Hemispherical differences in the two subgroups of schizophrenia identified by systematic cognitive neuropsychiatric mapping

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Original articles the thesis is directly based on

I. **Szendi I**, Racsmány M, Cimmer C, Csifcsák G, Kovács ZA, Szekeres G, Galsi G, Tóth F, Nagy A, Garab EA, Boda K, Gulyás G, Kiss JG, Dombi J, Pléh C, Janka Z. Two subgroups of schizophrenia identified by systematic cognitive neuropsychiatric mapping. Eur Arch Gen Psychiatr Clin Neurosci 2009 Oct 15. [Epub ahead of print] *(IF: 2.852)*

II. **Szendi I**, Kiss M, Racsmány M, Boda K, Cimmer C, Vörös E, Kovács ZA, Szekeres G, Galsi G, Pléh C, Csernay L, Janka Z. Correlations between clinical symptoms, working memory functions and structural brain abnormalities in men with schizophrenia. Psychiatry Res Neuroimag 2006;147:47-55. *(IF: 2.755)*

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Articles closely related to the thesis

- Racsmány M, Conway MA, Garab EA, Cimmer C, Janka Z, Kurimay T, Pléh C, **Szendi I**. Disrupted memory inhibition in schizophrenia. Schizophr Res 2008;101:218-224. *(IF: 4.240)*
- Cimmer C, **Szendi I**, Csifcsák G, Szekeres G, Kovács ZA, Somogyi I, Benedek G, Janka Z, Kéri S. Abnormal neurological signs, visual contrast sensitivity, and the deficit syndrome of schizophrenia. Prog Neuro-Psychopharmacol Biol Psychiatry 2006;30:1225-30. *(IF: 2.584)*

Selected papers related to the thesis

- Kéri S, Juhász A, Rimanóczy Á, Szekeres G, Kelemen O, **Szendi I**, Benedek G, Janka Z. Habit learning and the genetics of the dopamine D_3 receptor: evidence from patients with schizophrenia and healthy controls. Behav Neurosci 2005;119:687-693. *(IF: 3.071)*
- Kéri S, Szekeres G, **Szendi I**, Antal A, Kovács Z, Janka Z, Benedek G. Category learning and perceptual categorization in schizophrenia. Schizophr Bull 1999;25(3): 593-600. *(IF: 6.579)*
- **Szendi I**, Kovács ZA, Szekeres G, Galsi G, Boda K, Boncz I, Janka Z. Effects of a hypnotically altered state of consciousness on intensification of semantic processing. Int J Clin Exp Hypnosis 2009; 57(4): 382-401. *(IF: 1.551)*

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Szendi I, Cimmer C, Csifcsák G, Racsmány M, Szekeres G, Kovács ZA, Galsi G, Garab EA, Boda K, Janka Z. Splitting up nondeficit syndrome by the boundary of the two clusters identified by cognitive neuropsychiatric mapping. Eur Neuropsychopharm 2007;17(Suppl.4):S416. *(IF: 4.430)*

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Szendi I. A szkizofrénia változatossága. Neuropsychopharmacol Hung 2007;9(Suppl 1): 7-13.
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Selected book chapters related to the thesis:

Szendi I, Kis G, Racsmány M, Pléh Cs, Janka Z: Kognitív működések neuropszichológiai vizsgálata. In: Tariska P. (szerk.): Kortünet vagy kórtünet? Mentális zavarok idős korban. 2002 Budapest: Medicina. pp. 114-160.

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SUMMARY

We performed a robust cross-sectional study, including a systematic neuropsychological battery, assessment of clinical symptoms, neurological soft signs, morphogenetic anomalies and smell identification, and measurement of event-related potentials on 50 outpatients with schizophrenia in their compensated states. An explorative fuzzy cluster analysis revealed two subgroups in this sample that could be distinguished from each other on symptomatological, cognitive and neurological levels. The analyses have demonstrated that cluster 'Z' had more favourable, and cluster 'S' had more unfavourable (more *s*erious) characteristics.

