CASE STUDY

ACTA Vol. 15, No. 2, 2017, 201-219
NEUROPSYCHOLOGICA

Received: 11.10.2016
Accepted: 12.06.2017

A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

SPECIFIC NEUROPSYCHOLOGICAL AND NEUROPHYSIOLOGICAL DYSFUNCTIONS OF A PATIENT WITH FIRST-ONSET SCHIZOPHRENIA AND COMORBID WHITE MATTER DAMAGE

Paweł Krukow[1(A,B,C,D,E,F)], Kamil Jonak[2,3(A,B,C,D,E,F)], Justyna Morylowska-Topolska[1(A,B,C,D,E,F)], Hanna Karakuła-Juchnowicz[1,3(A,B,C,D,E,F)]

[1] Department of Clinical Neuropsychiatry, Medical University of Lublin, Poland
[2] Lublin University of Technology, Poland
[3] 1st Department of Psychiatry, Psychotherapy and Early Intervention, Medical University of Lublin, Poland

SUMMARY

Background: Contemporary research on the neurobiological determinants of schizophrenia is focused on the role of white matter abnormalities, studied mainly at the cellular level using Diffusion Tensor Imaging. At the same time, there are few reports on the effects of white matter damage that can be visualized in a typical MRI scan, on the brain function of schizophrenic patients. The aim of this study was to identify the specific features of the neuropsychological and neurophysiological functioning of a female patient with first-onset schizophrenia and comorbid white matter damage, which discriminated her from a healthy control and from a patient with an identical psychiatric diagnosis, but having no structural brain changes seen in an MRI scan. Identification of those features may help understand the role of subcortical brain dysfunctions in the aetiology and clinical picture of schizophrenia.

Case study: The investigation encompassed clinical, neuropsychological and neurophysiological assessment of two schizophrenic patients, of whom one had comorbid white matter damage imaged by structural MRI, and a healthy control. A number of areas of cognitive functioning were examined, including the speed of information processing and executive and memory functions. The study was conducted using EEG coherence analysis, power spectral density, and energy evaluation of neuronal activity with the Matching Pursuit algorithm.

Results: The study showed that, despite the fact that there were no differences in the psychopathological pictures of the schizophrenic patients, the neuropsychological and neurophysiological differences between them were substantial and related to the profile of cognitive impairments and the specific features of the brain function of the patient with abnormalities in the white matter: that patient's EEG showed discoherence in the anterior part of the brain, reduced diversity of the dominant frequency of neuronal activity, and pathologically increased energy parameters for low-frequency bands.

Conclusions: Comorbidity of white matter damage with schizophrenia has a potentially significant effect on cerebral activity giving rise to specific information processing deficits. Further research in this area should be conducted with a view to determining biomarkers of mental diseases and improving the validity of clinical psychiatric diagnosis.

Key words: schizophrenia, white matter, coherence, Matching Pursuit, cognitive speed

INTRODUCTION

Though it has been described for at least a dozen decades and is still a major cause of severe social disability of a relatively stable proportion of people coming from different cultures, schizophrenia remains a disease, or a group of diseases, whose nature is still not fully understood by medical science. Contemporary neuroscientific research on schizophrenia seems to be concentrated, among others, on dysfunctions of the white matter (WM), which is largely due to the development of neuroimaging methods, which have, for a few years now, allowed researchers to precisely visualize the structure of WM at the level of individual axonal fibres and to investigate other biochemical parameters relating to the function of WM (Kubicki et al., 2007), most often using Voxel-Based Morphometry (VBM) and Diffusion Tensor Imaging (DTI).

In most studies of patients with schizophrenia, structural assessment of WM using these techniques confirms the existence of abnormalities/differences compared with healthy individuals. What is more, it has been shown that these changes are not a result of pharmacological interventions and are already present in first-onset patients, which suggests that they do not result from factors secondary to the chronic condition (Friedman et al., 2008; Kubicki et al., 2002, 2003, 2007; Zalesky et al., 2011; Samartzis et al., 2013). The abnormalities relate primarily to the corpus callosum, white matter fibres of the internal capsule, arcuate fasciculus and uncinate fasciculus, and other fibres connecting basal ganglia with the frontal and the temporal cortex, i.e. long fibres and clusters of axonal, association, and projection fibres (Hubl et al., 2004). Moreover, global disturbances in WM pattern asymmetry/symmetry have been observed in patients with schizophrenia compared to healthy controls (Park et al., 2004; Geschwind & Galaburda, 1985). At the tissue level, the abnormalities imaged using DTI are mainly (but not exclusively) myelin damage, gliosis, and tissue oedema. The results of neuroimaging studies, which repeatedly confirm WM abnormalities in schizophrenia, give rise to the question of whether these changes affect brain function and, above all, whether they significantly correlate with the various dimensions of the psychopathology of psychosis. In one study (Zalesky et al., 2011), a question was posed whether the cytoarchitecture of WM in patients with schizophrenia, compared to healthy controls matched for demographic characteristics, was disturbed and whether these disturbances were accompanied by functional impaiment of neural networks. The study was conducted using hybrid neuroimaging techniques and mathematical modelling of neural networks. Two measures of global network organization were found to be reduced in patients with schizophrenia: 1) nodal degree, i.e. the total number of connections within a network and between networks, and 2) network efficiency, a measure of how well a network supports distributed processing of information. Additionally, the researchers identified specific networks characterized by a dysfunction in the clinical group, which were located in the temporal and frontal regions and fronto-temporal connections. These researchers also localized a micro-circuit which in

healthy individuals showed strong connectivity and a high information exchange efficiency but did not exhibit network characteristics in patients. This dysfunction affected a brain region which overlapped with the superior longitudinal fasciculus – one of the longest bundles of association fibres in WM. These results are one of the main empirical arguments in favour of an impact of structural abnormalities in WM in patients with schizophrenia on brain activity and neural network performance. The relationship between WM and the psychopathology of schizophrenia has been repeatedly confirmed in various studies (Szeszko et al., 2008; Volpe et al., 2008; Benetti et al., 2013). In an exploratory work by Makris and colleagues (2010), which involved 88 schizophrenia patients and 40 matched healthy controls, the association between WM abnormalities and schizophrenia symptomatology was demonstrated using an MRI volumetry-based semi-automated white and grey matter parcellation technique without limiting the imaging to the *Region of Interest*. Based on a preliminary analysis of the results of neuroimaging, 81 brain regions (parcellation units) were isolated and then 12 larger regions with high volumetric specificity were identified. The clinical picture of the patients was assessed using PANNS, SANS, and SAPS. The authors found that the regions with abnormally increased WM volume (occipital and subcortical temporal regions) correlated positively with positive symptoms, e.g. auditory hallucinations and delusions, while regions with an abnormally decreased volume (e.g. paralimbic regions) correlated negatively with negative symptoms, e.g. alogia. All the results cited above, which are only a small part of the data available in world literature, confirm the significant relationship between the risk of schizophrenia, its psychopathology, response to drug treatment (Reis-Marquez et al., 2014) and other features of the clinical picture of schizophrenia on the one hand and the structure and functions of the white matter on the other. At the same time, it should be noted that there exist neurodegenerative diseases of WM with an onset age similar to that most common for schizophrenia, in the course of which, patients show neuropsychiatric symptoms and a clinically significant change in behaviour, which may be incorrectly diagnosed as schizophrenia. A WM disease that is most often confused with schizophrenia is metachromatic leukodystrophy, a condition which affects children and young adults and is caused by a deficiency of arylsulphatase A (ARSA) and accumulation of metachromatic sulphatide deposits in the nervous system and internal organs. There are reports of cases of onset of psychiatric symptoms (hallucinations and psychomotor agitation) in young adults initially diagnosed as signs of schizophrenia, which were unequivocally identified in later genetic tests to be symptoms of metachromatic leukodystrophy (Baleja-Stawicka et al., 2008). Similarly, neuropsychiatric symptoms which can initially be diagnosed as schizophrenia, have been described to predominate in some individual patients in the early stages of multiple sclerosis (Aggarwal et al., 2011), in acute disseminated encephalomyelitis (ADEM), which is a rare, delayed complication of measles manifesting, among others, in adolescents and young adults (Nasr, Andriola, Coyle, 2000), and potentially in many more WM diseases of different etiologies (e.g. secondary neuropsychiatric symptoms have

