

## **Internal capsule integrity and its sex-related structural differences in early-onset schizophrenia – diffusion tensor imaging study**

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### **Summary**

**Objectives:** In schizophrenia, the most repeatable DTI findings concern reduced FA in temporal and frontal lobes with associated abnormalities in connecting neural fibers. The goal of study was to evaluate the differences in FA of the internal capsule in EOS-patients and healthy controls and to place emphasis on the sex as a potential factor determining a predominant pathological pattern of described changes.

**Methods:** 30 EOS patients and 30 healthy controls were studied using DTI. FA measures within internal capsules were performed in selected ROIs. For statistical analyses the one-way ANOVA test was used ( $p < 0.05$ ).

**Results:** Significant differences of FA between EOS-patients and controls in the right ALIC with lower values of FA in EOS were observed. Within the women sub-groups, statistical differences of FA were observed only for the right ALIC. There were no statistically significant differences within men sub-groups.

**Conclusions:** 1. Statistically significant differences were found between EOS – subjects (subgroups of woman only) and the control group within the WM diffusivity of the brain in

the right ALIC. 2. These results indicate possible involvement of the structures of internal capsule in the EOS development.

**Key words:** schizophrenia, internal capsule, neuroimaging

## Introduction

Changes in the structure of the ALIC (anterior limb of internal capsule) have been repeatedly described in schizophrenia and are likely to be associated with, at least some of, schizophrenia symptoms. ALIC contains descending motor and ascending sensory fibers interconnecting brain regions implicated in the pathophysiology of schizophrenia – including regions of neocortex, striatum, thalamus and pons [1]. It serves as the main efferent tract of the thalamus, carrying two major fiber systems – the ATR (anterior thalamic radiation) and the fronto-pontine tract [2]. The ATR consists of fiber bundles connecting mediodorsal thalamic nuclei with the frontal cortex and fibers between anterior thalamic nuclei and the anterior cingulate cortex [1, 3]. Fronto-pontine fibers are descending cortical fibers with proven motor functions [4]. The thalamic nuclei have multiple projections via the internal capsule to and from the frontal cortex regions involved in memory, emotion, motivation and directed attention. Disruption of ALIC may result in cognitive deficits of a subcortical profile, similar to those observed in schizophrenia [5–7].

A specific group of schizophrenia patients, described in this study, are EOS (early onset schizophrenia) individuals. EOS is defined as a form of disease in which first symptoms develop in childhood or adolescence (with the onset before age 18). EOS was shown to be on a continuum with the adult form of the illness although it is characterized by its own, specific features [8–10]. It was shown that schizophrenia is twice as prevalent among first-degree relatives of EOS individuals [11], while in AOS the risk of developing schizophrenia in first-degree relatives is estimated as 10 to 15-fold higher [12]. These facts suggest that in the development of EOS environmental factors (e.g. hypoxia, nutritional deficiencies, infections and other) may have greater impact than genetic predisposition and that manifestation of this form of disease is different than AOS. Developmental and/or behavioural abnormalities are more prevalent at premorbid phase in EOS than AOS – with the incidence of about 90% [13]. This may reflect greater neurodevelopmental failure in these patients. EOS patients usually show more pronounced negative symptoms compared to those with AOS [14].

Results from relatively few DTI (diffusion tensor imaging) studies on EOS patients confirmed the presence of brain structure abnormalities. Regional decreases in WM (white matter) diffusivity in EOS patients were observed in frontal and parietal lobes bilaterally, in the right occipital lobe and in the cerebellum [15, 16]. WM abnormalities were also found in limbic structures, including the anterior cingulate regions [17, 18] and the left posterior hippocampus [19]. EOS patients revealed significantly reduced

FA in the right anterior cingulum compared to healthy controls. Moreover, a negative correlation between mean regional FA in the right anterior cingulum and PANSS positive symptom score was also demonstrated [18]. In none of the above studies increased FA was observed in the groups of patients compared to controls [15–19].

To our knowledge, none of the available DTI studies described significant differences in the internal capsule diffusivity. Due to the limited and inconsistent data from the EOS – related studies further studies on this group of patients are needed.