The aim of a complementary analysis was to investigate the correspondence or incongruence between the S-Z neuropsychiatric schizophrenia clusters and the deficit-nondeficit syndromes. According to our analyses, the neuropsychiatric cluster S proved to be homogeneous, we did not find any parameters which would appropriately set apart deficit syndrome patients from nondeficit ones within cluster S. The nondeficit group in our study, however, proved to be inhomogeneous in several parameters, it was cleft in two along the border of the clusters S and Z fundamentally by cognitive features.

The third component of the research was a pilot study on cerebral structure in which we observed the reversal of normal L>R asymmetry to R>L asymmetry of the volumes of straight gyri (BA 11) in 13 young, male patients with schizophrenia. This gyrus in part plays a role in the short-time storing of visuo-spatial information. The main study established that 12 of the examined 13 patients belonged to cluster Z. The volume of the right straight gyrus was greater than the left one, and the visuo-spatial working memory performances were at the normal-level in the patients who belonged dominantly to the cluster Z.

On the basis of the above observations, the patterns of cognitive dysfunctions and neurological developmental anomalies equally indicate that in cluster Z there may be a predominantly unilateral, left frontal dysfunctioning, while in the more severe cluster S bilateral morbidity processes, with left and right frontal neural substrates may be present. These subgroups may have had partly different morbidity bases, therefore they might represent different types of schizophrenia, not only forms with different seriousness of the same type. However, as we did not find group differences in the more elementary levels, it is possible that there is a common morbidity root in the depth of the etiological basement of the clusters.

EXPLORING CLUSTERS

During the first decades of systematic research on schizophrenia, investigators attempted to determine the phenotype mainly by describing cross-sectional constellations of clinical symptoms and the longitudinal characteristics of their course. We can regard this as a phenomenological, horizontal surface analysis of the range of phenomena. According to recent observations, the dimensions currently describing the symptoms of schizophrenia (disorganization, psychosis and negative factors, or deficit-nondeficit) are supposedly not specific to the disease.

This study provides (’vertical’) insights into various levels of phenomenological mental, pathophysiological and etiological cerebral processes. The main question of our study was whether schizophrenia can be divided into subgroups with a series of systematic cross-sectional cognitive neuropsychiatric studies. We had two accessory questions as well: If subgroups could be separated from each other, what depths of the systems could their divergence be traced back to? And, if such diverging subgroups exist, do they suggest a unified morbidity or multiple ones?

Materials and methods

Subjects

Fifty patients (27 male, 23 female) with schizophrenia (DSM-IV) were selected from the outpatient clinic of the Department of Psychiatry, University of Szeged. All subjects were 18 to 69 years of age, the average number of years of education was 11.00 (SD=2.17), and the average full-scale IQ (WAIS) was 100.17 (SD=15.40). All of them were outpatients in stable interepisodic states under antipsychotic medication.

Clinical symptoms and neurosomatic alterations

Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS), the Scale for the Assessment of Negative Symptoms (SANS), and the Schedule for the Deficit Syndrome (SDS). Neurological developmental signs were assessed using the Neurological Evaluation Scale (NES). The potential pharmacogenic extrapyramidal symptoms were

assessed with the Simpson-Angus Scale (SAS), the Abnormal Involuntary Movement Scale (AIMS), and the Barnes Akathisia Rating Scale (BAS). A list of minor physical anomalies (MPAs) was used for mapping the malformations. The cross-cultural smell identification test (CC-SIT) was used for assessing smell identification.

Neuropsychological mapping

Verbal working memory capacity was measured with the Hungarian Digit Span Task and the Hungarian Nonword Repetition Task. The Corsi Blocks Task and the Visual Patterns Test (VPT) were used to measure visuo-spatial working memory capacity. Executive functions were assessed with the Wisconsin Card Sorting Test (WCST), the Tower of Hanoi Task, and the Letter Fluency and Category Fluency Tasks. To measure inhibitory control of memory, we used the directed forgetting (DF) procedure with lists. As for mentalization, the subjects were given first- and second-order mentalization tasks as well as metaphor and irony tasks.

Electrophysiology

Recordings were done with a Nicolet Bravo Multimodality System using the Pegasus software (EMS Co, Korneuburg). We measured the habituation of the P50 auditory evoked potential, the auditory mismatch negativity (MMN) and the auditory P300 wave.