been described in severe leukodystrophies due to toluene poisoning). This suggests blurring of the boundary between endogenous development of schizophrenia and *„schizophrenia-like"* diseases, in which primary damage to WM, especially in the early stages of these diseases, produces psychopathological symptoms without obvious neurological damage.

Though it is true that structural changes to WM in schizophrenia are well-documented, it should be noted that most of the results come from studies which use advanced high-resolution neuroimaging methods which allow researchers to observe changes in brain tissue which are imperceptible in classic structural neuroimaging used in clinical practice. Relatively few studies address the specificity of neuropsychological and neurophysiological functioning of those patients who have developed schizophrenia which meets the diagnostic criteria of both ICD-10 and DSM-V, with axial symptoms and changes to WM which can be captured in a typical neuroimaging examination and which can be identified by visual evaluation of MRI scans. The few works which do concern such patients suggest that WM hyperintensities are typical of older patients, who have suffered from schizophrenia for a long time, and that they have a genesis similar to WM changes that occur in other populations, i.e. angiogenic or neurodegenerative (Rivkin et al., 2000).

The present work is a comparative case study which describes the clinical, neuropsychological, and neurophysiological functioning of a young female patient with a first psychotic episode and numerous changes to WM identified during her first psychiatric hospitalization by a routine MRI of the head. It was assumed that the patient would differ in these specific dimensions from a demographically matched healthy control and a patient diagnosed with schizophrenia without perceptible structural abnormalities in the MRI scan. Taking into account the findings of neuropsychological studies of damage to WM in other diseases (Filley, Kleinschmidt-DeMasters 2001; Filley, 2012; Krukow, 2014), we hypothesized that the patient with schizophrenia and WM damage would be characterized by greater impairment of those cognitive and regulatory functions which required integration of multiple individual cognitive processes, such as executive functions, and a significant cognitive retardation. We also supposed that the patient's neurophysiological indicators would point to incoherence of neuronal activity. An important problem to be considered was also the hypothetical similarity between the two schizophrenic patients, given the findings on WM function in patients with schizophrenia outlined above.

METHODS

Clinical evaluation

The clinical evaluation of the patients included a review of their medical history, especially the data related to the dynamics of their clinical pictures, some biological and neuroimaging tests, pharmacotherapy used during the experiments and their scores on PANSS and the Birchwood Insight Scale (Birchwood et al., 1994). The patients completed the scales twice: on admission, when they

suffered exacerbation of the disease, and before discharge, after partial remission had been achieved.

Neuropsychological assessment

The neuropsychological evaluation focused on the analysis of those functions which, according to literature data, may be impaired as a result of damage to WM, namely, executive functions, including working memory, learning, short- and long-term memory, and the speed of information processing. Additionally, we considered the potential impact of WM damage on social cognition – a process which is often impaired in patients with schizophrenia and is related to their functional outcome.

Executive functions were evaluated using methods derived from the ™MATRICS Consensus Cognitive Battery, which is a battery of neuropsychological tests specifically designed to assess cognitive deficits of patients with psychotic disorders. The Letter–Number Span (LNS) test was used to evaluate auditory working memory. The test material consisted of strings of letters and numbers listed in different orders, with an increasing number of stimuli. A respondent's task was to rearrange the order of the stimuli she heard and to report them beginning with the numbers in ascending order, and then the letters in alphabetical order. For instance, if the input string was J-3-N-1, the subject had to report the stimuli as 1-3-J-N. This task was, therefore, not dependent solely on auditory short-term memory (as are parts of the Digit Span subtest of the WAIS-R and WAIS-III scales), but required an active processing of stimuli using the phonological loop in working memory (Neuchterlein et al., 2008). Visual-spatial working memory was evaluated using the two-part Spatial Span Test (SST) taken from Wechsler's Memory Scale – Third Edition (WMS-III). In the first part of the test, the subjects were asked to repeat a sequence of cubes arranged in a spatial array and unnumbered (on the side shown to the respondent) as they were given. More cubes were presented each time. In the second part of the test, the subjects had to reproduce the sequence of cubes displayed by the investigator but in a reverse order. The result of the two tests was the sum of raw scores obtained for each task, reported as normalized T-scores and as a percentage. Another instrument used for assessing executive functions, especially planning, foresight and monitoring of one's own activity was the MATRICS™ Neuropsychological Assessment Battery® mazes subtest, which in the original battery is part of the Executive Functions Module (Ster and White, 2004). The test consists of seven tasks of increasing difficulty in which a subject has to find her way out of a paper-and-pencil maze as fast as she can but in keeping with specific rules. The mazes are scored based on whether the subject has completed the tasks in accordance with the rules (participants are cautioned not to cross the solid lines marking the maze walls and not to lift their pencils from the paper once they have started the task) and completion time, which translates into extra points. If the subject reaches a dead end, she can go back, but must cross back over her own lines, which adds to completion time. The test also measures qualitative features such

