytoarchitectonic Brodmann areas, the Talairach Client 2.4.3 software was used. For this purpose, the *MNI* coordinates were converted into Talairach and Tournoux coordinates [22] with the GingerALE 2.3.1 software. The relationships between the *BOLD* signal in the contrast (experimental condition minus control) and the age of the subjects and *BOLD* signal in the contrast and gray matter volume was conducted using SPM8 software, where the age and the gray matter volume were included as covariates in the analysis of the second level, while the voxel threshold $p < 0.001$ (*unc.*) was used with the corrected threshold of the significance of cluster-level *p* (*FWE-corr*) <0.05.

The volumes of gray and white matter were calculated using VBM analysis [23] in the SPM8 software using the *get_totals* script (http://www0.cs.ucl.ac.uk/staff/g.ridgway/vbm/) based on Matlab R2012b. To analyze the relationship of the *BOLD* signal with the volume of gray matter in different brain areas, the regions of interest were selected using the WFU_PickAtlas_3.0.4 software. The frontal, parietal, occipital, and temporal regions were selected for this analysis, since some authors observed a positive correlation between the deterioration in carrying out neuropsychological tasks on the executive functions and the reduction of the gray matter volume with age [24], and the activation of the inferior and middle frontal gyri and the inferior parietal lobule was observed in fMRI studies of TS [25, 26]. The statistical analysis of the behavioral data (the reaction time, the number of correct and incorrect responses), the comparison of the volume of gray and white matter were performed using the SPSS 22.0 software. First, the data were checked for normal distribution using the Kolmogorov–Smirnov test. To investigate the differences between the groups, as well as the relationship between the independent variables, generalized linear models were used; Pearson's correlation coefficient (for the variables with the normal distribution) and Spearman's coefficient (for the variables that do not fit the normal distribution) were used to study the relationship between dependent and independent variables.

RESULTS

The results of the Kolmogorov–Smirnov test showed that the dependent variable (the reaction time) and the volumes of gray and white matter had a normal distribution ($p > 0.1$), and the number of correct and incorrect answers under the experimental and control conditions were not normally distributed ($p < 0.05$).

First, to identify the differences in the functional activity of the brain and quality of task performing during fMRI scanning between the two extreme age groups, we compared the younger adults (20 to 30 years) and older adults (51 to 65 years) of the same sex, and then between the sexes, to see the development of differences with age. Next, to investigate at what stage of the younger adulthood to the older adulthood the differences appear and how they change, the correlation analysis of changes in the *BOLD* signal with age was performed, taking into account the contribution of each participant, who took part in the study, with an interval of five years.

At the initial stage, the success of TS execution was analyzed based on the result of behavioral data of groups in the fMRI study. In general, all groups have successfully managed the experimental condition: in the group of young men, there was 98% of correct answers on average; in the group of older adult men, 97%; in the group of young women, 98%; in the group of older adult women, 97% of correct answers. On average, 99% of correct answers were given in all groups in the control block.

The "net" time of TS (the reaction time for the experimental condition minus the reaction time for the control condition) between groups of men and women ($B = -29.37$, $p = 0.57$), younger and older adulthood groups ($B = -58.19$, $p = 0.25$), the interaction between sex and age ($B = 39.02$, $p = 0.59$) and the number of errors in the control block between groups of males and females ($B = -0.64$, $p = 0.60$), younger and older adulthood groups ($B = 1.50$, $p = 0.06$), the interaction between sex and age ($B = -0.81$, $p = 0.57$) showed no significant differences. The comparison of the number of errors between men and women in the experimental condition ($B = -0.97$, $p = 0.72$), the interaction between sex and age ($B = 0.22$, $p = 0.64$), showed no significant differences; however, significant differences between younger and older adulthood groups ($B = -7.28$, $p = 0.03$) were detected. The mean values for the groups are presented in Table 2.