Statistical analysis

Clustering

In many real situations, fuzzy clustering is more natural than hard clustering, as objects on the boundaries between several classes are not forced to fully belong to one of the classes, but are instead assigned membership degrees indicating their partial memberships. One of the most widely used algorithms is the Fuzzy c-Means algorithm. With this approach, clusters are determined by the use of cluster prototypes. The prototype is in most cases a point in an n-dimensional space. The similarity is measured by calculating the distance from this point.

Comparing the groups

The analysed sample size was sufficient for the explorative, cluster-searching mathematical methodology. The viability of the clustering process does not depend on the number of

elements; in addition, our control examination - done according to the scientific praxis on a slightly smaller sample (in our case by five subjects) - resulted in the same outcome.

After the explorative clustering, statistical tests were applied to determine which variables are important in forming clusters, i.e., the explored clusters were compared. Distribution of continuous variables was tested using the Kolmogorov-Smirnov test with a Lilliefors significance level for testing normality. Continuous variables in the explored clusters were compared with a Mann-Whitney *U* test, and categorical variables were compared by Fisher's exact test.

We employed statistical corrections on the results to avoid the problem of multiple hypothesis testing (which increases the probability of declaring false significances). Although there are different opportunities available, we considered the False Discovery Rate (FDR) as the most appropriate method for our study. Instead of controlling the chance of any false positives (as Bonferroni or random field methods do), FDR controls the expected proportion of false positives. SPSS 15.0 for Windows (SPSS Inc., Chicago, IL) was used.

Results

Cluster analysis

The data set contained 50 subjects, 60 variables, and 6.27% missing variable values. A Fuzzy C-Means (FCM) clustering algorithm was executed for each number of centroids between 2 and 5, picking the one with the best validity index as the true partition. The analysis identified two separate clusters. We named these clusters 'S' and 'Z' based on the abbreviations of the schizophrenia in the literature (*SZ)* (S could suggest more serious features); these names are not meant to implicate superiority or inferiority, or closedness of partitioning.

In order to assess the repeatability of the produced clustering results, 100 independent runs of the clustering algorithm were executed: 96% of the runs produced the same partition.

Comparing the subgroups

Demographic features

There were no significant differences between the clusters as far as most of the demographic and course features were concerned, however, the clusters differed significantly with regard to

education and IQ, both of which were significantly lower in cluster S. In addition, the two groups differed in handedness as determined by the NES: mixed-handedness was significantly more frequent in cluster S. The type of pharmacotherapy influenced neither the subgroup formation, nor the neurocognitive performance.

Symptomatologic differences between the clusters

Cluster S patients, in their compensated state, had more emphasized symptoms in every aspect of the examined dimensions of clinical symptoms. However, while in the interepisodic state the cluster Z patients in general had no relevant clinical symptoms (possibly questionable negative signs), the cluster S patients commonly had some possible or definite positive and general symptoms and also obvious, mild negative signs.

Secondary cognitive differences between the clusters

Cluster S patients performed significantly worse on visuo-spatial working memory tasks, but there was no difference between the two clusters in their verbal working memory capacities. Patients in cluster S also exhibited significantly poorer performance in the semantic fluency task and robustly worse WCST.

Primary executive functions in the clusters

We found no overall difference in working memory functions between the two clusters, as the participants scored in the same range on the verbal memory tasks. However, we found strongly significant differences in tasks measuring shifting and visual working memory functions and a nearly significant difference in inhibition function.

Neurological alterations in the clusters

The total frequency of signs was notably higher in cluster S, in which sensory integration disorder was remarkably frequent. Of the 14 neurological signs that can be assessedby body side, those belonging to sensory integration showed significant differences. Motor coordination, motor sequencing, other symptoms, and the total number of differences were represented in the two clusters either equally on the two sides or slightly more frequently on the right side of the body. However, in cluster S, besides the frequent right-sided anomalies of

stereognosis and graphesthesia (found similar in cluster Z), the disorder was even more marked on the left body side. We did not find differences between the two groups with regard to the occurrence of extrapyramidal symptoms (EPS).