as long latency before starting a maze, an impulsive start, a haphazard approach, and crossing line errors. The overall result of the test is the sum of raw scores reported as normalized T-scores and as a percentage. Impaired performance on the maze-tracing test traditionally has been found to be related to frontal lobe lesions. Learning and verbal memory were evaluated using the California Verbal Learning Test (CVLT, Delis et al., 1987) adapted into Polish by Łojek and Stańczak (2010). CVLT is an instrument which draws on the process-oriented approach. It is based on learning a list of semantically related words presented as a shopping list, and is often used in neuropsychological assessment of patients, including those with schizophrenia (Fiszdon et al., 2003; Stone et al., 2011). CVLT is used to evaluate short- and long-term memory, learning strategies, stimulus retrieval and recognition, and learning errors. The test, also the Polish version, has good psychometric properties, which makes it a reliable and valid method of assessing various memory mechanisms (Strauss, Sherman and Spreen, 2006; Łojek and Stańczak, 2012). The last diagnostic instrument used in the present study was the Reading the Mind in the Eyes Test Revised Version (Baron-Cohen et al., 2001) designed for the assessment of social cognition. This tool consists of 36 photographs of the eye region of the face. A participant is asked to recognize the mental state (e.g., terrified, amused, sceptical) of the person in the picture and choose one of four response options that describes it accurately. The scores on this test significantly discriminate between healthy people and adults with Asperger syndrome or high-functioning autism, i.e. those clinical populations which have been identified to have problems with mentalisation. As the examples given above show, the facial expressions presented in the photographs do not correspond solely to basic emotions, but also to cognitive states, which broadens the range of the aspects of social cognition the test evaluates compared to the traditional Ekman–Friesen set of emotional expressions (1978). Research indicates that patients with schizophrenia also achieve worse results in this area (Geraci et al., 2012), even after controlling for the mediating effect of IQ.

Neuropsychological examination was conducted during one meeting, in the same order in all subjects.

Neurophysiological assessment: methods of EEG analysis

Recording

Electroencephalographic examination was performed continuously for 20 minutes in the same way in all subjects. The sampling frequency was 256 Hz, and the signal was filtered using a bandpass filter with a range of 0.5–200 Hz. The EEGs were recorded with a 22-channel recorder, from Ag/AgCl electrodes mounted on an elastic cap. During the recording, the patients were subjected to photostimulation and hyperventilation. The patients kept their eyes closed most of the time, and opened them only when asked to do so by the technician. The impedance of the electrodes was <10 kOhm.

Preliminary analysis of the signal

The signal was stored digitally in the form of EDF (European Data Format) files using DigitTrack software. The first signal analysis was carried out by a technician after the examination and was focused on removing the most visible muscle and motion artifacts. The next step was independent component analysis (ICA) performed in MATLAB (Eeglab toolbox). Signal filtering using the ICA algorithm was performed to remove artifacts that could mask/interfere with the information contained in the signal, and which could not be removed by conventional methods (Paszkiel, 2013).

Spectral analysis of the signal

The first numerical analysis used to process the EEG signal was spectral analysis based on the power spectral density (PSD) function. Spectral analysis was carried out in the MATLAB computing environment. The aim of the analysis was to decompose the EEG signal into bands corresponding to the individual EEG rhythms (Ahirwal & Iondhe, 2012). 10-second time windows selected from the entire resting recording of each individual subject were analyzed. The power spectral densities were obtained using the Fast Fourier Transform (FFT) separately for each channel. The simplest representation of power spectral density is the multiplied Fourier integral of the signal and its conjugate:

To make the results clearer, power spectral density plots were presented in a logarithmic form. The logarithmic scale shows the results in dB, which means that the successive values on the power spectral density axis (e.g., 20, 10 , 0, -10, -20 correspond to 100, 10, 1, 0.1, 0.01, respectively).

Coherence

To better understand the changes in the EEG signal, we used the results of PSD to calculate the coherences of pairs of electrodes. According to the dependency saying that cross-spectra provide information about how components with specific frequencies differ from one another, we used the cross-spectrum module to obtain information about the common component amplitude and, by determining the phase, to obtain the value of the phase lag at a given frequency. A normalized measure of the relation between signals in the frequency domain is called coherence, and it is used when there are linear relationships between signals given by (Kay & Steven, 1988):

Where <> is the mean and are complex spectra calculated using the Fourier transform for signal X and Y, respectively, in the i-th time window.

The Matching Pursuit Algorithm

To see how the energy of the EEG signal was distributed in the time–frequency domain, we used the Matching Pursuit algorithm (Durka, 2007). The analysis was performed using the same portions of the EEG signal as in the spectral analysis. The algorithm decomposed the signal into a linear expansion of waveforms selected from a redundant dictionary (Mallat & Zhang, 1993). The

dictionary functions can be described as translations (u), dilations (s), and modulations () of a window function:

A Gabor atom obtained for a Gaussian envelope is a function given by (Durka, 1999):

Signal energy analysis is best performed using a time-frequency dictionary of Gabor functions, because these functions are well localized in time–frequency space. Gabor atoms represent the areas of largest concentration of energy in the signal. By using a combination of Wigner transform and signal represented as a sum of Gabor functions of the matching algorithm, we obtained signal energy density in the time–frequency domain:

An EEG signal decomposed by MP is represented by a spectrogram which shows the precise energy density distribution in the signal.

RESULTS

Clinical data

The patient with schizophrenia and structural changes to the white matter (SCH+WM) was a 23 year old single woman, a third year student of humanities. She lived with her family. The first prodromal symptoms had begun two years prior to hospitalization. The woman was admitted to hospital on account of a considerable deterioration in her mental state presenting as attention deficit, anxiety, and prominent disorganization of behaviour and thinking. At the beginning of hospitalization, the patient presented with grossly disorganized speech, especially evident in semantic abnormalities; she also periodically showed strong anxiety and inappropriate affect not suited to the content of her utterances. The patient's behaviour suggested that she most probably suffered from auditory hallucinations. She also expressed persecutory and referential delusions. She admitted to having thoughts of resignation. Routine laboratory tests, an EEG test and an MRI of the head were performed. The patient was consulted by a neurologist; the neurologic examination revealed no deviations from the norm. Following the recommendation of the neurologist, the patient was tested for Lyme disease (infection caused by the spirochete Borrelia burgdorferi) – negative test results were obtained.

The patient was treated with Olanzapine 20 mg. The mental state of the patient gradually improved and positive symptoms resolved. The improvement also concerned her activity in the ward. Her sleep and appetite gradually stabilized. The patient, however, gained only partial insight into her disease. She was discharged home with instructions to continue her treatment on an outpatient basis and have the MRI repeated in six months as recommended by the consultant.

The patient's score on the PANSS was 113 points on admission and 75 points at the time of discharge from the clinic – a difference of 38 points. On admission, she scored 7.5 points on the Birchwood Insight Scale, and 8 points at discharge, which shows there was no major change in her insight into the disease.

The clinical neurophysiologist who interpreted the results of the patient's resting EEG found *„Bilateral changes in the fronto-temporal region, with a marked tendency to generalize; groups of slow theta and delta waves, more rarely short paroxysmal discharges (slow and sharp waves). Irregular basic activity, with quite a high alpha activity and diffuse slow delta and theta waves. An abnormal recording*".