To determine whether there is a relationship between reaction time and a number of errors in the experimental condition, the correlation analysis was conducted between the two variables throughout the

Table 2. Mean values and standard deviation of the number of errors and response time in younger and older adult men and women

groups	Number of errors				Response time	
	experimental condition		control condition			
	M	*SD*	*M*	*SD*	*M*	*SD*
1	0.79	1.98	0.12	0.31	322.94	157.95
2	1.31	1.66	0.05	0.23	342.11	140.40
3	0.70	1.65	0.45	0.88	313.30	179.85
4	1.45	1.82	0.10	0.31	371.49	177.32
5	1.05	1.83	0.08	0.27	332.53	147.72
6	1.07	1.75	0.27	0.67	342.39	178.73
7	0.74	1.8	0.28	0.68	318.00	167.38
8	1.38	1.7	0.08	0.26	357.18	159.00

M, mean; *SD*, standard deviation; 1, the group of younger adult men; 2, the group of older adult men; 3, the group of younger adult women; 4, the group of older adult women; 5, men; 6, women; 7, younger adulthood; 8, older adulthood.

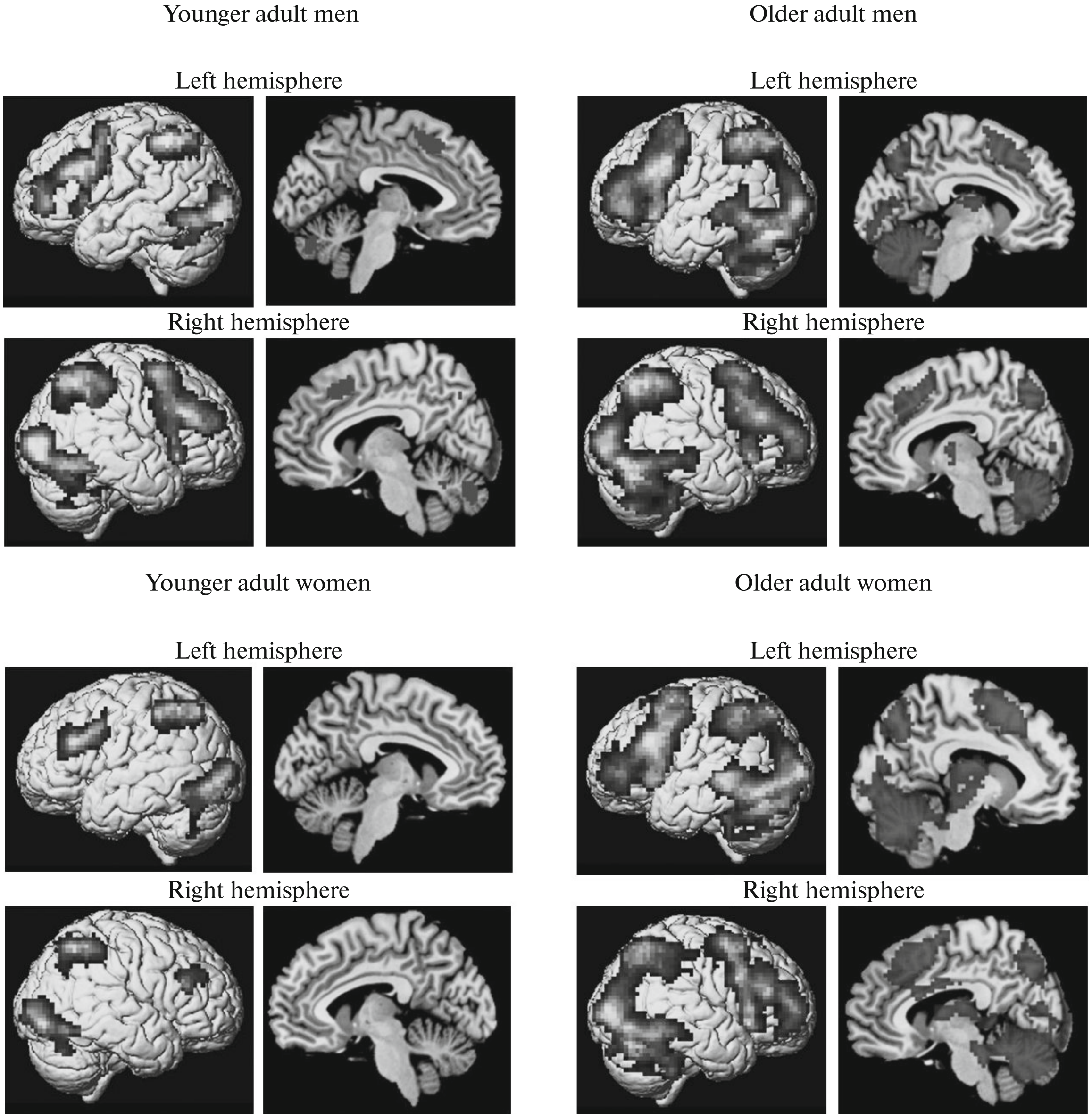

Fig. 1. The results of fMRI studies in the attention switching task compared to the control condition in groups of younger and older adults (p (*unc.*) < 0.001, a cluster correction for multiple comparisons p (*FWE-corr*) < 0.001).

whole group of subjects. The highly significant positive correlations between the reaction time and the number of errors in the experimental condition were found ($r = 0.48$, $p = 0.000$); a greater reaction time corresponds to a greater number of errors.

