

Diffusional Characteristics of Brain Matter after Stroke

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We analyzed characteristics of diffusion and its kurtosis obtained using diffusion-kurtosis MRI in the hemisphere contralateral to the one affected by acute cerebrovascular accident. Diffusion characteristics in the white and gray matter were compared using analysis of covariance (ANCOVA) in healthy subjects and stroke patients with consideration for the age and sex factors. Significant differences between the groups were revealed for apparent diffusion coefficient and mean kurtosis in the white matter. Age dependence was studied using regression analysis and, according to the results of ANCOVA, this factor was found to be significant for apparent diffusion coefficient and diffusion kurtosis in the white matter. Metrics are proposed that can be used to determine the risk of stroke.

Key Words: *diffusion kurtosis magnetic resonance imaging; stroke*

Diffusion MRI techniques (diffusion tensor and diffusion kurtosis MRI) are the gold standard for assessing the integrity of the pathways and brain matter. The development of methods of diffusion MRI for determining the risk of stroke is extremely important. Diffusion tensor MRI allows obtaining maps of the apparent diffusion coefficient and diffusion fractional anisotropy. Additionally, diffusion kurtosis MRI (DK-MRI) provides information about diffusion kurtosis, *i.e.* deviation of the diffusion distribution from the Gaussian shape. At the same time, kurtosis in this context should be considered as a measure of the degree of brain tissue structuring [4].

According to the DK-MRI results, diffusion kurtosis has a good chance to be more sensitive to early pathological changes in brain tissue in comparison with other diffusion parameters, in particular for predicting motor disorders after stroke [1,5,6]. It was noted that diffusion kurtosis characteristics depend on age, therefore, some factors should be taken into account when studying changes in these parameters during the pathological processes [2,3].

The aim of this work was to analyze and identify the significance of various characteristics of diffusion, including diffusion kurtosis obtained using DK MRI, considering age differences and changes in diffusion characteristics in the hemisphere contralateral to the one affected by the cerebrovascular accident. The hypothesis under consideration is that the condition of the intact contralateral hemisphere reflects a priori risk of stroke, therefore, its diffusion characteristics can be seen as an indicator of stroke probability. Thus, the results will be potentially useful in determining stroke probability and in predicting recurrent cerebrovascular accidents.

MATERIALS AND METHODS

For this study, a control (healthy volunteers) and an experimental (after stroke in one of the hemispheres) groups were formed. The control group included 11 healthy volunteers without neurological complaints and morphological changes in the brain according to MRI data. The experimental group included 24 stroke patients who had no other significant brain changes according to MRI data. The age of participants in both groups varied from 40 to 70 years. All subjects signed informed consent form approved by the Ethics Committee of the International Tomography Center, Siberian Division of the Russian Academy of Sciences.

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According to the medical history and MR-semiotics, the stroke patients were divided into groups with conditionally acute (<3 weeks; AS) and chronic (>3 weeks; CS) strokes. The groups were also divided into age groups (Fig. 1)

MRI was performed on a Philips Ingenia 3T scanner (Philips Healthcare). The scanning protocol included 3D T1 MP RAGE (Magnetization-Prepared Rapid Acquisition Gradient Echo) and DKI (Diffusional Kurtosis Imaging) sequences. DKI is a variant of diffusion MRI implemented with a spatial resolution of one-millimeter order; nevertheless, it provides an idea of the microstructural properties of human brain tissue *in vivo*. This is due to the fact that the image contrast provided by diffusion MRI is sensitive to micron-scale distances that are of our interest and are investigated by assessing the random movements of water over a short period of time between two gradient pulses. DKI images were acquired with 3 b-factor values (0, 1500, and 2500 sec/mm²) in 32 directions of the diffusion gradient using enhanced mode that provided diffusion coding directions located mainly along the edges of the cube. Such distribution ensured optimal sharing of power of the gradient amplifiers, resulting in a better signal-to-noise ratio compared to the uniform spherical distribution. The disadvantage of this mode was the smaller number of slices and corresponding decrease in the studied volume. Other DKI sequence parameters: TR/TE=10,724/72 msec, voxel size=2.33×2.33×2.33 mm, number of slices=25, acquisition matrix=96×96, acquisition time=14 min. DKI data were processed using DKE software (Diffusional Kurtosis Estimator, Center for Biomedical Imaging, Medical University of South Carolina, USA) obtaining maps of mean, axial, and radial coefficients of diffusion and kurtosis and fractional anisotropy. The diffusion characteristics of the white and gray matter of the brain in all groups were compared using analysis of variance, and the effects of several factors (age, sex, and comparison groups) on diffusion characteristics were studied using analysis of covariance (ANCOVA).

