The diffusion-tensor MRI data analysis for cerebral microangiopathy influence detection on the integrity of the brain white matter in Alzheimer's disease patients

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Abstract. The analysis of diffusion-tensor magnetic resonance tomography data is carried out to assess the contribution of cerebrovascular disease to the violation of the microstructural integrity of the brain white matter in Alzheimer's patients. The values of DTI (Diffusion Tensor Imaging) indicators are studied for 19 regions of the brain. The issues of data pre-processing, their analysis by statistical and neural network methods, including visualization using Kohonen self-organizing maps, are considered. It provided a number of anatomical structures of the brain that have the greatest specificity in Alzheimer's disease combined with cerebral microangiopathy in contrast to isolated Alzheimer's disease. This approach provides important diagnostic information about the involvement of various brain areas in the pathological process.

1. Introduction
Increasing the lifespan of the world's population has led to the growth of the number of patients with impaired higher brain functions of various etiologies. Cerebrovascular (microangiopathy), as well as neurodegenerative (Alzheimer's) etiology are the brain lesions most frequently detected among the reasons that lead to cognitive impairment in patients of middle and old age. Quite often, such patients have a joint course of the diseases under consideration [1,2]. Currently, it is believed that various cardiovascular diseases not only lead to secondary brain damage but also increase the possibility of the emergence and acceleration of the neurodegeneration progression. In a number of pathological and neuroimaging studies [3,4,5] it was shown that these pathological processes lead to the brain parenchyma damage, in particular, the pathways that make up its white matter. Both vascular and neurodegenerative pathological processes cause pronounced and irreversible damage to brain structures, which makes the process of their diagnosis, using the advanced neuroimaging techniques, extremely important and significant.

Currently, magnetic resonance imaging (MRI) is widely used to visualize various anatomical structures. A large number of proceedings can be noted which are related to this technique and aim at studying the issues of MRI data arrays automated analysis, including those, which were obtained during the brain examination, and capable of identifying morphological signs typical of Alzheimer's...
disease [6,7,8,9]. One of the modern and promising MR-techniques is diffusion-tensor magnetic resonance imaging (DTI), which allows visualizing the diffusion of water molecules (Figure 1) and non-invasively assess the microstructural integrity of tissues (in particular, white matter of the brain) [10,11,12]. Its physical principle is based on the fact that the movement of water molecules in the white matter of the brain occurs much easier along the nerve fibers, since the membranes of the axons and their myelin sheath are poorly permeable.

Figure 1. View under microscope: the structure of the white matter pathways according to the results of diffusion-tensor magnetic resonance imaging (axial projection on the left, coronary on the right).

An important task for the construction of advanced automated decision support and diagnostic tools is a comprehensive analysis of the DTI data to identify areas of the brain that are most susceptible to the pathological changes in the white matter structure in the case of vascular etiology with dementia of the Alzheimer type.

2. Input data and postprocessing
Baseline data is the outcome of a survey of 20 patients from 45 to 85 years old. The brain damage of mixed etiology (cerebral microangiopathy and Alzheimer's disease) was diagnosed in 9 patients aged 76.3 ± 5.3 years (according to MRI) and in 11 individuals aged 66.3 ± 10.2 years (estimated MRI results) an isolated brain matter lesion associated with exposure to a neurodegenerative process (Alzheimer's disease) was revealed. The survey was conducted on a magnetic resonance tomograph "Siemens Magnetom Skyra" with a magnetic induction of 3T. The MR protocol has included diffusion-tensor visualization of DTI (Diffusion Tensor Imaging) in addition to the standard pulse sequences used to evaluate brain architectonics.

Figure 2. Co-registered colored maps of fractional anisotropy and T1-weighted images.
Four parameters were measured using the Olea Medical Sphere 3.0 software for post processing the raw data in 19 brain regions (Table 1). These parameters are: FA (Fractional Anisotropy), MD (Diffusion Media), AxD and RxD (Axial and Radial Diffusion). Areas of interest were selected manually in accordance with the human brain atlas from Kenichi Oishi et al [13]. Jointly registered T1-weighted images and color maps of fractional anisotropy were adapted from this atlas (Figure 2). T1-weighted images give an idea of the anatomical structure of the brain and color maps of fractional anisotropy allow to assess the localization and direction of the brain pathways.