The analysis of fMRI data was carried out to identify the areas of the brain involved in the TS. The relative difference between the *BOLD* response in two blocks was determined: the experimental minus the control. During the performance of the TS, in the group of younger women, the areas of activation were found in the dorsolateral prefrontal, inferior parietal region, the secondary areas of the visual cortex of the left hemisphere (LH) and the right hemisphere (RH), and cortical areas of the left and right hemisphere of the cerebellum. In men of the same age, the same areas of activation were found, and additionally, activation in the supplementary motor area, the right insula, and left thalamus was detected. In groups of older adult men and women, quite diffuse activation involving a large number of activated areas of the brain (dorsolateral prefrontal, parietal, occipital, cerebellum, supplementary motor cortex, island, thalamus, and basal ganglia of LH and RH) was found. The results of the fMRI data are presented in Fig. 1.

Comparison of groups of older adult men and younger adult men revealed the clusters with maximum signal intensity in the cerebellum, on the medial

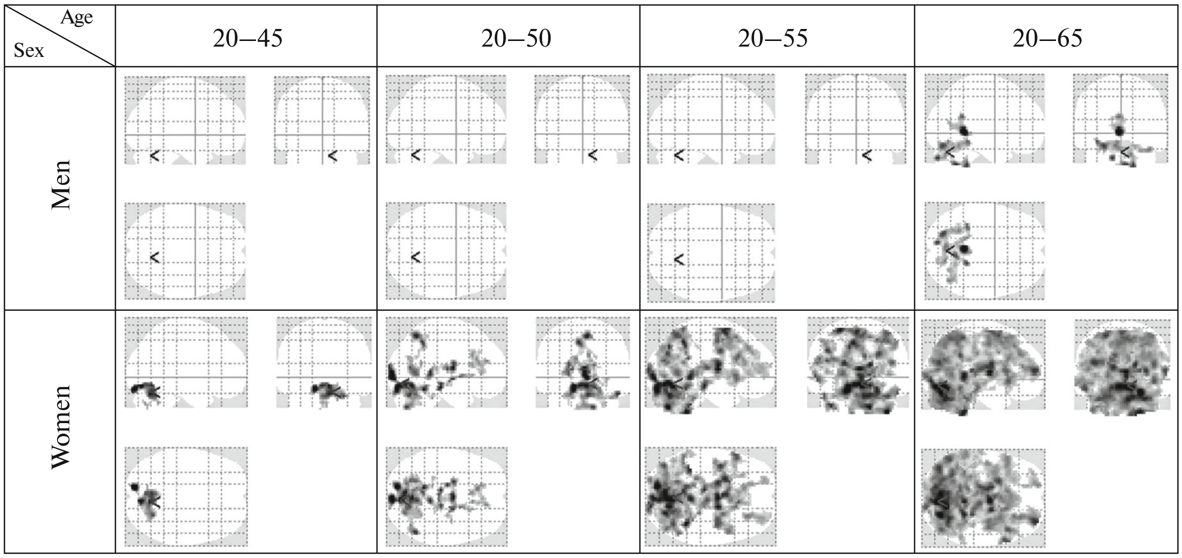

Fig. 2. Correlations between the *BOLD* signal and age in men and women of different age groups.