Morphogenetic, smell identification and electrophysiological anomalies in the clusters

We did not find a difference in the occurrence of somatic developmental anomalies between the two groups, either in the case of minor malformations or in the case of phenogenetic variants. We found no significant difference between the two groups' performances on the smell identification task. We found no difference in the early, preattentive phase of acoustic information processing between the two groups.

Discussion

In a group of 50 patients diagnosed with schizophrenia, the analysis credibly identified two separate clusters by performances on a part of a set of tests which can consequently separate patients with schizophrenia both from healthy and patient controls with other mental disorders, as well. The cluster Z had more favorable and cluster S had more unfavorable characteristics. It seems as if within the group of patients, there were fewer differences at the more elementary levels of functioning than at higher ones.

The lower education and IQ values indirectly reflect a more pronounced cognitive disorder even during interepisodic periods in cluster S, and these patients had more pronounced symptoms in every aspect of the examined symptomatic dimensions. Instead of an overall difference in working memory functions, we found significant differences in shifting function and in visual working memory domain and a tendency toward alteration of inhibitory performance. In addition, S cluster patients performed robustly worse on so-called frontal lobe tasks, such as the semantic fluency task and WCST. Comparing the level of working memory components to normative data, it was interesting that Z cluster patients' performance was in the lower, but normal, range of the population in the updating and shifting tasks, and, as the positive value of the inhibitory index shows, they produced some inhibition in the Directed Forgetting task as well. On the contrary, S cluster patients exhibited impaired performance on the VPT and WCST and, as the negative value of the inhibitory index indicates, they did not produce inhibition in the Directed Forgetting task. One possible

interpretation of this pattern of results is that S cluster patients consistently performed worse than Z cluster patients on tasks measuring right frontal functions, which could reflect a lateralization difference between the two patient groups. There is a bulk of evidence that the functions of inhibition and shifting are associated with the right frontal lobe, in addition, updating and rehearsing visual and spatial information is associated with the activation of the right fronto-parietal and fronto-temporal circuits. Taken together, the pattern of cognitive differences between the two clusters allows the assumption that a right frontal deficit is a candidate underlying factor behind the memory differences between the patients assigned to the S and Z clusters. They performed equally poorly on the tasks demanding left hemispherial neural substrates.

Further, we found significant differences in the occurrence and laterality of neurological signs between the clusters. Mixed-handedness was significantly more common in cluster S, which may reflect a more frequent disorder in the development of hemispheric asymmetry in this group. A more pronounced disorder of sensory integration was demonstrable in cluster S. Additionally, in cluster S, besides the frequent right-sided stereognosis and graphesthesia disorder, the anomalies were even more marked on the left body side.

THE INCONGRUENCE BETWEEN THE S-Z CLUSTERS AND THE DEFICIT-NONDEFICIT DIVISION

There was a remarkable statistical correspondence between the S-Z clusters identified by our robust neuropsychiatric mapping, and the deficit-nondeficit categorization, which was detected by using the SDS. It was an essential difference that while the definition of deficit syndrome was based on clinical symptoms, our clusters were identified by a complex neuropsychiatric analysis from which the deficit syndrome as an attribute was omitted. Since all patients participated in both kinds of groupings, it was theoretically possible to statistically analyze the overlaps by the comparison of subgroups. Four statistical subgroups were generated by a bidirectional partition (Group1: cluster S and deficit syndrome; Group2:

cluster S and nondeficit syndrome; Group3: cluster Z and nondeficit syndrome; Group4: cluster Z and deficit syndrome). We found only one patient in the whole testgroup with deficit syndrome who belonged to the more favourable cluster Z, this mini ‚group' was dismissed from the analysis. Since we could not perform a full statistical comparative analysis, we could not examine comprehensively the question of the correspondence between the S/Z clusters and deficit/nondeficit subgoups. Instead, we could analyze the homogeneity of groups identified by the two different grouping methods. So the limited and focused question of this analysis was whether the cluster S can be splitted by the border of the deficit-nondeficit grouping, or maybe the nondeficit syndrome could be divided by the border of clusters S and Z.

Statistical analytic methods

In comparison of two-two subgroups we used Mann-Whitney *U* test and chi-square test for continuous and categorical variables. To avoid the increase of Type I error when comparing several variables, raw *p*-values were corrected by Step-down Bonferroni method.