The first 16 structures are represented both in the right and in the left hemispheres of the brain, therefore, 8 measured parameters (4 for the left, 4 for the right) correspond to them. The total number of measured values for each patient is 140.

### Table 1. List of brain areas list under study.

| 1 | Radiatio Thalamica Anterior          | 11 | Fornix leg                      |
|---|--------------------------------------|----|--------------------------------|
| 2 | Radiatio Thalamica Centralis         | 12 | Anterior thigh of the internal capsule |
| 3 | Radiatio Thalamica Posterior         | 13 | Rear thigh of the internal capsule |
| 4 | Fasciculus Longitudinalis Superior   | 14 | Parahippocampal gyrus           |
| 5 | Fasciculus Longitudinalis Inferior   | 15 | Cuneus                          |
| 6 | Superior Fronto-Occipital Fasciculus | 16 | Hippocampus                     |
| 7 | Inferior Fronto-Occipital Fasciculus | 17 | Corpus callosum knee            |
| 8 | Fasciculus Uncinatus                 | 18 | Corpus callosum body            |
| 9 | Gyrus Cinguli (front)                | 19 | Corpus callosum cushion         |
|10 | Gyrus Cinguli (back)                 |    |                                |

3. **Data Analysis and detection of brain regions most susceptible to pathological changes**

The process is based on checking the distribution normality of the obtained values, searching for the main characteristics of the sample, such as mean, standard deviation and etc., the null hypothesis test and the significance level calculation [14]. The disadvantage of this approach is determined by the consideration of each indicator separately and regardless of the others.

A set of indicators could be used in the multiple linear regression models, where the dependent variables values is calculated by substituting the values of the independent variables in the regression equation, taking into account the pre-calculated regression parameters [14]. This approach allows the construction of the simplest classifiers but is limited by the linearity of the reproducible dependencies.

Neural network (NN) methods of data analysis are applicable if it is necessary to display complex dependencies taking into account nonlinearities. Especially it is suitable if there is no prior information about the sample structure and the distribution type of the analyzed indicator [15,16].

All three of the above approaches were used to analyze the data and identify the most susceptible to pathological changes in anatomical structures of the brain. Additionally, Kohonen Self-Organizing Maps (SOM) [17] were used to visualize the values of the multidimensional DTI feature space for each of the studied areas on a two-dimensional map.

A linear normalization of the initial data was carried out by bringing the value sets of each measured parameter to a single interval for all brain areas. The following values were taken to indicate the type of the dominant pathology: the presence of isolated Alzheimer's disease (AD) - 0; cerebral microangiopathy together with Alzheimer's disease (AD + CMA) - 1.

The results are presented in table 2.

The “P-value” column corresponds to the statistical analysis method, where the null hypothesis about the coincidence of distributions for DTI indicators with regard to pathology (AD or AD + CMA) was tested. Only those anatomical structures were identified, where the significance level was P <0.05 simultaneously for all indicators (FA, MD, AxD, RxD).

The column "R2" defines the multiple coefficient of determination or the quality of the regression model obtained. The proximity to 1 means a high degree of consistency between the original data and the regression model. The value of $R^2 \geq 0.8$ was taken as a condition for the model adoption. This was satisfied by 5 areas: the Radiatio Thalamica Centralis, the Fasciculus Longitudinalis Superior, the
Fasciculus Longitudinalis Inferior, the Gyrus Cinguli (back) and the Corpus Callosum knee. R2 values were in the range (0.5; 0.8) for such areas as: Radiatio Thalamica Anterior; Radiatio Thalamica Posterior; Inferior Fronto-Occipital Fasciculus; Parahippocampal gyrus; Cuneus; Hippocampus; Corpus Callosum cushion. The value of R2 is less than 0.5 for the remaining areas.