### Aim of the study

The goal of our study was to evaluate differences in FA of the internal capsule in a sample of EOS-patients and healthy controls. Special attention was put to the role of sex as a potential factor determining a predominant pathological pattern of the described changes. Due to the fact that sex-related differences in schizophrenia were analyzed only in a small sample of available DTI studies, the obtained results are not sufficient to explain whether and/or how gender determines localization and intensity of WM abnormalities. We hypothesized that these differences may be present at an early stage of the disease and that sex-related genetic, hormonal or constitutional factors may strongly affect the course of the early-onset psychoses.

### Material

#### Examined groups

30 EOS (DSM-IV) patients (mean age 20.2 +/- 2.5 years; 15 males, 15 females; all Caucasians) were studied (Table 1). 30 normal controls comparable for age, gender, race and socio-economic status to the patients (mean age 21.5 +/- 2.7 years; 15 males, 15 females; all Caucasians) were studied (Table 1).

Table 1. Demographic factors of examined group and healthy controls

	Examined group (EOS-patients)	Healthy controls
Demographic factors:		
Patients mean age ± SD	20.2 ± 2.48	21.53 ± 2.66
Sex, males:females	15:15	15:15
Handedness, right-handed:left-handed	24:6	29:1
Race	Caucasians	Caucasians
Socioeconomic status	good	good
Clinical characteristics:		
Onset of symptoms, mean age ± SD	16 ± 2.05	-
Duration of symptoms, years ± SD	4.2 ± 2.4	-

*table continued on the next page*

Duration of antipsychotic treatment, years $\pm$ SD	3.28 $\pm$ 2.29	-
Genetic load (positive family history of schizophrenia)	8:22	0:30

SD – standard deviation

Diagnosis of EOS was confirmed with the clinical consensus of two staff psychiatrists – using polish version of CIDI (Composite International Diagnostic Interview). Patients with comorbid psychiatric disorders, alcohol or substance abuse within the 6 months preceding the study, history of traumatic head injury with loss of consciousness, epilepsy or other neurological and/or severe somatic diseases were excluded. All patients were receiving antipsychotic medications (2nd generation antipsychotics) at the time of imaging. Patients were recruited from inpatient and outpatient clinics.

The control individuals had no DSM-IV axis I disorders, as determined by the standardized interview CIDI, no history of psychiatric disorders among their first-degree relatives, no history of alcohol or substance abuse and no current major medical conditions. The socio-economic status in both groups was evaluated on the basis of a clinical interview and estimated using a simple five-grade scale (very bad–bad–moderate–good–very good). Normal controls were medical studies students or university staff volunteers.

The study was approved by the Bioethical Committee of the Medical University of Lodz (RNN / 66/09 / EC). All subjects were explained the study procedure prior to signing informed consents. In case of patients under the age of 18 a consent from their caregivers and assent from the subjects were obtained (according to the Polish law).

## Methods

### MRI

All MRI scans were obtained Księży Młyn Medical Center of Diagnostic Radiology using a 1.5T General Electric SIGNA HDi System (GE Medical Systems, Milwaukee, WI). Diffusion-weighted imaging data were 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 ( $b = 1000\text{s/mm}^2$ ) and two without diffusion weighing ( $b = 0$ ). Twenty seven contiguous axial slices were acquired with a slice thickness of 5mm and no gap. The acquisition parameters were as follows: echo time TE = 103.5ms; repetition time TR = 8500ms; field of view = 30cm; number of excitations NEX = 1 and matrix = 128 $\times$ 128.

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

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

### DTI data processing

A Functool DTI software (GE Medical Systems, Milwaukee, WI) was used for DTI data processing. After computing FA images, ROIs within the internal capsule were defined. A radiologist blind to diagnosis placed ROIs in white matter tracts using identifiable landmarks on FA images and with reference to the Mori MRI atlas of human white matter. Selected ROIs were placed within right and left anterior and posterior limbs of internal capsules and – additionally – within external capsules (bilaterally).

Quality control measures included the inspection of each image with traced ROIs by two experienced radiologists for the quality of the image and the correct placement of ROIs. The correct placement was confirmed by display of the ROIs on the anisotropy image as well as on the coloured orientation images. (figures 1, 2).