Results

Group1 versus Group2: Patients with deficit or nondeficit-syndrome within cluster S

We did not find any parameters by which deficit and nondeficit syndrome patients within cluster S diverged with reliable significance.

Group2 versus Group3: Patients with nondeficit syndrome belonging to cluster S or Z

As for demographic parameters, patients who belonged to cluster S had significantly lower education. A significant difference was found within the nondeficit group between the two clusters regarding clinical parameters, especially the severity of negative symptoms measured by the PANSS scale, which was more stressed in patients of cluster S. Similarly, we found more pronounced cognitive disturbances indicated by the alogia and inattention dimensions of the SANS-scale in subjects of cluster S. The measured scores of WCST indicated a more

expressed cognitive shifting disturbance in cluster S. As for inhibiting executive function a significant difference was found between the statistical groups on raw significance level, and although this significance diminished after correction, the values represented relevant differences. In contrast to the cluster Z patients whose positive index suggested an effective intentional inhibition, in the case of the cluster S patients the negative value of the inhibitory index indicates that they did not produce inhibition in the Directed Forgetting task. In addition, the disturbance of sensory integration measured by the NES scale was more pronounced on raw significance level for nondeficit patients in cluster S than in cluster Z, but this difference attenuated after correction.

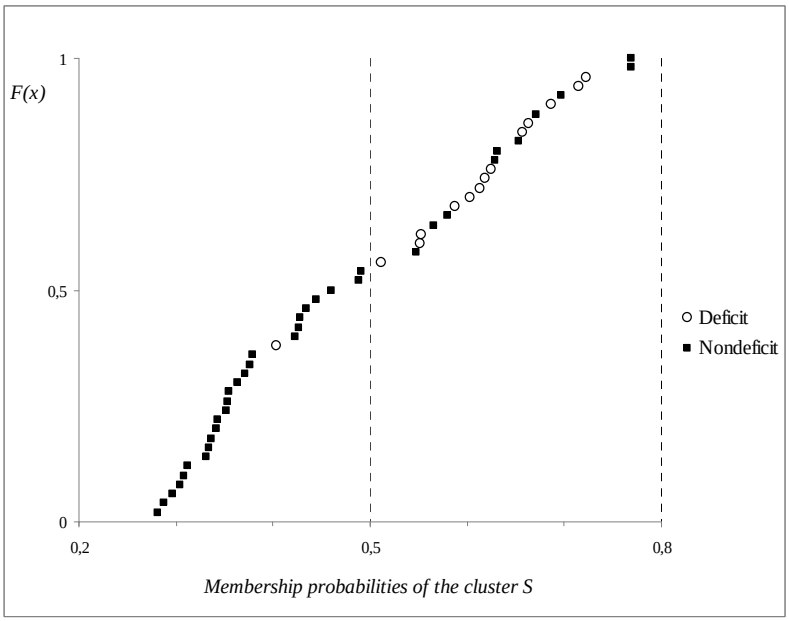
Discussion of results of the statistical analysis

According to our results, cluster S proved to be homogeneous, contrary to the nondeficit syndrome. Throughout our systematic analysis we did not find any parameters which would appropriately set apart deficit syndrome patients from nondeficit ones within cluster S. The nondeficit group in our study, however, proved to be inhomogeneous in several parameters, it was cleft in two along the border of the clusters S and Z fundamentally by cognitive features. We found relevant differences between patients with nondeficit syndrome from S and Z clusters in cognitive demographic, certain cognitive (alogia, inattention), and negative clinical symptomatic dimensions. We also found differences in cognitive psychological parameters especially in the executive shifting dimension and in cognitive inhibitory abilities.

A mathematical grasping of the difference of the S-Z clusters and the deficit-nondeficit syndromes

Although there was a remarkable statistical correspondence between the clusters and the deficit-nondeficit syndromes (p=0.0003, Chi-square test and False Discovery Rate), yet the two divisions were not the same. In cluster Z (N=27) 96.30% of the patients had nondeficit and 3.70% of the patients had deficit diagnoses; while in cluster S (N=23) only the 56.50% of the patients had deficit and 43.50% of them had nondeficit diagnoses. The distinctness of the patients' membership in the clusters S versus Z and in the deficit or nondeficit subgroups is demonstrated with a distribution function in Figure 1.