In the neuroimaging examination, the neuroradiologist found the presence of more than seven foci of white matter hyperintensities seen on PD and T_2-weighted MR including fluid attenuated inversion recovery sequence imaging present in both hemispheres, size up to 8 mm. The changes were localized both in the deep white matter and periventricular. One of them (on the border of the left frontal and parietal lobes, with a diameter of 3 mm) showed a strengthening intensity after intravenous administration of contrast. The neuroradiologist did not point to any specific aetiology of the changes he described, suggesting that they may have had a post-inflammatory, demyelinating or ischemic character.

The schizophrenic patient without changes to the white matter (SCH-WM) was a 25-year-old single woman. At the time of the study, she lived with her parents and siblings. She had a university degree but was currently unemployed and financially supported by her family. The onset of symptoms had likely occurred during her university years with the patient presenting with symptoms of derealisation and depersonalisation. The disease had exacerbated four years prior to the study. Since that time, the patient had expressed delusions of suffering from a disease caused by bacterial poisoning; she was convinced that the parasites passed out through the skin and subcutaneous tissue and that she was healed that way. The patient had not left home for many months; she avoided contact with family and friends and periodically showed psychomotor agitation and aggressive behaviour towards members of her household.

At discharge, the woman was calm and behaved appropriately; her mood and psychomotor drive were regulated. She denied having hallucinations or suicidal thoughts. She did not spontaneously express delusions. The subject did not gain insight into her disease. She was treated with Olanzapine at a dose of 20 mg daily. An MRI was performed in the same laboratory and encompassed the same parameters as that of patient SCH+WM. The report said that the visualized brain structures did not show any structural abnormalities. Also the resting EEG of the patient showed no abnormal patterns.

On admission to the Department of Psychiatry, her score on the PANSS scale was 96 and at discharge it was 76, a difference of 20 points. At the first examination using the Birchwood scale, the patient scored 11 points, and at the second examination, before discharge, 10.5 points, which showed, just as in the case of patient SCH+WM, that there were no significant changes in insight over the study period.

It should be noted that the severity of psychopathological symptoms measured with PANSS was almost identical for the two patients at the time of the neuropsychological and neurophysiological assessments; the patients also received similar pharmacological treatment.

The healthy control (HC) was also a woman, aged 24, with a university degree. She was given an MRI scan and an EEG, using the same equipment and parameters as in the previous two cases. The tests did not show any structural changes in the nervous tissue or pathologies of the electrophysiological activity.

Results of neuropsychological assessment

The participants' scores on the various neuropsychological assessment scales are shown in Table 1. The cognitive dimensions studied were divided into eight categories, which included, among others, executive functions, working memory, memory functions and learning, cognitive processing speed and social cognition.

An analysis of the results showed that the schizophrenic patients generally had poorer scores than the healthy control. The difference between patients SCH-WM and SCH+WM concerned, in particular, executive functions, with SCH+WM patient having scored very low on the Mazes subtest (1.1%), which showed her neurological functions within this area were distinctly impaired. Another difference concerned the speed of cognitive processing for which patient SCH + WM again obtained a very low score compared to the other schizophrenic patient. Differences in other areas of cognition were not so pronounced. A comparison of cognitive performance, as indicated by T-scores, relating to auditory

Table 1. The participants' scores on the various neuropsychological assessment tests as indicators of their functioning in specific cognitive domains

Cognitive dimensions	Indicators	HC	SCH-WM	SCH+WM
Executive functions: planning and problem solving	Maze subtest from MATRICS™ Battery: - total points - qualitative features	47 T-Score / 38%	40 T-Score / 16% Long latency before beginning mazes	27 T-score / 1.1% Impulsive start, haphazard approach
Auditory working memory	Letter-Numbers Span test from MATRICS™ Battery: - total points	56 T-Score / 73%	44 T-Score / 27%	38 T-score / 11%
Visuo-spatial working memory	Spatial Span Test from MATRICS™ Battery: - total points	55 T-Score / 69%	48 T-Score / 42%	45 T-score / 34%
Memory: retrieval and recognition in verbal learning	CVLT: - Level of total recall / List A - Interference / List B - Long-Delay Recall - Recognition	 9* 9 8 10	 5 6 6 5	 4 7 6 5
Learning strategies	- Semantic Clustering - Serial Clustering - Recall Consistency	8 7 7	4 6 7	7 5 4
Errors in learning	- Perseverations - Intrusion errors	8 8	7 4	8 5
Cognitive processing speed	Symbol Coding test from WAIS-R	13**	6	3
Social cognition	Reading the Mind in the Eyes Test-Revised Version	34 points / 89%	22 points / 58%	27 points / 71%

*Note. * standard ten scale, ** standard scores (with a mean of 10 and a standard deviation of 3)*

and visuo-spatial memory showed that the differences were smaller than for the cognitive areas discussed above; however, SCH+WM patient was characterized by poor auditory working memory quantified as percent of correct responses. Memory processes discriminated the least between the two schizophrenic patients. Patient SCH+WM performed better than the other subjects in Semantic Clustering and made fewer learning errors, which showed that these aspects of memory organization were not impaired in this patient, in stark contrast to executive functions. A comparison of the results of RMET-R, measuring some aspects of social cognition, indicated that patient SCH - WM scored the lowest in this area, also when compared to SCH+WM patient, which may be associated with the clinical picture of this former person, in which there dominated symptoms of delusions, commonly correlated in the literature with impaired social cognition (Bentall et al., 2009). One should also pay attention to the internal differences in the results of neuropsychological assessment of each subject. In the case of the healthy control and SCH-WM patient, the differences between the results were minor: the healthy person obtained high and higher-than-average scores across the tests and SCH-WM patient, average and lower than average; the cognitive profile of patient SCH+WM was the most varied. On the one hand, she scored very low on executive function and cognitive speed tests and, on the other hand, obtained higher-than-average scores on CVLT scales related to the use of the semantic learning strategy and resistance to interference. This suggests that SCH+WM patient had isolated cognitive deficits against the background of relatively normal memory and social cognition. This brings the cognitive profile of the patients with schizophrenia and comorbid damage to WM close to that of patients with acquired, relatively localized, or at least not generalized, brain damage. The results of neuropsychological tests indicate a dysfunction of prefrontal and subcortical areas (cognitive speed) in this patient, contrasted with more generalized cognitive deficits observed in SCH-WM patient.

Analysis of neurophysiological data

Coherence analysis

Coherence analysis of EEG signal was conducted for eight pairs of electrodes which were divided into interhemispheric pairs, with both electrodes located over one hemisphere, and interhemispheric pairs, with electrodes located over homologous areas of the two hemispheres. We selected electrodes located over the anterior part of the brain, which was dictated by the localization of the structural abnormalities of WM in the patient who was the main subject of analysis (SCH+WM). Coherence was calculated separately for each frequency band; the analysis included alpha and theta bands, because we expected to find the largest differences among the subjects in these ranges. The table below shows the results of coherence analysis (Table 2).