surface of the occipital and posterior cingulate gyrus. In the group of older adult women, in comparison with younger adult women, large clusters of activation were detected in the cerebellum, lingual, inferior and middle frontal, middle temporal, precentral, lateral occipital, anterior and middle cingulate gyrus, inferior parietal lobule, precuneus, insula, thalamus, and the basal ganglia of both hemispheres of the brain (Table 3).

Comparison of groups of younger adult men and women showed a significant difference with respect to the increase in the *BOLD* signal in the posterior part of the inferior and middle frontal gyrus, supplementary motor area of both hemispheres, the insula, the middle part of the cingulate gyrus, and the inferior parietal area of the right hemisphere in men. In women of the younger adult age, there was no increase in the *BOLD* signal in comparison with men of the same age group. Comparison of men and women of the older adult age showed no significant differences (Table 3).

To assess the changes and the age of these changes, the correlation analysis was performed between the *BOLD s*ignal and age of men and women separately. No significant correlations were found between the *BOLD s*ignal and an increase in the age of women in the 20–40 years age range. However, significant correlations were found with the addition of each of the following five years; the older the age of women was the more areas of the brain had an increase in the *BOLD s*ignal. An increase in the activation in the cerebellum and medial surface of the occipital lobe took place by the age of 45 years; by 50 years, the activation in the medial surface of the temporal lobe, thalamus, striatum increased along with the former; by 55 years, the activation of the medial surface of the frontal lobe, the lateral surface of the occipital and frontal lobe was added; by 65 years, in addition to the activated areas, the activation of the insula and the inferior parietal lobe appeared. No significant correlations between the *BOLD s*ignal and a decrease in age were found in women (Fig. 2).

The analysis of the relationship between the *BOLD* signal and an increase in age in men at the age from 20 to 55 years showed no significant correlations. Significant correlations were discovered with further increase in age: an increase in the *BOLD s*ignal in the cerebellum, the medial surface of the occipital region, and posterior cingulate gyrus appeared by the age of 65 years. No significant correlations with a decrease in age were found in men (Fig. 2).

Then, we analyzed the age-related dynamics of the volume of gray and white matter of the brain. Significant correlations between the changes in the gray matter volume and age were found in both men and women: the older the age, the smaller the volume of the gray matter was (men: $r = -0.276$, $p = 0.022$, women: $r = -0.325$, $p = 0.006$). No significant correlations of the change in the volume of white matter with age were found (men: $r = 0.073$, $p = 0.552$; women: $r = 0.031$, $p = 0.796$). Therefore, since we obtained statistically significant age-related changes in the volumes of gray matter only, further analysis of the possible relationship between the revealed age-related changes and the morphology of the brain would be appropriate only for the gray matter of the brain.

In addition, the correlations of the *BOLD s*ignal with the gray matter volumes of the whole brain and of specific brain regions in different age and sex groups, as well as in the entire group of subjects, were calculated. No connection of the *BOLD s*ignal with the volume of the whole brain, the frontal, parietal, occipital, and temporal regions were found in men, women, the