Figure 1 Distribution function of the membership probabilities



The patients' cluster membership probabilities are represented on this figure. The symbols represent patients with (empty circles) or without (filled squares) deficit syndrome. Higher probability values indicate memberships of cluster S, while lower values mark membership of cluster Z. The border line between the two clusters is found to be at the 0.5 probability value. While nearly each patient in cluster Z had nondeficit diagnosis, only hardly more than half of the patients had deficit syndrome diagnosis in cluster S.

PILOT STRUCTURAL MRI FINDINGS AS INDIRECT EVIDENCES OF PARTLY DIFFERENT NEURAL SUBSTRATES IN THE BACKGROUND OF THE S-Z CLUSTERS

Before the subgroup-exploring, robust cross-sectional research, we executed a pilot MRI-study in groups of patients with schizophrenia and healthy controls on observation of relationships between some detectable brain structural anomalies and certain phenomenological alterations. The questions of this preliminary report were whether specific volumetric changes could be observed in schizophrenia in areas thought to be involved in working memory and, in addition, whether the brain size changes would correlate with changes in cognitive functions and with symptomatology.

Materials and methods

Subjects

Only male subjects participated in the experiment, as we enrolled a relatively low number of subjects in this research and we wanted to exclude the variance of brain size attributable to gender differences. Thirteen patients were selected from the outpatient clinic of the Department of Psychiatry, University of Szeged. All patients had a diagnosis of schizophrenia defined by DSM-IV and ICD-10 criteria for research. All patients were in a stable interepisodic state, during the early stages of the illness, and under antipsychotic medication. The 13 normal control subjects were recruited from hospital staff and community volunteers. They were evaluated with a modified structured interview (Mini International Neuropsychiatric Interview (MINI), and we excluded normal control subjects with a family history of psychotic and affective spectrum disorders. All subjects were 25 to 37 years of age, had scores above 85 in full scale IQ (WAIS, Hungarian version), had a minimum of 8 years of education, and were able to give informed consent.

Clinical tests

Clinical symptoms were assessed by PANSS, SANS, SDS, NES, SAS, AIMS, BAS, with assessment of the demographic and epidemiologic data at the time of the MRI study.

Working memory tasks

The working memory capacities were measured with the Digit Span Task, the Hungarian Nonword Repetition Task, the Corsi Blocks Task, the VPT, the WCST, the Tower of Hanoi Task, the Letter and also the Category Fluency Tasks.

MRI scans

All the multimodal MRI examinations were performed on a Signa Horizon 1 Tesla MR Unit (General Electric, GE) at the International Medical Center (Szeged, Hungary). Three-dimensional T1 weighted images using the spoiled gradient echo (SPGR) sequence were obtained in the coronal plane. MRI data were postprocessed on an Advantage Windows (Silicon Graphics) workstation with Advantage 3.1 software (developed by GE). Single

manual measurement with intra-rater control and inter-rater supervision was performed on serial coronal or axial slices of all regions of interest. After manual tracing, the volume of the ROI was calculated by means of the „volume analysis" program.

Statistical analysis

A Mann–Whitney U-test was used to examine group differences on demographic, brain structural, cognitive and clinical variables. Pearson's product-moment correlations tested relationships between variables. The measures of laterality of ROI volumes were subjected to two-way repeated measures analysis of variance (ANOVA). The level of significance was p=0.05 in all cases. In this preliminary report we presented the uncorrected p-values.

Results

Differences in brain volumes

There were no significant group differences in the total brain volume and in the intracranial volume. There was also no difference in the absolute volume of the target areas or in the relative volume compared with total brain volume: the patient and the control groups did not differ significantly in the volume of external cerebrospinal fluid (CSF) space, third ventricle, bilateral hippocampi, straight gyri (SG), and the grey matter of the orbitofrontal cortex, the middle frontal gyri and the anterior cingulate gyri.