A comparison of coherence coefficients allowed us to observe the specific characteristics of the brain function of the subjects. The means of intra- and in-

Table 2. Summary of coherence coefficients for the three subjects in the theta and alpha bands

		Theta			*Alpha*		
		HC	SCH-WM	SCH+WM	HC	SCH-WM	SCH+WM
Intrahemispheric pairs	F7 – T5	0.34	0.13	0.56	0.18	0.19	0.16
	F8 – T6	0.17	0.45	0.21	0.40	0.43	0.04
	F3 – P3	0.67	0.40	0.53	0.68	0.54	0.21
	F4 – P4	0.73	0.50	0.47	0.70	0.65	0.12
	M	**0.47**	**0.37**	**0.44**	**0.49**	**0.45**	**0.13**
Interhemispheric pairs	F3 – F4	0.68	0.75	0.73	0.85	0.87	0.75
	F7 – F8	0.33	0.34	0.17	0.54	0.46	0.35
	T3 – T4	0.25	0.43	0.18	0.40	0.26	0.16
	P3 – P4	0.68	0.76	0.55	0.78	0.73	0.52
	M	**0.48**	**0.57**	**0.40**	**0.64**	**0.58**	**0.44**
Mean of intra- and interhemispheric coherences		**0.475**	**0.47**	**0.42**	**0.56**	**0.51**	**0.28**

Note. HC: healthy control, SCH - WM: patient with schizophrenia without structural brain changes recorded in MRI, SCH + WM: patient with schizophrenia and comorbid white matter changes

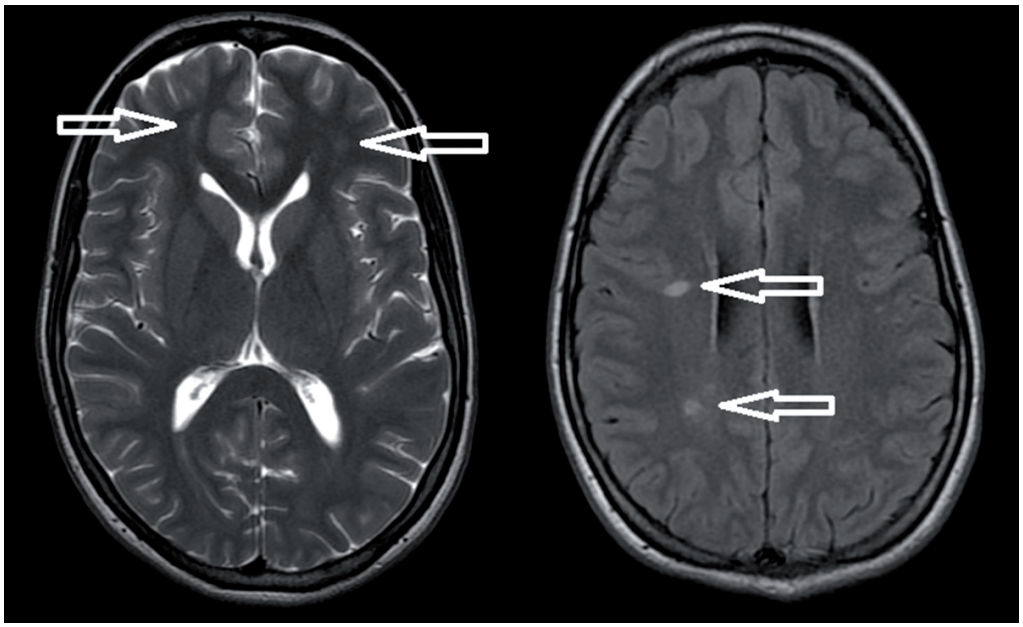
terhemispheric coherences indicated that the EEG of the healthy control (HC) had the best coherence parameters: HC had the highest intrahemispheric coherences and generally the highest coherences for the alpha frequency. The results of patient SCH-WM were only slightly different from those of the healthy individual, but were lower for the alpha band and minimally lower for the theta band. It should be noted that both of these subjects had higher coherence values in the alpha frequency range compared with the theta range. The coherence values for patient SCH+WM were markedly different from those of the other subjects. First of all, mean coherence in the theta band was substantially higher than in the alpha band. This patient generally had the lowest coherence values, with particularly low coherences for the alpha band, especially with regard to intrahemispheric coherences which were very low compared with those of the other subjects, even the one with schizophrenia. The mean intrahemispheric coherence for the alpha band (M = 0.13) suggests a major impairment in the frequency synchronization of fronto-temporal and fronto-parietal connections in the cortex.

Power Spectral Density (PSD)

In order to present the global changes in the EEG signal, spectral analysis was performed. The results are presented as power–frequency plots for all electrodes, separately for each person.

Figure 2 compares three frequency domain plots of power distribution. Each figure shows a set of 19-EEG signals, each representing a separate electrode arranged according to the 10-20 standard. Fig. 2 (a) shows the power–frequency relationship for the healthy person. In this case, the value of the dominant α rhythm was the highest among the analysed cases. The second plot (b) shows the PSD of the EEG recording of patient SCH-WM. The PSD for this subject, just like for the previous subject, was the highest for the α rhythm; there were no

a. b.



Note: a) arrows pointing white natter damage in the frontal areas, b) arrows pointing white natter damage in the temporal and parietal areas. White matter hyperintensities are visible in MR images made with and without contrast