Table 3. Clusters of activation in the brain of younger and older adult groups

Cluster size (voxels)	*p* (*FWE-corr*)	H	Localization	Coordinates *MNI* {*x*; *y*; *z*}	*peak T value*	≈BA
Older adult men > younger adult men						
279	,000	L	*Cerebellum*	–21; –76; –20	5.01	–
135	,001	L	*Calcarine*	–6; –67; 13	3.96	30
			Posterior cingulate cortex	–6; –46; 22	3.74	30
107	,004	L	*Cerebellum*	–12; –52; –44	4.78	–
		R	*Cerebellum*	9; –55; –44	4.52	–
Older adult women > younger adult women						
13201	,000	R	*Lingual gyrus*	9; –67; –11	8.76	–
			Cerebellum	24; –76; –17	8.05	–
			Thalamus	3; –4; 10	7.66	–
			Caudate nucleus	18; –4; 22	6.64	–
			SMA	8; 17; 61	4.00	6
			Middle frontal gyrus	37; –3; 61	5.33	6
			Insula lobe	38; 25; –1	4.62	13
			Precuneus	11; –58; 51	4.36	7
			Angular	50; –48; 34	4.59	40
			Middle occipital gyrus	38; –76; 28	5.38	19
			Anterior cingulate cortex	9; 25; 28	3.89	32
		L	*Cerebellum*	–12; –76; –14	8.38	–
			Thalamus	–12; –10; 19	7.06	–
			SMA	–6; 17; 57	4.38	6
			Precentral gyrus	–36; 1; 61	4.87	6
			Middle frontal gyrus	–47; 13; 46	3.43	6
			Precuneus	–2; –57; 51	3.64	7
			Angular gyrus	–49; –58; 34	3.62	39
			Middle occipital gyrus	–29; –79; 28	4.53	19
			Middle cingulate cortex	–8; –22; 38	5.41	31
355	,000	L	*Inferior frontal gyrus*	–51; 17; 25	4.99	9
			Insula lobe	–27; 29; –2	4.39	–
321	,000	L	*Inferior occipital gyrus*	–54; –64; –14	4.94	37
			Middle temporal gyrus	–54; –40; 1	5.84	22
Younger adult men > younger adult women						
246	,000	R	*Middle frontal gyrus*	48; 8; 52	6.30	6
			Middle cingulate cortex	15; 8; 40	4.68	24
173	,000	R	*Inferior parietal lobule*	36; –49; 52	3.63	7
161	,000	R	*Insula lobe*	45; 20; –5	4.43	13
			Inferior frontal gyrus	42; 14; 13	4.97	13
128	,001	L	*Superior medial gyrus*	–3; 29; 49	5.75	8
			SMA	–3; 5; 55	3.55	6
		R	*Middle cingulate cortex*	9; 29; 34	4.14	32
			SMA	6; 14; 46	3.89	32
88	,009	L	*Inferior frontal gyrus*	–51; 14; 28	5.20	9
			Precentral gyrus	–57; 5; 25	4.38	6

H, hemisphere; L, left hemisphere; R, right hemisphere; BA, Brodmann cytoarchitectonic area; *p* (*FWE-corr*), the significance level of clusters.

entire group of subjects, and in the groups of younger and older adult people.

In order to investigate whether the *BOLD s*ignal during the execution of the studied type of task depended on the age-related changes in the gray matter volume, these variables were included in the analysis of the second level as covariates. No significant correlations were found between the age-related changes in the volumes of gray matter and *BOLD* signal in men, women, the entire group of subjects, as well as in people of the younger and older adult age in the whole brain, the frontal, parietal, occipital, and temporal regions.

DISCUSSION

The comparison of the number of errors in the control condition and the "net" time of TS did not reveal significant differences between the groups of men and women, younger and older adulthood groups, as well as interaction with sex and age. However, significant differences were found in the number of errors in the experimental condition in the younger and older adulthood groups, which showed that the older subjects made more mistakes. The comparison of women of different age groups, different age groups of men, and men and women showed no significant differences in the number of errors in the TS. This result is probably due to the fact that the subjects were not asked to respond as quickly as possible, and they should have answered as correctly as possible to reduce the number of errors. This assumption was made because when we used the psychological method to study TS, in which subjects had to respond as quickly as possible, the significant differences were found between young men and women [20]. This assumption is also supported by a significant correlation between the "net" time of TS and the number of errors in the experimental condition. The subjects who made more errors, had longer response time, which could reflect the strategy of the task execution (subjects with a large number of errors had to take more time to execute the TS, and, most likely, they had to slow down to do fewer errors, while subjects who almost did not make mistakes carried out the task at a usual pace). Since the subjects had enough time to make a decision and give an answer, no differences were found in the response time and in the number of errors between the different groups. Differences were discovered between the younger and older adult age groups and showed that, in general, the perfoming of TS tasks worsens with age.

