# 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)*

**Szendi I**, Cimmer C, Csifcsák G, Szekeres G, Kovács ZA, Galsi G, Racsmány M, Boda K, Janka Z. Subgroups within schizophrenia differentiated by clinical and neurocognitive parameters. Eur Neuropsychopharm 2006; 16(Suppl 4): S374-375. *(IF: 3.510)*

**Szendi I**, Juhász A, Szekeres G, Cimmer C, Csifcsák G, Kovács ZA, Rimanóczy A, Galsi G, Boda K, Janka Z. Examination of specific genetic aspects of the dopaminergic neurotransmission and neuronal plasticity in neurocognitive subgrouping of schizophrenia. Eur Neuropsychopharm 2006; 16(Suppl 4): S375-376. *(IF: 3.510)*

**Szendi I**, Kiss M, Vörös E, Kovács ZA, Szekeres G, Cimmer C, Kéri S, Galsi G, Boda K, Csernay L, Janka Z: Correlations between clinical symptoms, neurocognitive alterations and structural brain abnormalities in men with schizophrenia. Eur Neuropsychopharm 2002;12(Suppl 4): S296.*(IF: 2.437)*

## Selected papers related to the thesis in Hungarian:

**Szendi I.** A szkizofrénia változatossága. Neuropsychopharmacol Hung 2007;9(Suppl 1): 7-13.
**Szendi I**, Kiss M, Vörös E, Csernay L, Janka Z. Az agyi anatómiai szerkezetek és a kognitív működések kapcsolatának vizsgálata. Clin Neurosci/Ideggy Szle 2001;54(11-12):328-36.

## 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.

**Szendi I**: A neuropszichiátria fejlődése. In: Racsmány M, Kéri Sz (szerk.): Architektúra és patológia a megismerésben. 2002 Budapest. Books in Print Kiadó, pp. 101-124.

# Table of contents

## SUMMARY

The description of the heterogeneous phenomenological, pathophysiological, and etiological nature of schizophrenia is under way; however, the relationships between heterogeneity levels are still unclear. 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 patterns of cognitive dysfunctions and neurological developmental anomalies equally indicate that there maybe hemispherical differences between the patients belonging to the different clusters. Based on earlier results in the literature, we selected tasks and procedures from existing batteries that seem to separate patients with schizophrenia not only from healthy controls, but also from other groups with mental disorders. In our opinion, one of the significant aspects of our results was that we could demonstrate that performance on these tasks could also draw distinctions within the group of compensated schizophrenic patients. Differences within the group could be detected with only a subset of the methods used. Similar performances of the functions tested with the other techniques might indicate common features of the group of patients as a whole, which might reflect a common, overlapping morbidity that characterizes both of the clusters equally. 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 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 more unfavourable neuropsychiatric cluster S proved to be homogeneous, while the nondeficit group was found to be heterogeneous as it was divided by the border of the two neuropsychiatric clusters. 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 significant differences within the nondeficit group in the level of negative symptoms (affective flattening, total weight of negative symptoms), in cognitive demographic (education), in cognitive symptomatic (alogia and inattention) and also in certain cognitive psychological parameters (shifting executive dimension, visual working memory updating). On the grounds of these results it seems to be a feasible conclusion that cluster S is not identical with deficit syndrome, and the more favourable cluster Z is not identical with nondeficit syndrome.

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 thirteen 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 - these earlier results might partly support our main indirect observations on the hemispherical differences.

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, and, 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 can feature a more unfavoured subgroup within the illness.

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.