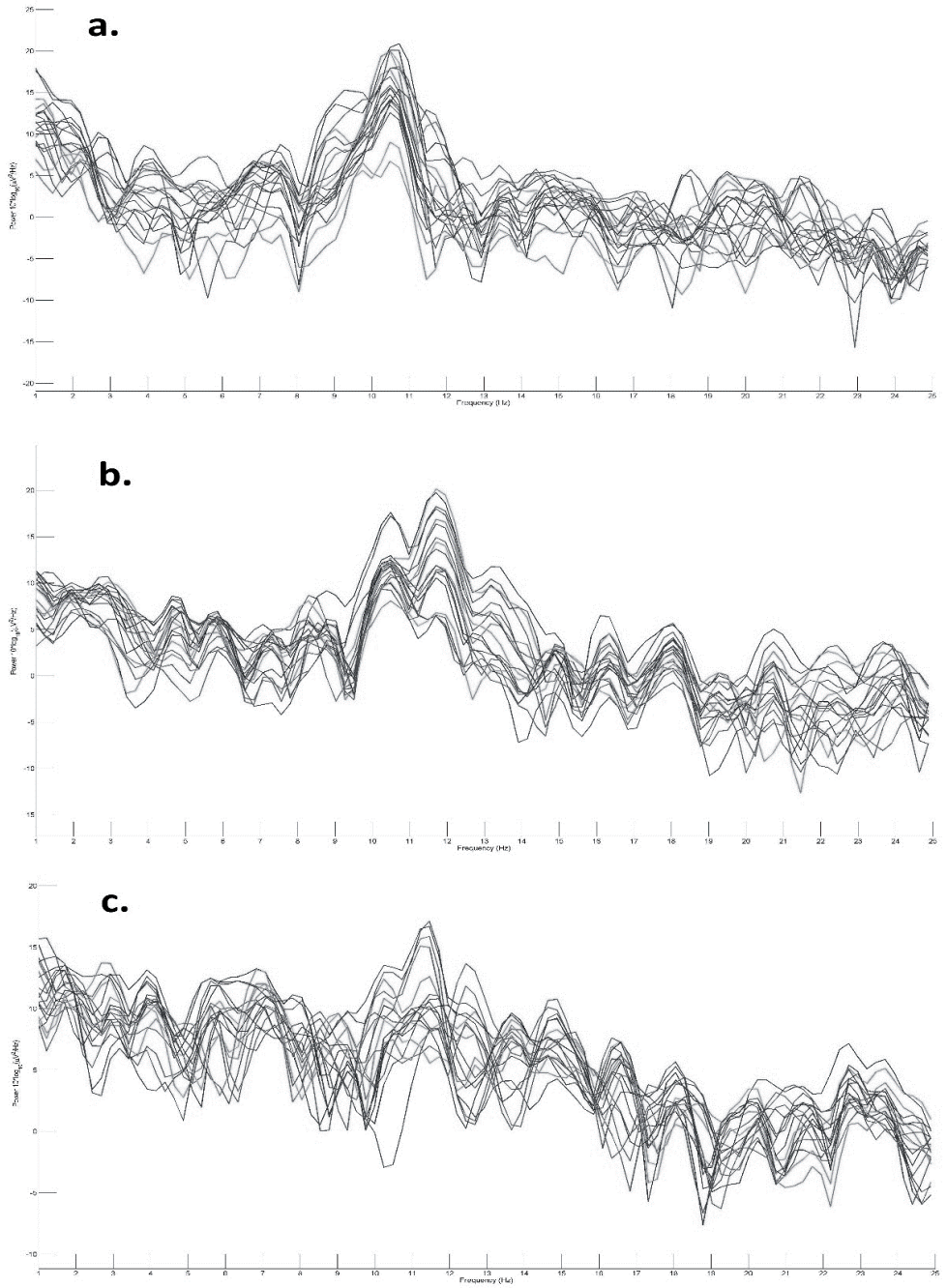
Figure 1. MRI scan of SCH+WM patients brain

significant increases in PSD for the remaining rhythms. The last plot (c) shows the PSD of patient SCH+WM. In this plot, high PSD values were recorded for each of the rhythms. As in the two previous plots, the α rhythm was the dominant activity, but PSD values for the other rhythms were only slightly lower than for the α rhythm.

A special case was the PSD value for waves in the θ (theta) band, which was more than five times higher (the curves are plotted in the logarithmic scale) than for patient SCH-WM and nine times higher than for the healthy person. Also β waves had higher values in patient SCH+WM than in the remaining two subjects, for whom β waves were only found in trace amounts. This may indicate that in patient SCH+WM, there was no dominant frequency of biosignals polarizing the cerebral cortex. It is difficult to unequivocally define the etiological causes of these dysfunctions; one of the reasons for those abnormalities may be the pathological changes to WM visualized in the MRI image.

Matching Pursuit Analysis

The MP algorithm was used to show changes in signals for the individual electrodes. Based on the results of the analysis of coherence between pairs of channels, the following electrodes were selected for MP analysis: F8, T6, T3, and T4. MP analysis was performed using SVAROG software.



Note: a) a recording of the EEG signal for the healthy control, showing a marked increase in power for the α rhythm. b) An EEG recording for the patient with schizophrenia without structural abnormalities visualized in MRI (SCH - WM); again maximum power was found for the α rhythm. c) A plot showing small fluctuation in EEG power for the patient with schizophrenia and white matter abnormalities (WM + SCH), the α rhythm still dominates, but the difference is not significant

Figure 2. Power – frequency curves for all electrodes for each of the three subjects

Table 3. Results of the MP algorithm applied to data for all subjects for electrodes F8, T6, T3, and T4

	HC								SCH-WM								SCH+WM							
Channels:	F8		T6		T3		T4		F8		T6		T3		T4		F8		T6		T3		T4	
	E	An	E	An	E	An	E	An	E	An	E	An	E	An	E	An	E	An	E	An	E	An	E	An
Delta:	701	17	710	15	606	13	487	10	664	14	532	11	498	14	583	13	843	14	950	14	1061	15	830	13
Theta	225	8	213	6	205	5	232	8	314	8	308	7	266	9	250	6	658	10	674	10	892	13	685	11
Alpha	705	14	1522	22	1082	15	634	14	862	17	1236	18	803	17	972	17	708	15	1309	16	782	13	754	13
Beta:	235	10	198	6	641	17	439	16	354	11	516	12	293	10	499	13	447	11	589	10	453	9	635	13
ΣE:	1866		2643		2534		1792		2194		2592		1860		2304		2656		3522		3188		2904	

Note: E – value of energy in a band; ΣE – sum of energies; An – number of Gabor atoms in a band

Table 3 compares signal energies for the individual EEG rhythms for each channel and for each subject. The last row of the table shows the sum of energies of the signal recorded at each electrode in a 10s time frame. Maximum energy was recorded for all patients at electrode T6, where the dominant band was the rhythm, which is in line with the physiological characteristics of this cortical area. The energy of the trend was dominant for each measurement point in HC and patient SCH - WM; Patient SCH+WM was the only one for whom energy in the alpha rhythm was lower than in the and bands. This patient's EEG had the highest sum of energy (ΣE) for each electrode among the analysed EEG recordings.

Patient SCH + WM had increased energy values for other bands than patient SCH-WM and HC, namely, free bands were dominant in that patient's EEG, but not totally. These changes in the EEG recording of the patient with WM damage may have been caused by impaired generation of potentials in brain cells, which may have resulted in an increased voltage and changes in the polarization of the cell membrane. These types of impairments may lead to significant changes in an EEG recording, which is why we observed such fundamental differences in the PSD and MP of the analysed subjects.

DISCUSSION

The results of the present study indicate that the clinical picture and course of the disease, as well as psychopathological assessment of the two patients with a diagnosis of schizophrenia differed only slightly. Generally, it seems that the psychopathology of patient SCH + WM was dominated by symptoms of disorganization of cognitive processes and behaviour, while the clinical picture of patient SCH-WM was dominated by delusional symptoms. In contrast, a comparison of the results of neuropsychological and neurophysiological tests showed significant differences between the schizophrenic patients and the healthy control, and also between the two patients with and without WM abnormalities The neuropsychological profile of patient SCH + WM seems to resemble the profile of so-called subcortical type cognitive impairments (Cummings and Benson, 1984), with dominant executive impairment, cognitive slowing, but relatively preserved verbal memory, which, in turn, discriminates this patient from the typical profile of impairments described in the population of patients with schizophrenia, in which deficits of verbal memory are listed as one of the most common symp-