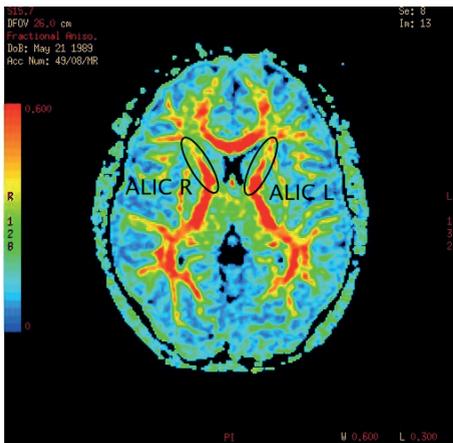


Figure 1: Fractional anisotropy map with ROIs placed in right and left anterior limb of internal capsules. Color scale reflects the degree of diffusivity.

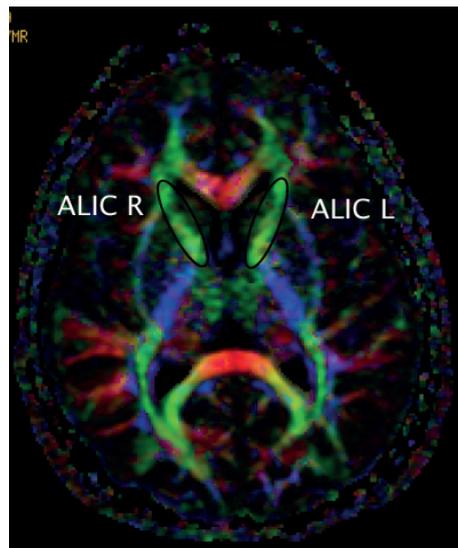


Figure 2: FA directionally encoded color (DEC) map with ROIs placed in right and left anterior limb of internal capsules. Color scale reflects directional information and the degree of diffusivity simultaneously.

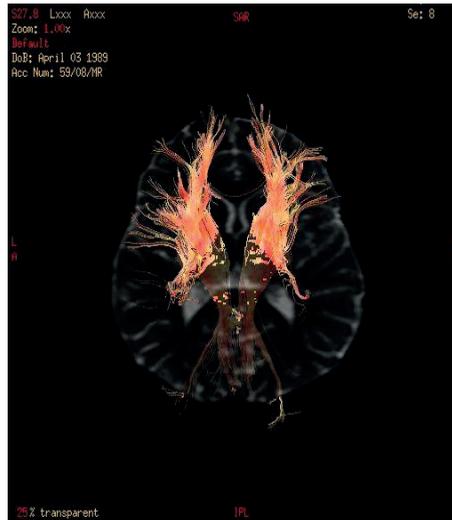


Figure 3: **Tractographic reconstruction of internal capsules.**

### Statistical analysis

For statistical verification of differences between the analyzed groups, the SPSS software was applied.

The differences between the analyzed groups (EOS-patients vs. controls) were tested by using mean values of FA and standard deviation of previously defined ROIs. To test the statistical significance of differences of FA values within and between groups, the one-way ANOVA test was used with statistical significance level set at  $p < 0.05$ .

In order to explain and verify the differences between experimental results and the ones observed with the use of ANOVA test, the ETA square test was also adopted.

### Results

According to the one-way ANOVA test, we observed significant differences of diffusivity between EOS-patients and healthy controls measured by FA parameter in the right anterior limb of internal capsule ( $p = 0.016$ ,  $df = 1$ ,  $F = 6.143$ ) with lower values of FA in schizophrenics group.

Within the women sub-groups, statistical differences were observed in diffusivity measured by FA parameter also for the right anterior limb of internal capsule ( $p = 0.023$ ,  $df = 1$ ,  $F = 5.913$ ).

There were no statistically significant differences within men sub-groups.

Among analyzed WM regions there were none of increased fractional anisotropy in EOS-subjects.

### Discussion

A comparison of the EOS group with the healthy control group revealed lower FA values in the region of the right ALIC in the EOS group ( $p = 0.016$ ). It was confirmed that the above changes are present in relatively early stages of schizophrenia.

