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Evaluation of white matter structure changes, as assessed in tractography, and cognitive dysfunctions in patients with early onset schizophrenia and their first-degree relatives

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Summary

Aim. The aim of the project was to assess the differences in the white matter (WM) fiber structure between patients with early onset schizophrenia (EOS), their first-degree relatives and controls using Fractional Anisotropy (FA), and an independent evaluation of the severity of working memory disturbances in the study groups.

Methods. The study included 20 patients diagnosed with paranoid EOS (diagnosed before the age of 18), a group of 20 parents of patients, matched for gender, and 18 healthy controls. All study participants were examined with Diffusion Tensor Imaging (DTI, 1.5 T) and selected neuropsychological tests to assess working memory, immediate memory and attention (Trail Making Test parts A and B: TMT-A and TMT-B, Digit Span Forward and Backward).

Results. No significant differences in FA parameters were found between the analyzed groups. The group of patients took significantly longer to perform the TMT-A and TMT-B than the control group, and achieved worse outcomes in Digit Span tests. The relatives of the patients achieved lower scores in Digit Span tests and needed more time to perform TMT-B compared to controls. There were no significant differences between all groups in terms of the number of errors when performing TMT-A and TMT-B.

Conclusions. The results of our study indicate a reduction in the capacity of immediate memory, working memory, cognitive plasticity and divided attention, both in EOS patients

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and their first-degree relatives compared to healthy subjects. The reported neuropsychological deficits were not reflected in WM integrity, as assessed with FA.

Key words: early onset schizophrenia, white matter, tractography, cognitive functions

Introduction

The pathogenesis of schizophrenia is still not fully understood, however, there is good evidence in favor of the neurodevelopmental hypothesis. It proposes that schizophrenia stems from structural deficits and dysfunctional activity of the brain neuronal circuits, caused by abnormalities arising in the early stages of CNS (central nervous system) development.

The symptoms of the illness occurring later in life are considered to be the clinical manifestation of structural irregularities and their functional abnormalities in specific neural circuits [1]. Recently, the possible involvement of white matter (WM) in the pathogenesis of schizophrenia has been awarded greater emphasis. Abnormal myelination and/or neuronal migration processes may contribute to the formation of a dysfunctional neuronal network and underlie the core schizophrenia symptoms [2].

Evidence for the presence of abnormal neuronal connections in schizophrenia has been provided by studies using relatively new neuroimaging techniques, diffusion tensor imaging resonance (DTI) and 3D-DTI (tractography), which provide a non-invasive insight into the anatomy of the WM pathways in vivo [3]. Several methods of data analysis are used during DTI examination, the most frequent being voxel-based analysis (VBA), which is automated and allows for evaluation of the tissue diffusion level throughout the brain at a single stage. A second technique is region of interest (ROI) analysis, which allows for the precise evaluation of the degree of diffusion in hypothetically designated locations, and the reconstruction of the neuronal pathways (tractography), however, this approach is a little repetitive and time-consuming [3].

The most reproducible results of DTI studies in schizophrenia are related to the reduction of Fractional Anisotropy (FA) in the prefrontal areas, temporal lobes and the fibers connecting these regions (including the arcuate and uncinate fasciculus and cingulum) [4]. In contrast, the results relating to abnormalities observed within the corpus callosum, the internal capsule and the cerebellum are ambiguous [4].

A correlation of clinical parameters following fractional anisotropy confirms the existence of a positive relationship between anisotropy reduction in particular regions, symptom severity and treatment results [5]. It was also shown that FA reduction correlates with the severity of negative symptoms, severity of aggression and impulsivity [6, 7]. Reduced FA within the fronto-temporal connections correlates with executive function impairment, concerning the cingulate gyrus [8], disorders of declaratory-episodic memory, concerning the uncinate fasciculus [8], and poorer semantic memory tests results, associated with abnormalities of the fornix structure [9].

Most studies involving patients with a diagnosis of schizophrenia have revealed deficits in neuropsychological test outcomes. More neurocognitive dysfunctions were

observed in patients than in matched healthy controls with similar IQ (Intelligence Quotient) [10, 11]. Although some publications suggest that the neuropsychological test results remain within the normal range for 27% of patients with schizophrenia [12], Kremen et al. [10] suggest that this result may be the result of omission of comparison with the estimated premorbid IQ.

Reduction of Global IQ (d = 0.98) and Executive IQ compared to Verbal IQ is typically observed in patients with schizophrenia [13]. Characteristic neuropsychological deficits in this group include deficits of: attention (d = 0.66–1.16), verbal (d = 1.20–1.22), non-verbal (d = 0.74–1.03) and episodic memory [13, 14], working memory (d = 0.8–1.1) [14, 15], verbal fluidity (d = 0.8–1.41) [13], psychomotor speed (d = 1.57) [16] and executive functions (d = 0.88) [13].

Currently, the prevailing view is that cognitive disturbances, especially working memory changes, are the primary feature of schizophrenia and appear before the active (psychotic) phase of the illness [17]. Disturbance of executive functions and attentional processes have been observed in the children of schizophrenia patients [18] and the speed of information processing was found to be slower in their first-degree relatives [19]. Working memory impairment is morphologically linked with dysfunctions of the dorsolateral frontal cortex [20].