toms, correlated with abnormalities in the temporal cortex which are typical of this clinical population (Guimond et al., 2016). The analysis of resting EEG performed using the indicators of coherence, PSD and the Matching Pursuit algorithm further confirmed the differences in the brain function of patients SCH + WM and SCH – WM. In patient SCH + WM, coherence analysis pointed to a highly probable existence of a functional disconnection within the anterior part of the brain, particularly intrahemispherically. Coherences of 0.04 and 0.16 point to an almost complete disappearance of frequency synchronization of the different areas of the frontal lobe and connections of the anterior part of the brain with the parietal and temporal lobes. Previous studies corroborate the observation that prominent decreases in coherence parameters are significantly associated with white matter damage, which confirms the impact of these lesions on brain function especially in terms of neural network efficiency (Nunez et al., 2015). The remaining advanced methods of EEG analysis, also generated results suggesting specific changes in brain function in SCH + WM patient. These results show a recurring pattern of a certain sort of shift in the electrophysiological frequency and strength of the signal to markedly lower ones – also when compared to the other schizophrenic patient – or a reduction in the variability of the signal energy spectrum which leads to the absence of a dominant rhythm of neuronal activity. Although a case study does not allow one to formulate cause-and-effect hypotheses, it seems that the deep discoherence observed in the EEG recording of patient SCH + WM may be one of the bases of disorganization of the dominant EEG frequency; this suggestion, obviously, requires further empirical exploration in a cohort study.

It should also be noted that the two patients with schizophrenia were only negligibly discriminated by clinical features relating to the psychopathology of their disease, including those measured by the PANSS scale, a method specifically developed to quantify symptoms of schizophrenia. By contrast, as noted earlier, the results of neuropsychological and neurophysiological assessment highlighted the differences between the patients; in accordance with the assumptions of the study, it was demonstrated that the patient with schizophrenia and co-morbid damage to the white matter scored lower on the previously described cognitive and neurophysiological dimensions. This gives rise to a question, which does seem legitimate, about the accuracy of psychiatric diagnosis based on purely symptomatic classifications, in which the assessment regards primarily the psychological sphere, and neuroimaging and neurophysiological examinations are used merely to exclude the diagnosis of an exogenous psychotic process, which cannot be confirmed using these methods due to the lack of biomarkers of the disease. The lack of such biomarkers in a situation in which the boundaries between mental and neurological illnesses are blurred seems to be particularly aggravating to the practice of clinical diagnosis in psychiatry.

A good example of differential diagnosis based on objective indicators of specific parameters of brain function is the diagnosis based on the functional biomarkers developed by Kropotov and his colleagues (Kropotov, 2016; Pąchal-

ska et al., 2013). In one case study, which describes such a diagnostic process, the investigators undermined a diagnosis of schizophrenia which had been established three decades earlier (Trystuła et al., 2015) and applied an effective therapeutic intervention consistent with the results of EEG and psychiatric diagnosis verified using biomarkers. It seems that widespread use of neuropsychological and neurophysiological examination as complementary to clinical diagnosis and a search for more and more accurate cognitive and neuronal markers, particularly in cases of patients who are found to have structural brain abnormalities, might significantly increase diagnostic validity, and hence the effectiveness of therapeutic interventions in psychiatry.

CONCLUSIONS

The neuropsychological and neurophysiological analyses of the functioning of the patient with schizophrenia and comorbid white matter damage showed specific abnormalities in cognitive processes and electrophysiological activity, other than those observed in the patient with schizophrenia but without structural abnormalities visualized by MRI. The results of these analyses demonstrated this specificity more prominently than the clinical analysis of psychopathological symptoms. Comorbidity of a mental illness and damage to the white matter generates specific EEG abnormalities which confirm the negative impact of WM damage on brain function. The present study corroborates the claim that psychiatric diagnosis should avail itself of the wide spectrum of contemporary neuroscientific methods, especially in cases which require differentiation between an endogenous mental disease and neuropsychiatric effects of acquired brain injury.

REFERENCES

Aggarwal, A., Sharma, D., Kumar, R., Sharma, R. (2011). Acute Psychosis as the Initial Presentation of MS: A Case Report. International MS Journal,17 (2), 54-57.

Ahirwal, M.K., Iondhe, N.D. (2012). Power Spectrum Analysis of EEG Signals of Estimating Visual Attention. International Journal of Computer Applications, 42 (15), 22-25.

Baleja-Stawicka, I., Kwiecińska, E., Kłoszewska, I., Ługowska A. (2008). Leukodystrofia metachromatyczna jako przyczyna zespołu otępiennego i organicznych zaburzeń urojeniowych u młodych dorosłych osób – opis przypadku. Postępy Psychiatrii i Neurologii, 17 (3), 237-241.

Baron-Cohen S., Wheelwright S., Hill J., Raste Y., Plumb I. (2001). The “Reading the mind in the eyes” test revised version: a study with normal adults, and adults with Asperger Syndrome or high-functioning Autism. Journal of Clinical Psychology and Psychiatry, 2, 241-151.

Benetti, S., Pettersson-Yeo, W., Allen, P., Catani, M., Williams, S., Barsaglini, A., et al. (2015). Auditory Verbal Hallucinations and Brain Dysconnectivity in the Perisylvian Language Network: A Multimodal Investigation. Schizophrenia Bulletin, 41(1), 192-200.

Bentall, R.P., Rowse, G., Shryane, N., Kinderman, P., Howard, R., Blackwood, N., et al. (2009). The cognitive and affective structure of paranoid delusions: a transdiagnostic investigation of patients with schizophrenia spectrum disorders and depression. Archives of General Psychiatry, 66, 236-247.

Cummings, J.L. and Benson, D.F. (1984). Subcortical dementia. Review of an emerging concept. Archives of Neurology, 41 (8), 874-879.

Delis, D. C., Kramer, J. H., Kaplan, E., Ober, B. A. (1987). CVLT, California Verbal Learning Test: Adult Version: Manual. Psychological Corporation.

Durka P. J. (1999-2004) Między czasem a częstością: element współczesnej analizy sygnałów. http://brain.fuw.edu.pl/~durka/as/

Durka, P.J. (2007). Matching Pursuit Unification in EEG Analysis. Engineering in Medicine & Biology. London: Artech House.

Ekman, P., Friesen, W.V. (1978). Investigator's guide to the facial action coding system. Palo Alto, California: Consulting Psychology Press.

Filley, C.M. (2012). The behavioral neurology of white matter. 2nd ed. New York: Oxford University Press.

Filley, C.M., Kleinschmidt-DeMasters, B.K. (2001) Toxic leukoencephalopathy. New England Journal of Medicine 345, 42—432.

Fiszdon, J., Steven, M., Silverstein, M. Buchwald, J., Hull, J.W., Smith, T.E. (2003). Verbal memory in schizophrenia: sex differences over repeated assessments. Schizophrenia Research, 61 (2-3), 235-243.

Friedman, J.I., Tang, C., Carpenter, D., Buchsbaum, M., Schmeidler, J., Flanagan, L., et al. (2008). Diffusion tensor imaging findings in first-episode and chronic schizophrenia patients. The American Journal of Psychiatry, 165 (8), 1024-1032.