To separate the white and gray matter, cerebrospinal fluid in the entire volume of the hemispheres, 3D

T1-MP RAGE images were obtained with the following scanning parameters: TR/TE=7.8/3.8 msec, voxel size=0.87×0.87×1 mm, number of slices=181, acquisition matrix=252×227, flip angle=8°, scan time=3 min. Separation of images by tissue types (segmentation) was performed using the SPM12 software (Statistical Parametric Mapping Wellcome Department of Imaging Neuroscience, University College London, UK). Further, maps of the white and gray matter were co-registered to the diffusion maps, and the stroke damaged hemisphere was excluded from the maps of the white and gray matter.

Statistical analysis of the results was carried out by averaging the diffusion characteristics using the R programming language in the RStudio environment (<https://www.rstudio.com/>). The null hypothesis was rejected at a significance level of $p < 0.05$. Statistical analysis included comparison of mean values and standard deviations of diffusion characteristics (axial, mean, radial coefficients of diffusion; fractional anisotropy; axial, mean, radial kurtosis; kurtosis anisotropy) for the gray and white matter and for CSF in the groups using analysis of variance with Tukey's correction for multiple comparisons.

To determine the morphological characteristics and verify the stroke area, scanning in the T2W and FLAIR modes was performed according to the standard neuroprotocol. The MRI data were analyzed by qualified radiologists of the MRI Diagnostic Department, Siberian Division of the Russian Academy of Sciences, with 25 years' experience in neuroradiology.

RESULTS

Comparison of diffusion characteristics of healthy subjects, patients with AS and CS for the white and gray matter was carried out using analysis of variance (Table 1). As diffusion characteristics of gray matter did not reveal differences between the groups, only the white matter was considered in further analysis. The white matter has ordered structure consisting of bundles of axons covered with myelin sheaths; therefore, it is of greater interest than gray matter

TABLE 1. Results of Analysis of Variance (p) of Mean Diffusion Characteristics for the White and Gray Matter in Healthy Subjects and Stroke Patients

Compared groups	White matter				Gray matter	
	mean diffusion coefficient	mean kurtosis	fractional anisotropy	mean diffusion coefficient	mean kurtosis	fractional anisotropy
AS—healthy	0.005	0.012	0.32	0.710	0.055	0.823
CS—healthy	0.012	0.095	0.109	0.541	0.429	0.248
CS-AS	0.693	0.48	0.867	0.975	0.368	0.577