According to fMRI results, during the TS in the visual modality in subjects of different age and sex, the bilateral activation appeared in the dorsolateral prefrontal areas, the inferior parietal lobes and the inferior occipital gyrus. These activation zones are found in the majority of imaging studies investigating the TS [25, 26]. It is important that the present study also revealed significant differences between the groups, which appeared as an increase in the *BOLD* signal in young men compared to women of the same age performing the TS. The transition from the local to diffuse activation occurring with age was common in both sex groups.

The comparison of the volumes of gray and white matter showed a significant decrease in the volume of gray matter with age. These data are consistent with other studies that examined the change of gray and white matter with age, and the volume of white matter was shown to remain intact almost until the elderly age [9, 10]. Giorgio et al. [9] found no differences in the volume of the white matter between younger adults (23 to 40 years) and older adults (from 41 to 59.6 years), while the group of elderly subjects (60 to 81.6 years) exhibited a significant decrease in the volume of white matter in comparison with the group of older adults. In this study, the authors observed a significant decrease in the volume of gray matter in the group of older adults in comparison with younger adults. This difference continued to grow in the elderly age. Since the average age of our older group was 56 years (the group included subjects not older than 65 years), that is probably why we did not observe age-related changes in the volume of white matter in our subjects.

The correlation analysis in groups of men and women, and the entire group of subjects showed no significant correlations between age-related changes in the volume of gray matter of the whole brain and its specific regions and the *BOLD* signal. These data suggest that age-related decrease in the volume of gray matter does not affect the change in the parameters of the *BOLD* signal during the TS, and the significant increase in activation in almost all areas of the brain in women, and in the cerebellum and medial surface of the cerebral hemispheres in men with age are associated with different causes. A possible reason is a change in the hormonal status. The differences between men and women in the change in the *BOLD* signal with age appearing as an increase in the diffuse activation in women by the age of 45 years, can be caused, e.g., by a reduction in estrogen levels, which are known to affect the higher mental functions in humans [27]. In men, in contrast to women, according to medical literature, hormonal status change is observed 10–15 years later [28]. In men, we found an increase in activation in the cerebellum and medial surface of the cerebral hemispheres occurring by 60 years of age. The assumption about the influence of hormones is supported by the significant difference in the *BOLD* signal in TS between groups of young men and women, when hormonal differences were prominent, which was not detected in the older age groups. In the younger group of men, the task execution was of the same quality as in the group of women and was accompanied by the significantly greater activation in the prefrontal areas, the inferior parietal lobule and the right insula. In addition, the men had bilateral activation of the supplementary motor area, which was not observed in women. This could indicate the involvement of larger brain resources in carrying out this type of task in men. The details of these differences are discussed in our paper [20].

Thus, the difference between sexes was prominent in young subjects, which, however, reduced with age, and approximately corresponded to the change in hormonal status in women. But since we did not carry out the measurement of hormone levels, we cannot experimentally confirm or reject this hypothesis.

It is interesting that an increased activation was first found in the cerebellum in both men and women during aging. It is assumed that one of the functions of the cerebellum is the calculation of the possible incorrect actions, because both afferent and efferent signals are conducted through it [29]. The cerebellum is suggested to predict the possible errors and correct the subsequent behavior by calculating the differences between the expected and obtained results, thus participating in the adaptive plasticity [30]. Although the subjects performed the task at the convenient rate, we still found an increase in the number of errors with age. It is possible that the initial increase in activation in the cerebellum is a compensatory mechanism associated with the adaptive plasticity, which is probably effective only at the early stages, but cannot fully compensate the productivity decrease occurring with age.

Further increase in the diffuse activation with age in different areas of the brain can be associated with some specific age-related alterations caused by different reasons. We should not exclude hormonal, genetic, and even socio-cultural factors. However, the mentioned explanations require further experimental verification.