Due to the necessary interaction with processes of attention, short-term and long-term memory, the proper functioning of working memory probably depends on the circuits connecting the prefrontal cortex with other structures, as well as on dysfunctions resulting from development abnormalities present in the hippocampal area and its connections with the frontal cortex.

Abnormalities within WM structures are found more often among relatives of schizophrenia patients than unrelated persons [21], although the evidence base for this remains equivocal [22]. Very little is known about the functional importance of abnormalities in the WM structure in this group.

Aim

The aim of this project is to evaluate quantitative differences in WM fiber structure between schizophrenia patients, their first-degree relatives and controls, based on FA analysis, and an evaluation of working memory impairments in all examined groups. In addition, the study will determine the morphological parameters, identified in neuroimaging, and functional capabilities, assessed using neuropsychological tests, that may indicate a higher susceptibility to the development of schizophrenia.

Materials and methods

Examined groups

The study group comprised 20 patients diagnosed with paranoid schizophrenia based on DSM-IV criteria before the age of 18 (early onset schizophrenia, EOS). EOS

diagnosis was confirmed by the clinical consensus of two independent psychiatrists using the Polish version of the CIDI (Composite International Diagnostic Interview).

Patients with comorbid psychiatric disorders, a history of alcohol and/or other psychoactive substances abuse during the six months prior to the study, confirmed head trauma with loss of consciousness, seizures or other serious neurological or somatic disorders were excluded from the study. During the study, all of the patients remained in stable mental condition and were treated with second generation antipsychotics. Patients were recruited from inpatient and outpatient clinics of the Central Clinical Hospital in Lodz.

The second of the studied groups consists of the first-degree relatives (parents) of recruited patients diagnosed with EOS. To avoid further differences in neuropsychological test results, only the same sex parent of the subjects were recruited to the study (research results are inconclusive, but some studies indicate that gender has an impact on the TMT and Digit Span (subtest of the WAIS-R) test results [23]).

18 healthy controls, comparable to the group of the EOS patients in terms of age, gender, race and socioeconomic status, were also enrolled. Control individuals had no DSM-IV axis I disorders, as determined by the standardized CIDI interview, no history of psychiatric disorders among their first-degree relatives, no history of alcohol or substance abuse and no current major medical conditions. The control group consisted of volunteers, recruited among medical students and the healthy children of department employees. All subjects were Caucasian. Detailed demographics are shown in Table 1.

The study design was approved by the Bioethical Committee of the Medical University of Lodz (permission No RNN/112/10/KE). All subjects were explained the study procedures prior to signing informed consent. The participation of minor subjects was confirmed or approved by parallel (over 16 years) or replacement (< 16 years) consent.

Tractography

All MRI scans were performed in NZOZ Diagnostyka Medyczna Księży Młyn (Lodz, Poland), using a 1.5 T General Electric SIGNA HDi System (GE Medical Systems, Milwaukee, WI). Diffusion-weighed imaging data was acquired with a single-shot echo planar imaging sequence in alignment with the anterior–posterior commissure plane. The diffusion sensitizing gradients were applied along 25 nonparallel directions ($b = 1000$ s/mm^2) and two without diffusion weighing ($b = 0$). 27 contiguous axial slices were acquired with a slice thickness of 5 mm and no gap. The acquisition parameters were as follows: echo time (TE) = 103.5 ms; repetition time (TR) = 8500 ms; field of view = 30 cm; number of excitations (NEX) = 1 and matrix = 128×128.

Additionally, morphological images were acquired for anatomical determinations. T1 and T2 weighted images were obtained in the sagittal, coronal and axial planes. The acquisition parameters for T1 images were: TE = 5 ms, TR = 24 ms, NEX = 2, FOV = 26×19.5 cm, slice thickness = 1.5 cm and matrix = 256×192. T2 sequences were acquired as follows: TR = 3000 ms, TE = 96 ms, NEX = 1, FOV = 26×26 and matrix = 256×192.

The total scan time was less than 30 minutes. Head movement was minimized with foam padding and a strap across the forehead. All scans were reviewed, and scans with significant artifacts were repeated or discarded.

Functool DTI software (GE Medical Systems, Milwaukee, WI) was used for DTI data processing. After computing the FA images, several ROIs were defined. The ROIs were placed in the WM tracts using identifiable landmarks on FA images and with reference to the Mori MRI atlas of the human WM. This stage was performed by radiologists who were blinded to the diagnosis.

Each image was assessed by two experienced radiologists in terms of image quality and accuracy of ROI location. The correct placement was confirmed by display of the ROIs on the anisotropy image as well as on the colored orientation images.

Cognitive functions

Subtests of the WAIS-R (Wechsler Adult Intelligence Scale-Revised) were used for the evaluation of selected cognitive functions: Digit Span Forward and Backward, Trail Making Tests A and B (TMT-A and TMT-B). Digit Span Forward measures the range of direct memory, attention and concentration [24]. Digit Span Backward allows working memory to be assessed [25], with the examined person required to repeat numbers successively starting from three to nine and subsequently from two to eight backwards [25]. The Trail Making Test (TMT) is used to assess attention, psycho-motor speed, cognitive plasticity and the ability to switch from one category to another [25, 26]. Both versions require the ability to track sequences and psychomotor speed, moreover version B also requires divided attention [25, 26]. In the TMT-A test, the person has to draw a line connecting numbers from 1 to 25, while in the TMT-B, the line should connect numbers from 1 to 13 and the letters A to L alternatingly.