The existing reports on WM structure in this localization in schizophrenia are ambiguous and based almost exclusively on the studies in patients with AOS. Most of the available studies on the AOS group confirm the presence of regions of reduced WM integrity in the internal capsule region, uni – [20] or bilaterally [21, 22], referring only to the anterior limb (anterior left thalamic peduncle on the left side [20]) or the whole structure [21, 22]. There are also negative observations which did not exhibit statistically significant changes in the internal capsule structure between schizophrenic patients and healthy controls [23, 24]. An earlier study of Kubicki, Levitt et al. confirmed the presence of bilaterally lowered FA in ALIC [21]. However, the latest studies conducted by Kubicki et al. did not confirm lowered FA in ALIC although they observed reduced volume of this region in adult schizophrenic patients [25].

Primary nature of the described abnormalities in the diffusivity of the WM in internal capsule is indicated by the results of the study conducted by Cheung et al. The abnormalities localized in the right posterior limb of internal capsule were described in neuroleptic-naïve patients [26]. Szeszko et al. demonstrated the presence of reduced FA within the left ALIC in the first episode of psychosis [27]. These observations suggest primary character and/or very early manifestation of the observed abnormalities in the course of schizophrenia.

The results of our study are partly consistent with the results of the research on AOS groups, which confirms shared pathological elements of the brain anatomy in both forms of the disease and/or possible continuum of WM changes in schizophrenic patients throughout their lives. The WM diffusivity differences shown by the above study in the ALIC region indicate a probable involvement of this structure in the development of the EOS symptoms.

We did not find any descriptions of changes in the WM integrity within the internal capsule region in any of the DTI studies on the EOS patients. In volumetric MRI studies conducted in this group a negative correlation between negative symptoms score and the volume of the right internal capsule was demonstrated by Paillere-Martinot et al. [28].

In the re-analysis of the results in the subgroups differentiated according to the patients' gender no statistically significant differences were found in the subgroup of healthy and ill men. In the subgroup of women we obtained a statistically significant reduction of FA in the right ALIC, which conformed with the results of the analysis

conducted for the whole group. The lack of statistically significant differences in the WM structure in the subgroup of men, with evident differences between the examined group and controls, may suggest that the indicated changes mainly depend on WM abnormalities present in the group of examined women. This hypothesis is confirmed by identical location of the changes found in the examined groups and the subgroup of women.

Few available DTI studies, concerning patients with psychosis, involve an analysis of the obtained results according to the patients' gender. Schneiderman et al. conducted an analysis of the dependence of the WM diffusivity on the age and gender of the subjects with diagnosed psychotic disorders (not only of schizophrenia) and observed associations for the internal capsule, anterior thalamic radiation, frontal occipital fasciculus, frontal superior longitudinal fasciculus, cingulum bundle and corpus callosum [29]. It was indicated that in female adolescents with EOS the FA indices for ALIC (including posterior limb) were lower on the right side as compared to the control group [29]. In our study we obtained results partly consistent with the findings considering lower values of FA for the right ALIC in the subgroup of EOS women. Discrepancy in the rest of results may be partly accounted for by an insufficient comparability with other studies (e.g. lower average age of the examined adolescents or inclusion of patients with schizoaffective psychosis).

In the study including exclusively men Peters et al., found no differences in the WM diffusivity between 3 groups of men: with a short history of psychosis, with a high risk of psychosis, and healthy controls, which conforms with our observations in the EOS group [30]. Price et al. indicated lowered FA within the genu of corpus callosum and uncinate fasciculus – with evidently lower FA values in female groups, as compared to the men. The above correlations were observed both in the examined group and in controls [31, 32]. No such correlations were found for ALIC, but the results of our study indicate their presence in the group of EOS patients.