It should be noted that men, unlike women, did not exhibit an increase in the activation of cortical areas of the cerebral hemispheres with age, which could be due to the absence of older subjects in the group. In women, an increase in the activation in different areas of the brain during the TS execution starts at the age of 45 years; in men, only after 55 years. The age range of subjects was limited by 65 years, since the subjects older than 65 years could not be included in the normal group due to various organic brain pathologies. If older subjects were included in the group of men, an increase in activation similar to that observed in women would have been found with age.

CONCLUSIONS

(1) The common features of the brain functioning during the performance of TS in different sex and age groups were found: bilateral activation in the dorsolateral prefrontal areas, the inferior parietal lobes and the inferior occipital gyrus.

(2) In younger subjects, a difference in the performance of this type of tasks was expressed as a prominent bilateral increase in the *BOLD* signal in the prefrontal areas, parietal lobe, and right insula in men in comparison to women. Additionally, the activation in the supplementary motor area was found in men, but was not observed in women. In subjects of the older adult age, no significant differences were found between men and women performing the TS.

(3) In healthy subjects of both sexes, during the task on the TS, a transition of the brain functioning from the local to diffuse activation takes place with age.

(4) VBM analysis has shown a significant reduction in the total volume of the gray matter, but not white matter, of the brain with age.

(5) The correlation analysis of *BOLD* signal in the TS and the volume of gray matter (according to the VBM analysis) has shown no significant correlations between the age-related decrease in gray matter volume and an increase in the *BOLD* signal with age.

REFERENCES

1. Luria, A.R., *Osnovy neiropsikhologii (Foundations of Neuropsychology)*, Moscow: Akademiya, 2013.
2. Akhutina, T. and Pylaeva, N., *Preodolenie trudnostei ucheniya. Neiropsikhologicheskii podkhod (Overcoming Learning Difficulties: A Neuropsychological Approach)*, St. Petersburg: Piter, 2008.
3. Miyake, A., Friedman, N.P., Emerson, M.J., et al., The unity and diversity of executive functions and their contributions to complex “frontal lobe” tasks: a latent variable analysis, *Cognit. Psychol.*, 2000, vol. 41, no. 1, p. 49.
4. Dove, A., Pollmann, S., Schubert, T., Wiggins, C.J., and von Cramon, D.Y., Prefrontal cortex activation in task switching: an event-related fMRI study, *Cognit. Brain Res.*, 2000, vol. 9, no. 1, p. 103.
5. *Eksperimental'naya psikhologiya (Experimental Psychology)*, Romanov, E.S., Ed., St. Petersburg: Lider, 2007.
6. Clarys, D., Bugaiska, A., Tapia, G., and Baudouin, A., Ageing, remembering, and executive function, *Memory*, 2009, vol. 17, no. 2, p. 158. doi 10.1080/09658210802188301
7. Raz, N., Gunning-Dixon, F.M., Head, D., et al., Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging, *Neuropsychology*, 1998, vol. 12, no. 1, p. 95.
8. Lemaitre, H., Goldman, A.L., Sambataro, F., et al., Normal age-related brain morphometric changes: nonuniformity across cortical thickness, surface area and

gray matter volume?, *Neurobiol. Aging*, 2012, vol. 33, no. 3, p. 617.