Table 2. The results of applying three different data analysis approaches.

| Brain area                              | P-value | R²     | NN    |
|-----------------------------------------|---------|--------|-------|
| 1 Radiatio Thalamica Anterior           | -       | 0.74   | 8-3-2 |
| 2 Radiatio Thalamica Centralis          | < 0.05  | 0.83   | 8-2-2 |
| 3 Radiatio Thalamica Posterior          | < 0.05  | 0.71   | 8-4-2 |
| 4 Fasciculus Longitudinalis Superior    | < 0.05  | 0.93   | 8-2-2 |
| 5 Fasciculus Longitudinalis Inferior    | < 0.05  | 0.83   | 8-4-2 |
| 6 Superior Fronto-Occipital Fasciculus  | -       | 0.57   | 8-6-2 |
| 7 Inferior Fronto-Occipital Fasciculus  | -       | 0.79   | 8-4-2 |
| 8 Fasciculus Uncinatus                  | -       | -      | 8-6-2 |
| 9 Gyrus Cinguli (front)                 | -       | -      | -     |
| 10 Gyrus Cinguli (back)                 | -       | 0.87   | 8-4-2 |
| 11 Fornix leg                           | -       | -      | -     |
| 12 Anterior thigh of the internal capsule| -       | -      | -     |
| 13 Rear thigh of the internal capsule   | -       | -      | -     |
| 14 Parahippocampal gyrus                | -       | 0.70   | -     |
| 15 Cuneus                               | -       | 0.71   | -     |
| 16 Hippocampus                          | -       | 0.71   | -     |
| 17 Corpus callosum knee                 | < 0.05  | 0.93   | 4-2-2 |
| 18 Corpus callosum body                 | -       | -      | -     |
| 19 Corpus callosum cushion              | -       | 0.62   | 4-2-2 |

In turn, the “NN” column characterizes the size of the multilayer perceptron neural network for which the learning process was completed successfully. Vector of 8 measured parameters was fed to the input of the network for the brain areas from 1 to 16, where 4 parameters were marched for each hemisphere (FA, MD, AxD, RxD). For areas 17-19, the input vector contained 4 features. The output of the network was a vector of two numbers (0.1) or (1.0), encoding one of two classes. The neural network included 1 hidden layer and neurons with a sigmoid activation function. The initial number of neurons in the hidden layer was chosen equal to 4. The number of neurons was decreased and the process of adjusting the weights was repeated while the training was successful. Otherwise, the number of neurons was increased. However, more than 8 neurons in the hidden layer were not considered. That was associated with a small number of examples of the training sample. Network training was carried out by the error backpropagation algorithm [15,16]. The training process was stopped if the number of iterations exceeded the value of 10,000, or the classification error was less than 0.1 for each example of the training set. A small number of examples determined the additional use of white noise with a variance of 0.01 for those brain areas where the training process was completed successfully.

The table shows that all three methods have identified such brain areas as: the Radiatio Thalamica Centralis, the Fasciculus Longitudinalis Superior, the Fasciculus Longitudinalis Inferior, the Corpus callosum knee. Thus, it can be concluded that these areas are typical and most susceptible to pathological changes in the case of vascular etiology for persons with Alzheimer's type dementia. However, it is worth noting a number of areas that were not identified by the first statistical method due to the fact that one of the DTI indicators did not meet the condition on the significance level P <0.05. These include the Radiatio Thalamica Anterior (P MD = 0.11) and the Gyrus Cinguli (back) (P RxD = 0.07). An interesting result was obtained for the Inferior Fronto-Occipital Fasciculus, for which the significance level satisfied the condition P < 0.05 only for the MD index, but for the multiple linear regression method the R2 value was very close to the model acceptance boundary, and the neural network classifier was successfully constructed.
4. Visualization of the analyzed indicators space

Visualization and presentation of source data in an accessible form can simplify its analysis and improve the understanding of the phenomenon being studied. The use of the Kohonen self-organizing maps (SOM) [16,17] has allowed to map the multidimensional space DTI values on the two-dimensional SOM for each of the studied anatomical brain structures.