Statistical analysis

Descriptive and statistical inference methods were used in the statistical analysis of the collected data. The compliance of data distributions with a normal distribution was assessed using the Shapiro-Wilk test. Analysis of covariance (ANCOVA) was used to assess differences between the study groups due to significant difference between the two groups in terms of age, a significant correlation between age and the dependent variables evaluated in the study (FA and cognitive function assessments), and correlation between age and parameters measured using a tractograph, as described in previous studies [27, 28]. The ANCOVA model included age as a covariate; it then evaluated the differences in FA and variables measuring selected cognitive functions in the analyzed groups, controlling the impact of the age variable. For discrete variables, the frequencies of various levels of the variables in the analyzed groups were evaluated. As the assumptions for the Chi^2 test were not met, the differences between the frequencies of discrete variables were assessed using Fisher's exact test.

Results

The characteristics of the study population are shown in Table 1. The analyzed groups differed significantly in terms of age. As the first-degree relatives were significantly older than the patients with schizophrenia and the members of the control group, the analysis of differences in dependent variables among groups included age as a continuous covariate.

The ANCOVA model did not reveal any significant differences in FA between the analyzed groups. Significant differences between groups were observed for selected cognitive functions assessed in TMT-A and TMT-B as well as Digit Span Forward and Backward. The completion time of the TMT-A test performed by the schizophrenia patients was significantly longer than that by the control group. In addition, first-degree relatives and patients with schizophrenia required significantly more time to complete the TMT-B test than controls. The execution of the Digit Span Forward and Backward was significantly worse in the group of patients with schizophrenia and the first-degree relatives in comparison to the control group. There were no significant differences between the groups in terms of the number of errors in TMT-A and TMT-B. Descriptive statistics, including the assessment of the significance of the observed differences between the groups are shown in Table 2.

Table 1. **Characteristics of the study groups**

Parameter	Controls n = 18	First-degree relative n = 20	Schizophrenia n = 20	Statistics	P
Quantitative variables; mean (SD)					
Age (years)	18.5 (3.348)	48.3 (7.575)	19.45 (3.734)	200.296[a]	< 0.001[c, d]
PANSS-P	-	-	15.0 (3.930)	-	-
PANSS-N	-	-	22.2 (4.740)	-	-
PANSS-G	-	-	38.85 (6.930)	-	-
PANSS-T	-	-	75.85 (12.43)	-	-
Qualitative variables; n (%)					
Female	8 (44.4)	9 (45.0)	9 (45.0)	0.071[b]	1.0
Education					
Primary	6 (33.3)	1 (5.0)	0 (0.0)		
Lower secondary	2 (11.1)	0 (0.0)	12 (60.0)	32.979[b]	< 0.001
Vocational	0 (0.0)	4 (20.0)	0 (0.0)		
Secondary	10 (55.6)	12 (60.0)	7 (35.0)		
Higher	0 (0.0)	3 (15.0)	1 (5.0)		

p – two-tailed probability value; PANSS-T – PANSS (Positive and Negative Syndrome Scale in Schizophrenia) total score; PANSS-P – positive symptoms subscale score; PANSS-N – negative

symptoms subscale score; PANSS-G – general psychopathology subscale score; [a] – value of F-test in analysis of covariance (ANCOVA); [b] – value of Fisher's exact test statistics; The significance of post-hoc differences: [c] – Control vs. First-degree relative; [d] – First-degree relative vs. Schizophrenia

Table 2. **Assessment of significance of differences in terms of efficiency of selected cognitive functions and variables assessed by tractography**