We investigated lateral volume differences with a two-way repeated measurements ANOVA with one between-subjects factor (group: controls vs. patients) and one within-subjects factor (side: left vs. right). We found a significant interaction in the case of the SG both for the absolute and the relative volume; however, there was no significant group or side main effects. That means that lateralization of the SG was different in the two groups. In healthy subjects the left SG was significantly larger than the right SG, but in patients with schizophrenia the case was just the reverse.

A similar tendency toward a hemispheric asymmetry reversal was found in the volume of the anterior cingulate gyri. There was a significant main effect of lateralization with left side

dominance in the volume of the orbitofrontal cortex for both the absolute and relative values, however, there was not a significant Group X Side interaction.

Differences in neurocognitive parameters

We found significant group differences in verbal working memory performance measured by the Digit Span Forward and Backward and the Nonword Repetition Tests and in controlled association performance measured by Letter (F,A,S) and Category (animals, fruits and vegetables, supermarket items) Fluency Tests, with a better performance for the control group in each case. We found a significant difference between groups in the frequency of neurological signs. The presence of abnormalities in sensory integration, motor coordination, and motor sequencing was significantly more frequent in the patient group. The appearance of neurological signs in the patient group was independent from the extrapyramidal side effects of the pharmacologic treatment. There was no significant group difference in the two visuo-spatial working memory tasks, the Corsi tapping task and the Visual Pattern Task, and similarly, there were no differences in the Tower of Hanoi task and in WCST performance.

Discussion

Our main finding was a change in asymmetry of the straight gyrus, a brain area where, according to our current knowledge, no such difference has been detected in schizophrenia. The SG is part of the emotional–memory network involved in the recall of episodic and autobiographical memories and also in the short-term maintenance of visuo-spatial information. The change in laterality of the SG may refer to the dysfunctional operation of this region which might play a significant role in the symptoms of self-disorder and hallucinations in schizophrenia.

The main study established that 12 of the examined 13 patients belonged to cluster Z. The volume of the right straight gyrus was greater than the left one, and the visuo-spatial working memory performances were at the normal-level in the patients who belonged dominantly to the cluster Z. The group of young male patients with schizophrenia predominantly from cluster Z differed from the group of healthy controls in performances of verbal working memory and verbal fluency, and in neurological soft signs. The performances of subjects, however, did not differ in the visuo-spatial and inhibiting (and planning) executive functions.

CONCLUSIONS OF THE THESES

In schizophrenia with a theory-driven, systematic neurocognitive study we could separate subgroups. Two subgroups (clusters S and Z) had been separated from each other by performances on a part of a set of tests which can consequently separate patients with schizophrenia both from healthy and patient controls with other mental disorders, as well.

Despite of a remarkable statistical correspondence between the deficit-nondeficit syndromes and these neuropsychiatric clusters, the two divisions were not the same. The nondeficit syndrome in our study proved to be inhomogeneous in several parameters, it was cleft in two along the border of the clusters S and Z fundamentally by cognitive features.

We favour an explanation that the patterns of the cognitive dysfunctions and of the neurological developmental anomalies equally indicate that there were at least two morbidity domains in the background of the two subgroups: in cluster Z there was a dominatingly unilateral, left frontal dysfunctioning, while in the more severe cluster S, bilateral morbidity processes with left and right frontal neural substrates might be present. Based on the results it seemed that these subgroups represented different types, not only forms with different seriousness of the same type. However, as we did not find group differences in the more elementary levels, it is possible, that there is a common morbidity root in the depth of etiological basement of the clusters.

We observed the reversal of normal L>R asymmetry to R>L asymmetry of the volumes of straight gyri (BA 11) in thirteen young, male patients with schizophrenia - of a brain area where, according to our current knowledge, no such difference has been detected in this illness.

Based on the results we can draw a cautious conclusion that disorders of the verbal working memory and the verbal fluency, and more frequent prevalence of neurological soft signs (and probably the change of asymmetry of the straight gyri also) can separate patients with schizophrenia from healthy subjects. Furthermore, in addition to these impairments, the associated disorders of the visuo-spatial working memory and the shifting executive functions, and the more pronounced impairment of sensory integration (becoming dominant on the left body side) can feature a more unfavoured subgroup within the illness.

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