The Kohonen network consists of an input and one competing cluster layer, which neurons are ordered into some structure. Two-dimensional grids (maps) are commonly used. This method allows entering the measure of interaction between the cluster layer neurons not in the input attribute space, but on the used map. The distance between the neurons on the map determines the magnitude of this interaction. During training, it is necessary to modify not only the winning neuron, but also its neighbors to a lesser extent. Thus, the similar vectors in the original space should be near on the resulting map. This allows distinguishing regions (clusters) and their mutual arrangement.

The coloring of a trained SOM allows multidimensional space visualization on a two-dimensional map. The coloring was carried out in accordance with known classes in the process of identifying areas of the brain most susceptible to pathological changes in the structure of white matter. First class corresponded to isolated Alzheimer's disease, the second - to the mixed etiology (cerebral microangiopathy and Alzheimer's disease).

Figure 3 shows the results of learning and coloring of SOM networks, both for the entire set of measured MRI indicators for all brain areas (A), and for individual anatomical structures using the most typical cases: (B) - classes are separable, (C) - not separable. The white color of the neuron indicates that it was not activated by any vector of this class samples. Grayscale characterize the number of samples belonging to the corresponding neuron.

![Figure 3. Examples for Kohonen maps colorings: (A) - The entire set of features from all areas; (B) - Radiatio Thalamica Centralis; (C) - Anterior thigh of the internal capsule.](image)

It should be noted that the training sample vector had a dimension of 140 for the entire set of DTI signs of all areas of the brain. The dimension was 8 (left and right hemisphere) for individual anatomical structures from 1 to 16 and it was 4 for areas 17-19. From Figure 3 (A, B) it can be concluded that the classes are separable, i.e. they are localized in different parts of the SOM card and do not overlap. In turn, in Figure 3 (C), activated neurons randomly fill the map. Some of them are activated upon presentation of examples from different classes, which makes it impossible to build a dividing surface.

The results of constructing SOM maps for individual anatomical brain structures have identified the following areas: Radiatio Thalamica Anterior, Radiatio Thalamica Centralis, Radiatio Thalamica Posterior, Fasciculus Longitudinalis Superior, Gyrus Cinguli (back), Corpus callosum knee, Corpus callosum cushion. In some cases, the regions had a rather complex form and intersections with single neurons. These include: the Fasciculus Longitudinalis Inferior, the Superior Fronto-Occipital Fasciculus, the Inferior Fronto-Occipital Fasciculus, and the Fasciculus Uncinatus. It was impossible to build a dividing surface for the remaining areas.
5. Dynamics in DTI indicators changes
Analysis of the dynamics in the DTI indicators changes revealed a general trend towards a decrease in FA and AxD and an increase in MD and RxD (Figure 4). This indicates a more pronounced violation of the microstructural integrity of the white matter with a combined lesion of the brain parenchyma (AD + CMA) in comparison with its isolated AD lesion.

![Figure 4](image)

**Figure 4.** The dynamics in the averaged values changes of the FA, MD, AxD, RxD indicators, depending on the dominant pathology. For all 19 areas is on the left, for most affected by pathological changes is on the right.

6. Conclusion
The analysis of diffusion-tensor magnetic resonance imaging data was carried out to assess the cerebrovascular disease contribution to the brain white matter microstructural integrity violation for Alzheimer's patients. The DTI values of FA, MD, AxD, RxD indicators were measured in 19 areas of the brain using the software Olea Medical Sphere 3.0 for postprocessing. A statistical analysis of the obtained values and the construction of the multiple linear regression equations were carried out. Also, it was used a neural network approach for classifiers construction and determining the presence of vascular pathology. Additionally, a SOM network was used for values visualization of the multidimensional space of DTI indicators for each of the studied areas. It was determined a number of anatomical brain structures, which are the most susceptible to pathological changes in the case of vascular etiology in individuals with dementia of the Alzheimer type. Analysis of the dynamics in the DTI indicators changes revealed a general trend towards a decrease in FA and AxD indices and an increase in MD and RxD in individuals with a combined lesion of the brain parenchyma.

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