Parameter	Group (mean, SD)			ANCOVA		Eta^2
	Controls n = 18	First-degree Relative n = 20	Schizophrenia n = 20	F	p	
Fractional anisotropy (FA)						
ARC_right	0.5048 (0.038)	0.4856 (0.052)	0.4857 (0.077)	0.501	0.608	-
ARC_left	0.4976 (0.060)	0.5239 (0.057)	0.4992 (0.088)	0.644	0.529	-
cingulum_R_ant	0.2953 (0.054)	0.3253 (0.059)	0.3192 (0.061)	0.964	0.388	-
cingulum_R_midd	0.4198 (0.055)	0.4425 (0.066)	0.4312 (0.086)	0.129	0.879	-
cingulum_R_post	0.3821 (0.039)	0.4104 (0.062)	0.3805 (0.071)	0.946	0.394	-
cingulum_L_ant	0.3347 (0.037)	0.3574 (0.067)	0.3195 (0.059)	0.387	0.681	-
cingulum_L_midd	0.4572 (0.092)	0.4956 (0.069)	0.4720 (0.074)	0.423	0.518	-
cingulum_L_post	0.3943 (0.060)	0.4029 (0.077)	0.3597 (0.071)	0.053	0.818	-
CC_R_forceps_minor	0.4142 (0.061)	0.3884 (0.043)	0.3716 (0.058)	2.905	0.063	-
CC_R_genu	0.6809 (0.118)	0.7020 (0.083)	0.6897 (0.093)	0.063	0.939	-
CC_R_trunc	0.6541 (0.072)	0.6516 (0.076)	0.6091 (0.1360	0.974	0.384	-
CC_R_splenium	0.7472 (0.058)	0.7773 (0.065)	0.7567 (0.098)	0.313	0.733	-
CC_R_forceps_major	0.4545 (0.079)	0.4379 (0.07)	0.4153 (0.071)	1.395	0.257	-
CC_L_forceps_minor	0.3989 (0.062)	0.3905 (0.041)	0.3736 (0.054)	1.178	0.316	-
CC_L_genu	0.6810 (0.118)	0.7020 (0.083)	0.6700 (0.093)	0.063	0.939	-
CC_L_trunc	0.6478 (0.069)	0.6664 (0.073)	0.6374 (0.115)	0.079	0.924	-
CC_L_splenium	0.7472 (0.058)	0.7772 (0.064)	0.7566 (0.098)	0.313	0.733	-
CC_L_forceps_major	0.4505 (0.091)	0.4530 (0.074)	0.4421 (0.097)	0.175	0.84	-
Capsule_R_ant_limb	0.4694 (0.054)	0.5194 (0.049)	0.4701 (0.081)	0.727	0.488	-
Capsule_R_post_limb	0.6081 (0.033)	0.6110 (0.034)	0.6171 (0.045)	0.809	0.451	-
Capsule_R_ext	0.3181 (0.038)	0.3390 (0.040)	0.3197 (0.049)	1.084	0.345	-
Capsule_L_ant_limb	0.4557 (0.059)	0.5241 (0.074)	0.4471 (0.076)	0.731	0.486	-
Capsule_L_post_limb	0.6047 (0.049)	0.6216 (0.045)	0.6111 (0.037)	0.465	0.630	-
Capsule_L_ext	0.3302 (0.037)	0.3704 (0.051)	0.3414 (0.045)	0.619	0.542	-
FX	0.3422 (0.046)	0.3381 (0.050)	0.3358 (0.054)	0.549	0.581	-

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UNC_right	0.4633 (0.053)	0.4837 (0.057)	0.4373 (0.056)	2.457	0.095	-
UNC_light	0.4569 (0.070)	0.4837 (0.077)	0.4534 (0.069)	0.142	0.868	-
IFO_right	0.4952 (0.045)	0.4850 (0.055)	0.4418 (0.094)	2.883	0.065	-
IFO_left	0.4934 (0.063)	0.5228 (0.067)	0.5093 (0.081)	0.586	0.560	-
Evaluation of cognitive functions						
TMT-A_time	25.5556 (8.219)	33.7 (12.616)	39.4 (18.588)	4.689	0.013[b]	0.148
TMT-A_errors	0.2778 (0.575)	0.25 (0.550)	0.3 (0.801)	0.181	0.835	-
TMT-B_time	59.1111 (22.978)	83.85 (27.062)	81.45 (34.854)	3.990	0.024[a, b]	0.129
TMT-B_errors	0.9444 (1.862)	2.0 (3.584)	0.4 (1.046)	0.520	0.597	-
Digit Span Forward	7.1667 (2.093)	5.1 (1.410)	5.4 (1.314)	7.254	0.002[a, b]	0.212
Digit Span Backward	6.0556 (2.600)	4.55 (1.538)	4.6 (1.353)	5.183	0.009[a, b]	0.161

SD – standard deviation; p – value of the two-tailed asymptotic probability for Fisher's test; significant differences between the groups are underlined; Eta^2 – a measure of the effect size observed in the analysis of covariance (ANCOVA); the significance of post-hoc differences: [a] – Controls vs. First-degree relatives; [b] – Controls vs. Schizophrenia; R – right; L – left; ant – anterior; midd – middle; post – posterior; ARC – arcuate fasciculus; CC – corpus callosum; UNC – uncinate fasciculus; IFO – inferior fronto-occipital fasciculus

Discussion

One of the objectives of this study was to evaluate and compare the variability within the morphology of WM between EOS patients, their first-degree relatives and healthy controls. In addition, the study aimed to identify WM structures with potential functional importance in schizophrenia. The neuroimaging part of our project failed to demonstrate statistically significant differences between the groups. Regions for which the FA differences between groups were closest to statistical significance were the right forceps minor of the corpus callosum ($p = 0.063$) and the right inferior fronto-occipital fasciculus ($p = 0.065$). Our results are inconsistent with most studies involving patients with EOS [29–32], and relatives of people diagnosed with psychosis [21, 33–40]. Our results are in part consistent with those of Harms et al., who showed no differences in FA comparing schizophrenia patients' relatives group and controls [22]. Results of borderline significance obtained in the forceps minor of the corpus callosum on the right side and the right inferior fronto-occipital fasciculus confirm the results of other research teams (Clark et al. [36] and Knochel et al. [38]).

A meta-analysis of 15 studies using DTI in schizophrenia confirmed the existence of areas of reduced FA in 112 non-overlapping locations. In all analyzed studies, significant changes in FA were demonstrated in two regions: the left frontal WM, comprising connections linking the frontal lobe, thalamus and cingulate gyrus, and the left temporal WM – with the fibers connecting the frontal lobe with the insular

cortex, hippocampus, amygdala, temporal and occipital lobe [41]. Changes in these regions are found in subjects at ultra-high risk of developing schizophrenia (UHR) [42], in patients with short course of psychosis [43], and in patients with early onset of psychosis, particularly interesting in the context of our study [29]. These findings suggest the presence of changes in FA in the early stages of the illness and/or expression of morphological susceptibility to the development of schizophrenia.