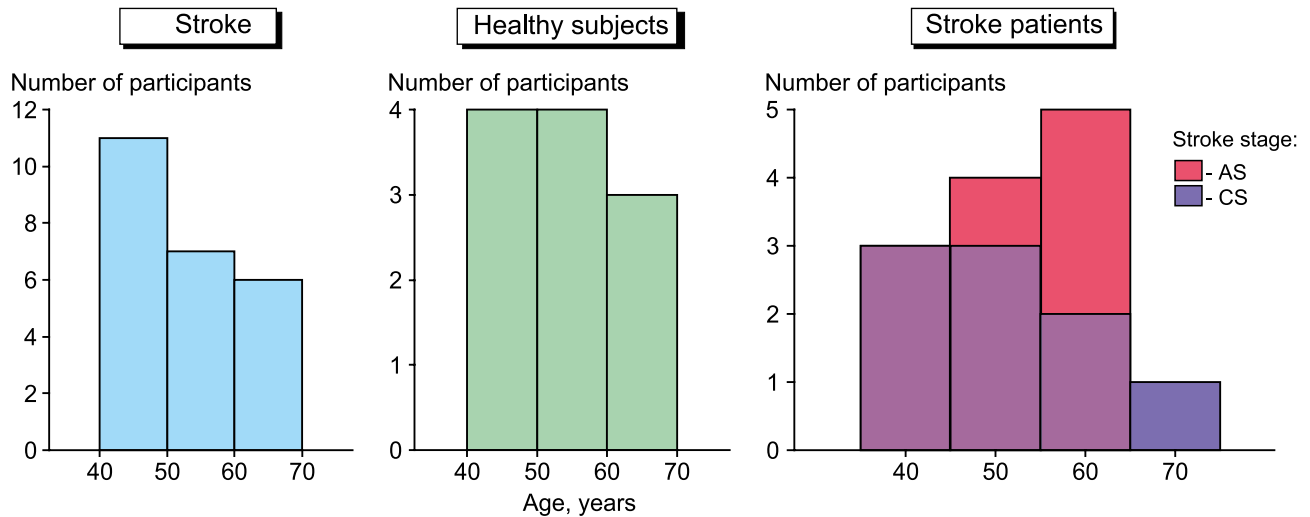


Fig. 1. Age distribution of subjects.

for the study of pathology associated with a decay of the structure of the brain matter, loss of axons, and demyelination.

The mean diffusion coefficient for the white matter in the AS and CS groups as well as the mean diffusion kurtosis for the white matter in AS groups significantly differed from the corresponding parameters in the control (healthy subjects). The mean diffusion kurtosis in CS groups did not differ from that in the control, although no significant differences were found between the characteristics in the CS and AS groups.

Thus, according to the results of analysis of variance, the difference in diffusion characteristics in the AS and CS groups was insignificant. Therefore, we combined these two groups into one. In connection with that, Mann—Whitney test was additionally applied for the control group and group of stroke pa-

tients (without division into AS and CS) that showed significant differences in the mean diffusion coefficient and mean kurtosis. The data for the three groups are presented on a graph displaying axial and radial diffusion coefficients (Fig. 2). Significant difference for the diffusion kurtosis is not as clear and obvious as for the diffusion coefficient, which is characterized by a “border area” between the groups of healthy subjects and stroke patients. After the groups were combined, the test confirmed the presence of significant differences between the healthy-stroke groups in the mean diffusion coefficient ($p=0.0009$) and mean kurtosis of the white matter ($p=0.007$).

To analyze the dependence of diffusion characteristics on age, regression analysis was applied, and graphs of the dependence for the diffusion characteristics of the white matter in the groups of healthy sub-