Geraci, A., Signorelli, M.S., Aguglia, E. (2012). Reading in the mind: a comparative study of out- and inpatients. Journal of Psychopathology; EPUB April 19.

Geschwind, N., Galaburda, A.M. (1985). Cerebral lateralization. Biological mechanisms, associations, and pathology: I A hypothesis and a program for research. Archives of Neurology, 42 (5), 428-459.

Guimond, S., Chakravarty, M.M., Bergeron-Gagnon, L., Patel, R., Lepage, M. (2016). Verbal memory impairments in schizophrenia associated with cortical thinning. NeuroImage: Clinical, 11, 20-29.

Hubl, D., Koenig, T., Strik, W., Federspiel, A., Kreis, R., Boesch, C., et al. (2004). Pathways that make voices: white matter changes in auditory hallucinations. Archives of General Psychiatry, 61 (7), 658-668.

Kay, S.M. (1988). Modern Spectral Estimation. Englewood Cliffs, NJ: Prentice-Hall.

Kropotov, J.D. (2016). Functional neuromarkers for psychiatry. Applications for diagnosis and treatment. London: Academic Press.

Krukow, P. (2014). Cognitive dysfunctions associated with white matter damage due to cardiovascular burden – determinants and interpretations. Polish Psychological Bulletin, 45 (3), 33-345.

Kubicki, M., McCarley, R., Westin, C.-F., Park, H.-J., Maier, S., Kikinis, R., et al. (2007). A review of diffusion tensor imaging studies in schizophrenia. Journal of Psychiatric Research, 41(1-2), 15–30.

Kubicki, M., Westin, C.F., Maier, S.E., Frumin, M., Nestor, P.G., Salisbury, D.F., et al. (2002). Uncinate fasciculus findings in schizophrenia: a magnetic resonance diffusion tensor imaging study. American Journal of Psychiatry, 159(5), 813–820.

Kubicki, M., Westin, C.F., Nestor, P.G., Wible, C.G., Frumin, M., Maier, S.E., et al. (2003). Cingulate fasciculus integrity disruption in schizophrenia: a magnetic resonance diffusion tensor imaging study. Biological Psychiatry, 54(11), 1171–1180.

Łojek, E., Stańczak, J. (2010). CVLT - Kalifornijski Test Uczenia się Językowego. Podręcznik. Warsaw: Pracownia Testów Psychologicznych PTP.

Makris, N., Seidman, L. J., Ahern, T., Kennedy, D. N., Caviness, V. S., Tsuang, M. T., et al. (2010). White Matter Volume Abnormalities and Associations with Symptomatology in Schizophrenia. Psychiatry Research, 183 (1), 21-29.

Mallat, S.G., Zhang, Z. (1993). Matching Pursuit With Time-Frequency Dictionaries. IEEE Transactions of Signal Processing, 41(12), 3397-3415.

Nasr, J.T., Andriola, M.R., Coyle, P.K. (2000) Adem: literature review and case report of acute psychosis presentation. Pediatric Neurology , 22 (1), 8-18.

Nuechterlein, K.H., Green, M.F., Kern, R.S., Baade, L.E., Barch, D.M., Cohen, J.D., et al. (2008). The MATRICS Consensus Cognitive Battery, part 1: test selection, reliability, and validity. The American Journal of Psychiatry, 165 (2) 203-213.

Nunez, P.L., Srinvasan, R., Fields, R.D. (2015) EEG functional connectivity, axon delays and white matter disease. Clinical Neurophysiology, 126 (1), 110-120.

Pąchalska, M., Pronina, M.V., Mańko, G., Chantsoulis, M., Mirski, A., Kaczmarek, B., Łuckoś, M., Kropotov, J.D. (2013). Evaluation of neurotherapy program for a patients with clinical symptoms of schizophrenia and severe TBI using event-related potentials. Acta Neuropsychologica, 11(4), 435-449.

Park, H.-J., Westin, C.-F., Kubicki, M., Maier, S. E., Niznikiewicz, M., Baer, A., et al. (2004). White matter hemisphere asymmetries in healthy subjects and in schizophrenia: a diffusion tensor MRI study. NeuroImage, 23 (1), 213-223.

Paszkiel, S. (2013). Wykorzystanie metody PCA i ICA do analizy EEG w kontekście usuwania zakłóceń. Pomiary Automatyka Kontrola, 59 (3), 204-207.

Reis Marques, T., Taylor, H., Chaddock, C., Dell'Acqua, F., Handley, R., Reinders, A. A. T. S., et al. (2014). White matter integrity as a predictor of response to treatment in first episode psychosis. Brain, 137 (1), 172-182.

Rivkin, P., Kraut, M., Barta, P., Anthony, J., Arria, A.M., Pearlson, G. (2000). White matter hyperintensity volume in late-onset and early-onset schizophrenia. International Journal of Geriatric Psychiatry, 15 (12), 1085-1089.

Stern, R. A., & White, T. (2004). Introduction to the Neuropsychological Assessment Battery (NAB). Journal of the International Neuropsychological Society, 10(Suppl. S1), S105.

Stone, W.S., Giuliano, A.J., Tsuang, M.T., Braff, D.L., Cadenhead, K.S., Calkins, M.E., et al. (2011). Group and site differences on the California Verbal Learning Test in persons with schizophrenia and their first-degree relatives: findings from the Consortium on the Genetics of Schizophrenia (COGS). Schizophrenia Research, 128 (1-3), 102-110.

Strauss, E., Sherman, E.M.S., Spreen, O. (2006). A compendium of neuropsychological tests (3rd edition). New York, USA: Oxford University Press.

Szeszko, P.R., Robinson, D.G., Ashtari, M., Vogel, J., Betensky, J., Sevy, S. et al. (2008). Clinical and neuropsychological correlates of white matter abnormalities in recent onset schizophrenia. Neuropsychopharmacology, 33, 976-984.

Trystuła, M., Zielińska, J., Półrola, P., Góral-Półrola, J., Kropotov, J.D., Pąchalska M. (2015). Neuromarkers of anxiety in a patient with suspected schizophrenia and TIA: the effect of individually-tailred neurofeedback. Acta Neuropsychologica, 13(4), 395-403.

Volpe, U., Federspiel, A., Mucci, A., Dierks, T., Frank, A., Wahlund, L.-O., et al. (2008). Cerebral connectivity and psychotic personality traits. A diffusion tensor imaging study. European Archives of Psychiatry and Clinical Neuroscience, 258, 292-299.

Zalesky, A., Fornito, A., Seal, M. L., Cocchi, L., Westin, C.-F., Bullmore, E. T., et al. (2011). Disrupted Axonal Fiber Connectivity in Schizophrenia. Biological Psychiatry, 69(1), 80–89.

Address for correspondence:
Department of Clinical Neuropsychiatry,
Medical University of Lublin,
ul. Głuska 2, 20-439 Lublin, Poland