A meta-analysis of eight studies involving a total of 271 patients, including those with a first episode of psychosis, provided partially coherent conclusions. In all analyzed studies, deep regions of the right frontal lobe and the left temporal lobe were demonstrated as areas with reduced FA [44].

Relatively few DTI studies have focused on EOS patients. In these studies, lower FA values were noted within the right anterior limb of the internal capsule (ALIC) compared with the control group, suggesting also that these changes are gender dependent [30]. Patients demonstrated lower FA values in the cortico-spinal pathways – on both sides, the left inferior longitudinal fasciculus and left inferior fronto-occipital fasciculus than healthy controls. Reduced FA values correlated with poorer neuropsychological test outcomes in patients with EOS [31]. Lower FA values were also demonstrated in the association cortex of parietal lobes (bilaterally), left cerebellar peduncle [32] and left cingulate gyrus [29] compared to control groups. In the largest DTI study to date in this group of patients, FA changes in the cuneus were described on both sides. Similar results were obtained in the group of healthy siblings of patients, which was interpreted as an indicator of increased susceptibility to the development of psychotic symptoms in this population [34].

Our present study also evaluates changes in FA in parents of EOS patients. Most of the available research, conducted in groups of first-degree relatives of patients with schizophrenia, examines nonhomogenous groups of relatives, usually involving the siblings of patients. A meta-analysis of 22 studies of psychotic patient relatives as the most consistent changes identifies disturbances of the integrity of WM regions in the frontal lobes, temporal lobes and corpus callosum [21]. Other DTI studies on first-degree relatives of patients with schizophrenia using – as in our project – an assessment of the FA for each region of interest (ROI), demonstrated a reduction of FA in the anterior limb of internal capsule (on the left and right side) [35], uncinate fasciculus (on both sides) [35], left arcuate fasciculus [35], both left inferior and superior longitudinal fasciculi [36], inferior fronto-occipital fasciculus (on both sides) [36], corona radiata [37], corpus callosum [38], cingulate gyrus [33] and associative fibers [33]. In these studies, the scores of the patients' relatives were between those of the patients and the healthy controls. These results may indicate that schizophrenia has a genetic background. Hereditary factors may determine susceptibility to the development of the illness, through the influence on changes in the structure and, most likely, the function of particular CNS areas.

In studies of siblings of patients with schizophrenia, reduced FA values were also confirmed in the cuneal WM [34], the medial regions of the frontal lobe [39], the left

prefrontal cortex and hippocampus [40]. These results were not confirmed in all available studies. The outcomes of independent studies showed no differences in FA in the relatives of schizophrenia patients [22], or any increase in FA in relatives in the left and right arcuate fasciculus (bilaterally) [45] – with no differences in FA in the group of schizophrenia patients [22, 45].

The difficulties in comparing these results to those of the resent study arise inter alia from a lack of common design (comparisons between patients with EOS and their parents matched by gender). The most common comparison is with healthy siblings of patients or a heterogeneous group of first-degree relatives. The available literature demonstrates that FA data is variable in most ROIs evaluated in the present study, both in the group of patients with psychosis and their relatives. These results, however, come mainly from the analyses in which the population of schizophrenia patients was not differentiated by age of illness onset.

In assessing selected cognitive functions, we conclude that compared to healthy controls, EOS patients needed significantly longer time to finish the TMT-A, and that EOS patients and their first-degree relatives required more time to complete the TMT-B. In addition, both EOS patients and their relatives obtained lower scores in Digit Span Forward and Backward than controls. The results suggest the presence of dysfunctions in attention, memory and storage capacity in EOS patients and their first-degree relatives. Moreover, the results indicate a reduced psychomotor speed, visual-spatial coordination, divided attention and cognitive plasticity in both EOS patients and their relatives.

Our results are consistent with those of Moritz et al. and Zalla et al., indicating a worse result in TMT in patients with schizophrenia [19, 46]. In contrast to Zalla et al. 2004, the healthy relatives of the EOS subjects examined in the present study obtained lower scores in TMT-B compared to the control group [19]. This might be related to the execution of TMT slowing with age [47, 48], and TMT completion speed being related to education level [49]. The relatives of EOS patients, i.e., the parents, were significantly older, with a higher level of education (Table 1). Furthermore, the only differences between EOS relatives and controls were found with regard to the TMT-B, not the TMT-A. These outcomes may be related to increased requirements in terms of psychomotor speed and visual-perceptual processing in TMT-B compared with the TMT-A [26], which are closely associated with age [47] or to the link between higher requirements of TMT-B and older age of people in the group of first-degree relatives. These hypotheses, however, require a separate verification study.

The poorer Digit Span test results observed in EOS patients and their first-degree relatives compared to healthy subjects is consistent with the results of previous studies [50, 51]; however, Conklin et al. report that while relatives and controls achieved similar results in Digit Span Forward (in contradiction to our results), the relatives demonstrated worse results in Digit Span Backward, as observed in the present study [52]. This difference, as in TMT, might be influenced by association of age and education level with both Digit Span Forward and Backward [53, 54].

The main limitations of our project were the relatively small size of the study group, smaller than most available research EOS groups [30, 31, 34], and the incomplete homogeneity of the group regarding education level and symptom severity. In addition, our groups differed in age and education level which could affect the results of both neuropsychological tests [26, 53, 54], and neuroimaging studies [55, 56].