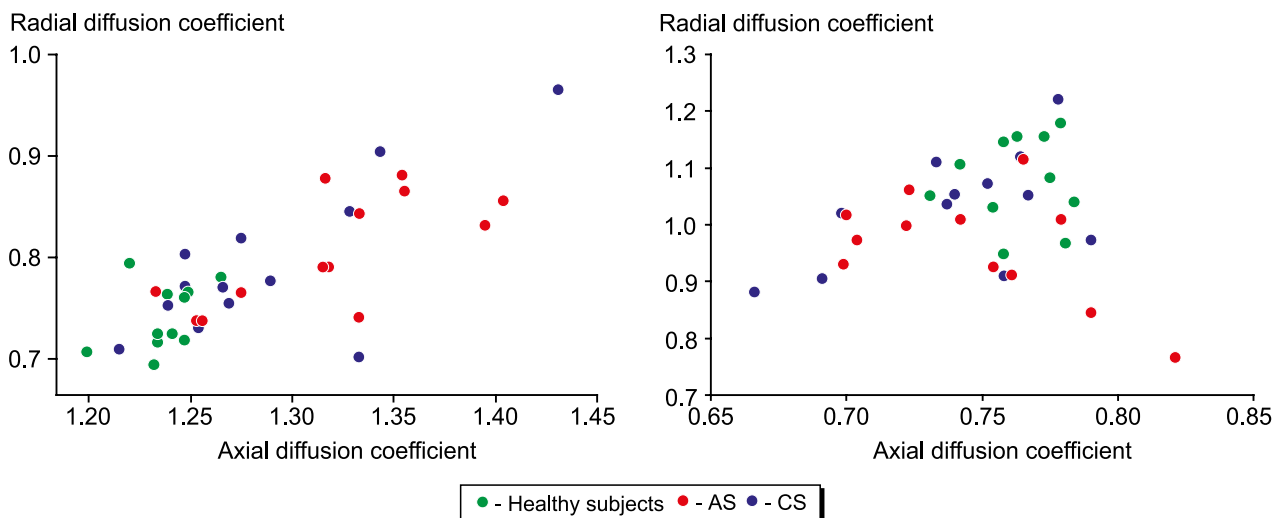


Fig. 2. Diffusion characteristics of the white matter in stroke patients and healthy subjects.

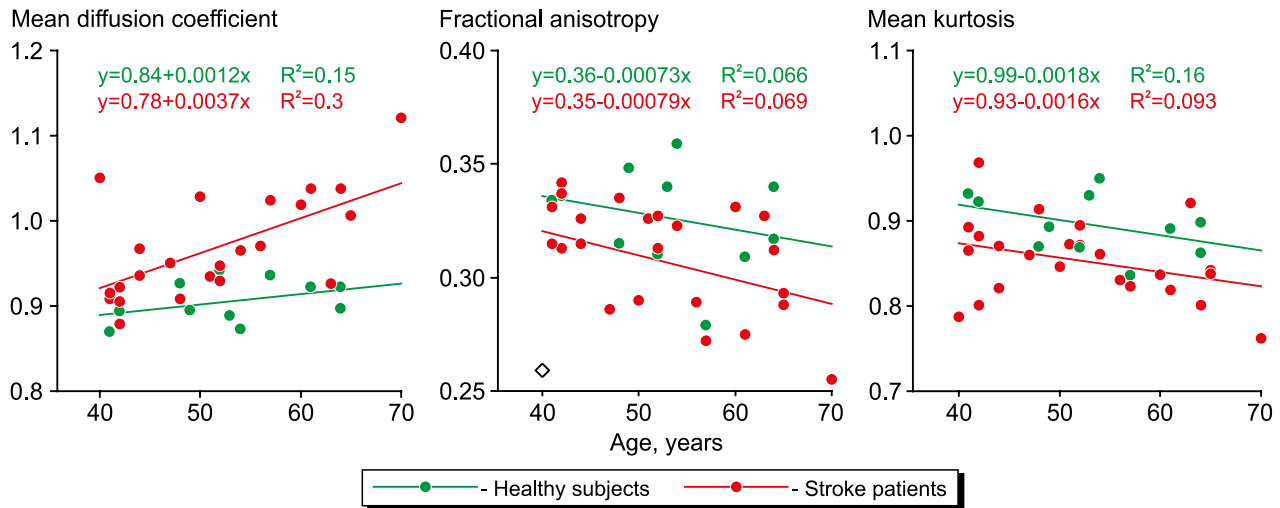


Fig. 3. Regression analysis of diffusion characteristics of the white matter in healthy subjects and stroke patients.