The patterns observed in our study may be partly explained by the gender differences in the development of the brain structures. Women achieve the maximum volume of the brain at the average age of 10.5 years, whereas men – 14.5 years. Moreover, total volume of the men's brain is approximately 10% bigger than women's. The development of GM (grey matter) both in men and women is most intense in the first decade of life, but women reach the maximum volume of GM on average 1–2 years earlier than men (on average: 8.5 vs. 10.5 years) [33]. An analysis of the course of the development of the WM structures indicates that they develop throughout the childhood, adolescence and early adulthood. However, dynamics of the observed changes differs, being much higher in men through the whole observation period [33]. Investigating the course of the most intense period of WM development and maturation (age: 12–18 years), Perrin et al. indicated that in males the total volume of WM increased while total content of myelin decreased with age (measured by the magnetization-transfer

ratio – MTR). In girls increase in the WM volume was insignificant and was not accompanied by changes in the MTR parameter except MTR increase in the frontal lobes, [34]. The authors assumed the presence of different predominant mechanisms of WM structures maturation in both genders, with predominant increase in the fibres diameter in men and enhanced myelination in women [34]. According to some reports, there are more evident abnormalities in the WM microstructure in females with schizophrenia. Unlike in healthy controls, where the WM fibre density is higher in women than in men, a reverse correlation was observed in schizophrenic patients [35]. Furthermore, ill women exhibited a reduced total number of the WM fibres – evaluated post mortem [35].

The above facts may partly account for the observed correlation. Abnormal course of myelination may be more responsible for the development of schizophrenia in women in whom the development of myelin is the main mechanism of the maturation of WM structures. Another hypothetical explanation of the observed correlation may be the fact that at the time of the study majority of participants (women) were at a more advanced stage of the development of WM structures (the examined groups of women and men were comparable according to average values of age). This may partly account for the presence of more pronounced changes in the diffusivity of the finally developed WM fibres.

The statistically significant differences in the diffusivity of WM tissues between the studied group and controls inform exclusively about the presence of quantitative or qualitative differences between the examined groups, however they do not allow to draw conclusions about their exact nature and possible functional importance. The confirmed decrease in FA in the ALIC region among EOS patients may result from the reduced number of axons in this area, shift in the axonal direction, decrease in their diameter or arrangement density, and a lower content of myelin or a change of its chemical composition. Furthermore, each of the assessed ROI contains, in different proportions, elements of WM, GM and cerebrospinal fluid. Hence, a decrease in the FA in a given ROI may reflect changes in each of the components present there.

#### Potential limitations of the study

A direct comparison of the FA values obtained in DTI studies between the examined group and healthy controls may be hampered and not reliable enough due to the reported different patterns of the brain's maturation in schizophrenia [36]. Similarly, a different pattern of major changes in the WM diffusivity in EOS and AOS patients groups was described [37].

Incomplete homogeneity of the examined group with respect to the duration of schizophrenia symptoms is another limitation of the project. 30 patients with a relatively short duration of schizophrenia and in a considerable symptomatic remission (assessed clinically) were included to the study. However, we cannot exclude the ef-

fects of other endo – and/or exogenous factors which might affect the WM diffusivity in the course of the disease.

In order to limit these factors, individuals (1) with confirmed active use of psychoactive substances, (2) with diagnosed intellectual retardation and/or other organic lesions in the CNS, (3) estimating their socio-economic status as less than “good” were excluded from the study.

All participants of the examined group were treated with the second generation neuroleptics. The impact of antipsychotic treatment on brain tissue parameters is not known precisely. Several available studies indicate that antipsychotic treatment may contribute to changes in the degree of WM diffusivity of the left frontal lobe [38] and central cerebellum peduncles [39]. No such correlations were described for ALIC.

To guarantee objectivity of the procedure the evaluating radiologist was blind to the study group. Each scan was assessed by two radiologists independently.

We used 1.5T magnets for DTI, which is the most accessible tool. Using 3T magnet would provide more precise data and should be considered in future research.

## Conclusions

Presence of statistically significant differences in the WM diffusivity of the brain in the right ALIC region between the EOS patients and the control group was found. Differences in tissues diffusivity were observed exclusively in the subgroups of women, which suggests that the final results of the comparison of groups largely depend on the variability found in the women-subgroup.

The lack of statistically significant differences in diffusion in men – with repeatedly confirmed higher frequency of schizophrenia diagnoses in this age group of boys – suggests that ALIC may be less important for determining the development of the disease in males.

The results of the study are one of the first findings which indicate possible involvement of the structures of the internal capsule in the development of EOS.

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