Recapitulation

The results of our study indicate a reduction in the direct memory capacity, working memory, cognitive plasticity and divided attention both in EOS patients and their first-degree relatives compared to healthy subjects.

Our findings, however, do not demonstrate any difference in WM coherence between the tested groups when tested using FA. This suggests that no abnormalities in WM structure integrity are present in EOS patients or their relatives. The presence of significant differences in neuropsychological test results in these groups indicates that either the cause of the deficits that occur in patients with EOS and their relatives is not structural.

The significant discrepancies present in the outcomes of other studies, as well as the range of localizations of identified changes in WM structure in EOS patients and their relatives, suggest the need for further research in these groups.

Larger number of participants in study groups, taking into account the potential effect of age, educational level, and antipsychotic drugs, on the morphological and neuropsychological parameters, could be beneficial for reliability of planned research.

Given the growing number of available DTI studies – application of easier to replicate and allowing simultaneous evaluation of the entire brain structure – the voxel-based-analysis could facilitate the comparison of results between research teams.

Current knowledge is clearly insufficient to draw definite conclusions about the possible significance of differences in integrity ascertained in the WM on functional aspects.

References

1. Gawłowska M. *Teoria neurorozwojowa.* In: Rabe-Jabłońska J, Kotlicka-Antczak M. ed. *Ryzykowny stan psychiczny. Czy można zapobiegać schizofrenii?* Poznan: Termedia; 2012. p. 9–18.
2. Honey GD, Pomarol-Clotet E, Corlett PR, Honey RA, McKenna PJ, Bullmore ET. et al. *Functional dysconnectivity in schizophrenia associated with attentional modulation of motor function.* Brain 2005; 128(11): 2597–2611.
3. Shizukuishi T, Abe O, Aoki S. *Diffusion tensor imaging analysis for psychiatric disorders.* Magn. Reson. Med. Sci. 2013; 12(3): 153–159.
4. Kubicki M, McCarley R, Westin CF, Park HJ, Maier S, Kikinis R. et al. *A review of diffusion tensor imaging studies in schizophrenia.* J. Psychiatr. Res. 2007; 41(1–2): 15–30.

5. Mitelman SA, Torosjan Y, Newmark RE, Schneiderman JS, Chu KW, Brickman AM. et al. *Internal capsule, corpus callosum and long associative fibers in good and poor outcome schizophrenia: a diffusion tensor imaging survey.* Schizophr. Res. 2007; 92(1–3): 211–224.
6. Wolkin A, Choi SJ, Szilagyi S, Sanfilipo M, Rotrosen JP, Lim KO. *Inferior frontal white matter anisotropy and negative symptoms of schizophrenia: a diffusion tensor imaging study.* Am. J. Psychiatry 2003; 160(3): 572–574.
7. Hoptman MJ, Volavka J, Johnson G, Weiss E, Bilder RM, Lim KO. *Frontal white matter microstructure, aggression, and impulsivity in men with schizophrenia: a preliminary study.* Biol. Psychiatry 2002; 52(1): 9–14.
8. Nestor PG, Kubicki M, Niznikiewicz M, Gurrera RJ, McCarley RW, Shenton ME. *Neuropsychological disturbance in schizophrenia: a diffusion tensor imaging study.* Neuropsychology 2008; 22(2): 246–254.
9. Takei K, Yamasue H, Abe O, Yamada H, Inoue H, Suga M. et al. *Disrupted integrity of the fornix is associated with impaired memory organization in schizophrenia.* Schizophr. Res. 2008; 103(1–3): 52–61.
10. Kremen WS, Seidman LJ, Faraone SV, Tsuang MT. *Intelligence quotient and neuropsychological profiles in patients with schizophrenia and in normal volunteers.* Biol. Psychiatry 2001; 50(6): 453–462.
11. Gold S, Arndt S, Nopoulos P, O'Leary DS, Andreasen NC. *Longitudinal study of cognitive function in first-episode and recent-onset schizophrenia.* Am. J. Psychiatry 1999; 156(9): 1342–1348.
12. Palmer BW, Heaton RK, Paulsen JS. *Is it possible to be schizophrenic yet neuropsychologically normal?* Neuropsychology 1997; 11(3): 437–446.
13. Heinrichs RW, Zakzanis KK. *Neurocognitive deficit in schizophrenia: a quantitative review of the evidence.* Neuropsychology 1998; 12(3): 426–445.
14. Aleman A, Hijman R, de Haan EH, Kahn RS. *Memory impairment in schizophrenia: a metaanalysis.* Am. J. Psychiatry 1999; 156(9): 1358–1366.
15. Lee J, Park S. *Working memory impairments in schizophrenia: a meta-analysis.* J. Abnorm. Psychol. 2005; 114(4): 599–611.
16. Dickinson D, Ramsey ME, Gold JM. *Overlooking the obvious: a meta-analytic comparison of digit symbol coding tasks and other cognitive measures in schizophrenia.* Arch. Gen. Psychiatry 2007; 64(5): 532–542.
17. Elvevag B, Goldberg TE. *Cognitive impairment in schizophrenia is the core of the disorder.* Crit. Rev. Neurobiol. 2000; 14(1): 1–21.
18. Keshavan MS, Kulkarni S, Bhojraj T, Francis A, Diwadkar V, Montrose DM. et al. *Premorbid cognitive deficits in young relatives of schizophrenia patients.* Front. Hum. Neurosci. 2010; 3: 62.
19. Zalla T, Joyce C, Szöke A, Schürhoff F, Pillon B, Komano O. et al. *Executive dysfunctions as potential markers of familial vulnerability to bipolar disorder and schizophrenia.* Psychiatry Res. 2004; 121(3): 207–217.
20. Geschwind DH, Iacoboni M. *Structural and functional asymmetries of the human frontal lobes.* In: Miller BL, Cummings JL. ed. *The human frontal lobes: functions and disorders*. 2nd ed. New York: Guilford Press; 2007.
21. Arat HE, Chouinard VA, Cohen BM, Lewandowski KE, Öngür D. *Diffusion tensor imaging in first degree relatives of schizophrenia and bipolar disorder patients.* Schizophr. Res. 2015; 161(2–3): 329–339.
22. Harms MP, Akhter KD, Csernansky JG, Mori S, Barch DM. *Fractional anisotropy in individuals with schizophrenia and their nonpsychotic siblings.* Psychiatry Res. 2015; 231(1): 87–91.