9. Giorgio, A., Santelli, L., Tomassini, V., et al., Age-related changes in grey and white matter structure throughout adulthood, *NeuroImage*, 2010, vol. 51, no. 3, p. 943. doi 10.1016/j.neuroimage.2010.03.004
10. Ge, Y., Grossman, R.I., Babb, J.S., et al., Age-related total gray matter and white matter changes in normal adult brain. Part I: volumetric MR imaging analysis, *Am. J. Neuroradiol.*, 2002, vol. 23, no. 8, p. 1327.
11. Schulze, E.T., Geary, E.K., Susmaras, T.M., et al., Anatomical correlates of age-related working memory declines, *J. Aging Res.*, 2011, vol. 2011, p. 606871. doi 10.4061/2011/606871
12. Saveliev, S.V., *Atlas mozga cheloveka (Atlas of Human Brain)*, Moscow: Vedi, 2005.
13. Oknina, L.B., Kuznetsova, O.A., Belostotskyi, A.V., et al., Amplitude-time characteristics of the long-latency components (N1, N2, andP300) of acoustic evoked potential in healthy subjects, *Hum. Physiol.*, 2011, vol. 37, no. 1, p. 49.
14. Gamezo, M.V., Petrova, E.A., and Orlova, L.M., *Vozrastnaya i pedagogicheskaya psikhologiya (Age and Pedagogical Psychology)*, Moscow: Pedagog. O-vo. Ross., 2003.
15. Hjelle, L. and Ziegler, D., *Teorii lichnosti (Personality Theories)*, St. Petersburg: Piter Kom, 1998.
16. Bizyuk, A.P., *Kompendium metodov neiropsikhologicheskogo issledovaniya (A Compendium of Neuropsychological Research Methods)*, St. Petersburg: Rech', 2005.
17. Delis, D.C., Kaplan, E., and Kramer, J.H., *Delis-Kaplan Executive Function System (D-KEFS) Examiner's Manual*, San Antonio, Tex.: The Psychological Corporation, 2001.
18. Kaplan, E., Fein, D., Morris, R., and Delis, D.C., *The WAISR as a Neuropsychological Instrument*, New York: The Psychological Corporation, 1991.
19. Kuptsova, S.V., Ivanova, M.V., Petrushevsky, A.G., et al., FMRI Study of Visual Task Switching in Healthy Individuals, *Zh. Vyssh. Nervn. Deyat. im. I. P. Pavlova*, 2015, vol. 65, no. 1, p. 61.
20. Kuptsova, S.V., Ivanova, M.V., Petrushevsky, A.G., et al., Sex-related differences in task switching: An fMRI study, *Hum. Physiol.*, 2015, vol. 41, no. 6, p. 611.
21. Eickhoff, S.B., Stephan, K.E., Mohlberg, H., et al., A new SPM toolbox for combining probabilistic cytoarchitectonic maps and functional imaging data, *NeuroImage*, 2005, vol. 25, p. 1325.
22. Talairach, J. and Tournoux, P., *Co-Planar Stereotaxic Atlas of the Human Brain*, Thieme: Stuttgart, 1998.
23. Ashburner, J., VBM Tutorial, 2010. http://www.fil.ion.ucl.ac.uk/~john/misc/VBMclass10.pdf.
24. Raz, N., Gunning-Dixon, F.M., Head, D., et al., Neuroanatomical correlates of cognitive aging: evidence from structural magnetic resonance imaging, *Neuropsychology*, 1998, vol. 12, no. 1, p. 95.
25. Gold, B.T., Kim, C., Johnson, N.F., et al., Lifelong bilingualism maintains neural efficiency for cognitive control in aging, *J. Neurosci.*, 2013, vol. 33, no. 2, p. 387.
26. Witt, S.T. and Stevens, M.C., Overcoming residual interference in mental set switching: neural correlates and developmental trajectory, *NeuroImage*, 2012, vol. 62, no. 3, p. 2055.
27. Sherwin, B.B., Estrogen and cognitive functioning in women, *Endocr. Rev.*, 2003, vol. 24, no. 2, p. 133.
28. *Kratkaya meditsinskaya entsiklopediya (A Brief Medical Encyclopedia)*, Pokrovskii, V.I., Ed., Moscow: Med. Entsikl., 2001.
29. *Fiziologiya cheloveka* (Human Physiology), Schmidt, R. and Thews, G., Eds., Moscow: Mir, 1996.
30. Guediche, S., Holt, L.L., Laurent, P., et al., Evidence for cerebellar contributions to adaptive plasticity in speech perception, *Cereb. Cortex*, 2015, vol. 25, no. 7, p. 1867. doi 10.1093/cercor/bht428

Translated by E. Suleimanova