jects and stroke patients were plotted (Fig. 3). Then, to determine the degree of influence of several factors (sex, age and group), multivariate analysis ANCOVA (type II) was performed for healthy subjects and stroke patients. The dependence was found significant only for the mean diffusion coefficient ($F=25.78, p=0.0007$) and fractional anisotropy ($F=7.731, p=0.02$) in the gray matter in healthy subjects and for the mean diffusion coefficient in the white matter ($F=11.42, p=0.002$) and gray matter ($F=10.96, p=0.002$) in the stroke group (F is an indicator of significance of factor interaction). Therefore, despite visual dependence of the diffusion characteristics on age, it does not have significance, which can be related to sample size, or nonlinear relationship of the diffusion characteristics with age, or the absence of such a relationship.

We also checked the normality of distribution of the residuals using the Shapiro—Wilk test. Deviation from normality was observed only for kurtosis in the gray matter in the stroke group ($p=0.02$). In addition, the homoscedasticity was tested for the homogeneity of variances for the two groups using the Leuven test. For none of the characteristics, the results were sig-

nificant ($p>0.05$), so we can assume homogeneity of residual variances for all groups.

The uniformity of the regression slopes for the groups of healthy subjects and stroke patients was tested according to the presence/absence of significance of the interaction between the factors of group and age in ANCOVA. The interaction turned out to be significant for the mean diffusion coefficient ($F=4.216, p=0.047$) and fractional anisotropy ($F=8.323, p=0.007$) in gray matter. To determine the degree of influence on the diffusion characteristics of the white matter for sex, age and group factors, multivariate analysis ANCOVA (type II) was applied to the model “Characteristic=Sex+Age+Group” and the model “Characteristic=Age+Group” (Table 2). Comparison of the diffusion characteristics of the brain matter in stroke patients and healthy subjects revealed the significance of group and age factors for the mean diffusion coefficient and kurtosis in the white matter. The sex factor and time after stroke were found to be insignificant for all white matter diffusion characteristics.

The quantitative characteristics of the diffusion of the white matter revealed in this study are con-

TABLE 2. Multifactor Effects on the Diffusion Characteristics of the White Matter

Model	Factor	Mean diffusion coefficient	Mean kurtosis	Fractional anisotropy
Sex+Age+Group	Sex	F=0.35	F=0.007	F=0.074
	Age	F=12.1**	F=4.23*	F=2.5
	Group	F=12.9**	F=8.01*	F=3.55
Age+Group	Age	F=12.97**	F=4.36*	F=2.72
	Group	F=18.5**	F=9.83*	F=5.04*

Note. F is an indicator of significance of factor interaction. Confidence levels: ** $p<0.001$, * $p<0.05$.

sistent with other studies of changes in the diffusion characteristics of the brain matter in stroke patients. The increase of the mean diffusion coefficient and the decrease of the mean kurtosis and fractional anisotropy can indicate pre- and para-stroke processes of axon loss and demyelination [2,3]. Thus, the results suggest that, considering the influence of age, the mean diffusion coefficient and kurtosis of the white matter can be significant metrics that allow predicting the risk of stroke occurrence and recurrence.

It remains unclear whether the revealed diffusion characteristics in the visually intact hemisphere can predict a stroke development or the reactive-compensatory changes accompanying stroke in subacute-chronic recovery periods. To answer this question, it is necessary to study the revealed quantitative indicators of diffusion in dynamics in the late recovery period, as well as to study patients at risk of stroke on the basis of clinical, laboratory and neuroimaging data.

Taking into account the consequences of the COVID-19 pandemic, with its direct and systemic damage to the nervous system and the development of post-COVID neurological syndrome ultimately manifested in a multifactorial increase of the risk of cerebrovascular accidents (including ischemic), the relevance of similar studies will grow in the future. Our preliminary study performed on a small sample in each of the studied groups requires results verification and further comprehensive approach to validate quantitative markers of altered diffusion of the brain matter after stroke and recommend them for clinical use in neuroradiology.

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