23. Grossi D, Matarese V, Orsini A. *Sex differences in adults' spatial and verbal memory span.* Cortex 1980; 16(2): 339–340.
24. Brzeziński J, Hornowska E. ed. *Skala inteligencji Wechslera WAIS-R: polska adaptacja, standaryzacja, normalizacja i wykorzystanie w diagnostyce psychologicznej.* Warsaw: Polish Scientific Publishers PWN; 1993.
25. Lezak MD. *Memory I: Tests.* In: *Neuropsychological Assessment*. 4th ed. Lezak MD. ed. New York: Oxford University Press; 2004. p. 414–479.
26. E. Strauss, Sherman EMS, Spreen O. *Attention.* In: Strauss E, Sherman EMS, Spreen O. ed. *A compendium of neuropsychological tests: administration, norms, and commentary*. 3rd ed. New York: Oxford University Press; 2006. p. 546–677.
27. Taki Y, Thyreau B, Hashizume H, Sassa Y, Takeuchi H, Wu K. et al. *Linear and curvilinear correlations of brain white matter volume, fractional anisotropy, and mean diffusivity with age using voxel-based and region-of-interest analyses in 246 healthy children.* Hum. Brain Mapp. 2013; 34(8): 1842–1856.
28. Schmithorst VJ, Wilke M, Dardzinski BJ, Holland SK. *Correlation of white matter diffusivity and anisotropy with age during childhood and adolescence: a cross-sectional diffusion-tensor MR imaging study.* Radiology 2002; 222(1): 212–218.
29. Kumra S, Ashtari M, Cervellione KL. *White matter abnormalities in early-onset schizophrenia: a voxel-based diffusion tensor imaging study.* J. Am. Acad. Child. Adolesc. Psychiatry 2005; 44(9): 934–941.
30. Gawłowska M*,* Jolanta Rabe-Jabłońska, Piotr Gębski, Piotr Chomczyński. *Internal capsule integrity and its sex-related structural differences in early-onset schizophrenia – diffusion tensor imaging study.* Psychiatr. Pol. 2015; 49(2): 349–361.
31. Epstein KA, Cullen KR, Mueller BA, Robinson P, Lee S, Kumra S. *White matter abnormalities and cognitive impairment in early-onset schizophrenia-spectrum disorders.* J. Am. Acad. Child Adolesc. Psychiatry 2014; 53: 362–372, e1–e2.
32. Kyriakopoulos M, Vyas NS, Barker GJ, Chitnis XA, Frangou S. *A diffusion tensor imaging study of white matter in early-onset schizophrenia.* Biol. Psychiatry 2008; 63: 519–523.
33. Knöchel C, O'Dwyer L, Alves G, Reinke B, Magerkurth J, Rotarska-Jagiela A. et al. *Association between white matter fiber integrity and subclinical psychotic symptoms in schizophrenia patients and unaffected relatives.* Schizophr. Res. 2012; 140(1–3): 129–135.
34. Moran ME, Luscher ZI, McAdams H, Hsu JT, Greenstein D, Clasen L. et al. *Comparing fractional anisotropy in patients with childhood-onset schizophrenia, their healthy siblings, and normal volunteers through DTI.* Schizophr. Bull. 2015; 41(1): 66–73.
35. Muñoz Maniega S, Lymer GK, Bastin ME, Marjoram D, Job DE, Moorhead TW. et al. *A diffusion tensor MRI study of white matter integrity in subjects at high genetic risk of schizophrenia.* Schizophr. Res. 2008; 106(2–3): 132–139.
36. Clark KA, Nuechterlein KH, Asarnow RF, Hamilton LS, Phillips OR, Hageman NS. et al. *Mean diffusivity and fractional anisotropy as indicators of disease and genetic liability to schizophrenia.* J. Psychiatr. Res. 2011; 45(7): 980–988.
37. Skudlarski P, Schretlen DJ, Thaker GK, Stevens MC, Keshavan MS, Sweeney JA. et al. *Diffusion tensor imaging white matter endophenotypes in patients with schizophrenia or psychotic bipolar disorder and their relatives.* Am. J. Psychiatry 2013; 170(8): 886–898.
38. Knöchel C, Oertel-Knöchel V, Schönmeyer R, Rotarska-Jagiela A, van de Ven V, Prvulovic D. et al. *Interhemispheric hypoconnectivity in schizophrenia: fiber integrity and volume differences of the corpus callosum in patients and unaffected relatives.* Neuroimage 2012; 59(2): 926–934.

39. Camchong J, Lim KO, Sponheim SR, Macdonald AW. *Frontal white matter integrity as an endophenotype for schizophrenia: diffusion tensor imaging in monozygotic twins and patients' nonpsychotic relatives.* Front. Hum. Neurosci. 2009; 3: 35.
40. Hao Y, Yan Q, Liu H, Xu L, Xue Z, Song X. et al. *Schizophrenia patients and their healthy siblings share disruption of white matter integrity in the left prefrontal cortex and the hippocampus but not the anterior cingulate cortex.* Schizophr. Res. 2009; 114(1–3): 128–135.
41. Ellison-Wright I, Bullmore E. *Meta-analysis of diffusion tensor imaging studies in schizophrenia.* Schizophr. Res. 2009; 108(1–3): 3–10.
42. Karlsgodt KH, Niendam TA, Bearden CE, Cannon TD. *White matter integrity and prediction of social and role functioning in subjects at ultra-high risk for psychosis.* Biol. Psychiatry 2009; 66(6): 562–569.
43. Szeszko PR, Ardekani BA, Ashtari M, Kumra S, Robinson DG, Sevy S. et al. *White matter abnormalities in first-episode schizophrenia or schizoaffective disorder: a diffusion tensor imaging study.* Am. J. Psychiatry 2005; 162: 602–605.
44. Yao L, Lui S, Liao Y, Du MY, Hu N, Thomas JA. et al. *White matter deficits in first episode schizophrenia: an activation likelihood estimation meta-analysis.* Prog. Neuropsychopharmacol. Biol. Psychiatry 2013; 45: 100–106.
45. Boos HB, Mandl RC, van Haren NE, Cahn W, van Baal GC, Kahn RS. et al. *Tract-based diffusion tensor imaging in patients with schizophrenia and their non-psychotic siblings.* Eur. Neuropsychopharmacol. 2013; 23(4): 295–304.
46. Moritz S, Birkner C, Kloss M, Jahn H, Hand I, Haasen C. et al. *Executive functioning in obsessive-compulsive disorder, unipolar depression, and schizophrenia.* Arch. Clin. Neuropsychol. 2002; 17(5): 477–483.
47. Lucas JA, Ivnik RJ, Smith GE, Ferman TJ, Willis FB, Petersen RC. et al. *Mayo's older African Americans normative studies: norms for Boston Naming Test, Controlled Oral Word Association, Category Fluency, Animal Naming, Token Test, WRAT-3 Reading, Trail Making Test, Stroop Test, and Judgment of Line Orientation.* Clin. Neuropsychol. 2005; 19(2): 243–269.
48. Bäckman L, Wahlin Å, Small BJ, Herlitz A, Winblad B, Fratiglioni L. *Cognitive Functioning in Aging and Dementia: The Kungsholmen Project.* Aging Neuropsychol. Cognition 2004; 11(2–3): 212–244.
49. Mitrushina MN, Boone KB, Razani J, D'Elia, LF. *Tests of attention and concentration: visual and auditory.* In: Mitrushina MN, Boone KB, Razani J, D'Elia, LF. ed. *Handbook of normative data for neuropsychological assessment*. 2nd ed. New York: Oxford University Press; 2005. p. 59–98.
50. Jabben N, Arts B, van Os J, Krabbendam L. *Neurocognitive functioning as intermediary phenotype and predictor of psychosocial functioning across the psychosis continuum: studies in schizophrenia and bipolar disorder.* J. Clin. Psychiatry 2010; 71(6): 764–774.
51. Galaverna FS, Morra C, Bueno AM. *Attention in patients with chronic schizophrenia: Deficit in inhibitory control and positive symptoms.* Eur. J. Psychiatry 2012; 26(3): 185–195.
52. Conklin HM, Curtis CE, Katsanis J, Iacono WG. *Verbal working memory impairment in schizophrenia patients and their first-degree relatives: evidence from the digit span task.* Am. J. Psychiatry 2000; 157(2): 275–277.
53. Ardila A, Ostrosky-Solis F, Rosselli M, Gómez C. *Age-related cognitive decline during normal aging: the complex effect of education.* Arch. Clin. Neuropsychol. 2000; 15(6): 495–513.
54. Hester RL, Kinsella GJ, Ong B. *Effect of age on forward and backward span tasks.* J. Int. Neuropsychol. Soc. 2004; 10(4): 475–481.

55. Chiapponi C, Piras F, Fagioli S, Piras F, Caltagirone C, Spalletta G. *Age-related brain trajectories in schizophrenia: a systematic review of structural MRI studies.* Psychiatry Res. 2013; 214(2): 83–93.

56. Wieselgren IM, Lindstrom LH. *A prospective 1-5 year outcome study in first-admitted and readmitted schizophrenic patients; relationship to heredity, premorbid adjustment, duration of disease and education level at index admission and neuroleptic treatment.* Acta Psychiatr. Scand. 1996; 93(1): 9–19.

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