## List of abbreviations

| | |
|---|---|
| AEP | auditory evoked potential |
| AIMS | Abnormal Involuntary Movement Scale |
| ANOVA | analysis of variance |
| BA | Brodmann area |
| BAS | Barnes Akathisia Rating Scale |
| CC-SIT | Cross-Cultural Smell Identification Test |
| CSF | cerebrospinal fluid |
| CSP | cavum septi pellucidum |
| DF | directed forgetting |
| DSM-IV | Diagnostic and Statistical Manual of Mental Disorders (4th edn) |
| EEG | electroencephalography |
| FCM | Fuzzy C-Means |
| FDR | False Discovery Rate |
| FGA | first generation antipsychotic |
| FOV | field of view |
| FSE | fast spin echo |
| ICD-10 | International Classification of Diseases ($10^{th}$ edn) |
| IQ | intelligence quotient |
| MINI | Mini International Neuropsychiatric Interview |
| MMN | mismatch negativity |
| MPAs | minor physical anomalies |
| MRI | magnetic resonance imaging |
| NES | Neurological Evaluation Scale |
| NEX | number of excitations |
| PANSS | Positive and Negative Syndrome Scale |
| PDS | Proxy for the Deficit Syndrome |
| ROIs | regions of interest |
| SI | primary sensory cortex |
| SII | secondary sensory cortex |

| | |
|---|---|
| SANS | Scale for the Assessment of Negative Symptoms |
| SAS | Simpson-Angus Scale |
| SD | standard deviation |
| SDS | Schedule for the Deficit Syndrome |
| SG | straight gyrus |
| SGA | second generation antipsychotic |
| SPGR | spoiled gradient echo |
| SPL | sound pressure level |
| SPSS | Statistical Package for the Social Sciences |
| STG | superior temporal gyrus |
| TE | echo time |
| TR | repetition time |
| VPT | Visual Patterns Test |
| WAIS | Wechsler Adult Intelligence Scale |
| WCST | Wisconsin Card Sorting Test |

EXPLORING CLUSTERS

## Introduction

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. The powerful and heuristic hypothesis of Crow [1] stimulated the multilevel conception and neurobiological research on the disease. 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 [2, 3]. Currently, description of the heterogeneous nature of the disease is underway in phenomenological, pathophysiological, and etiological terms [4]. However, the relationships between heterogeneity levels are still unclear.

In the very beginning of research on schizophrenia, Kraepelin and Bleuler supposed, and currently Andreasen [5] and Saugstad [6] assume, a unified morbidity process that underlies the disease, the phenomenological manifestations of which – e.g., at the level of clinical features - reflect a diverse distribution within a uniform dimension. In contrast, others see the heterogeneity of the disease as reflecting the distinct manifestations of different morbidity processes. The two-type concept of Crow and the most popular and widespread partition of our time, the deficit-nondeficit division [7], equally suppose the possibility and effects of multiple underlying morbidity processes (and their possible interactions).

Research results from recent decades have led to a shift from a categorical approach toward a dimensional one, both in understanding of the illness [8] and in its taxonomic concepts [see for review 9]: this approach is reflected in the theoretical design of this research. A robust cross-sectional study was performed. According to Wimsatt [10], robustness means multiple determinations: different features of objects in reality can be apprehended, measured, understood, and defined in a variety of independent ways. This study provides (’vertical’) insights into various levels of phenomenological mental, pathophysiological and etiological cerebral processes. Our study is theory-driven, and several fundamental hypotheses (according to the falsification criterion of the philosophy of science) underlie it. In our

working hypothesis, we presuppose that (1) schizophrenia (or schizophrenias) forms (or form) a so-called ’natural category’ from a scientific philosophical point of view; (2) the category is heterogeneous genetically, neurobiologically, and on both the cognitive and clinical levels, and the heterogeneities have a dimensional nature; (3) subgroups can be separated within this category, and partially distinct morbidity processes underlie them; (4) the expression of the morbidity processes characterizing the subgroups weakens as we move away from the center of the subgroups, which have a prototypical nature; and (5) one patient can belong to several subgroups at the same time; the patient’s location within the multidimensional space of the subgroups of the category can be characterized by the distances from the subgroup centroids, i.e., from the measures of the expressions of morbidity processes typical in the different subgroups.

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) were selected from the outpatient clinic of the Department of Psychiatry, University of Szeged. The inclusion criteria were not restrictive; the only enrollment criteria were a relatively stable clinical state and cooperation with the study. The exclusion criteria were related to possible organic brain dysfunctions (a lifetime history of neurological illness, any medical illness known to affect brain structure, head injury with loss of consciousness for more than 10 minutes) that could significantly constrain neurocognitive performance. The selected patients were representative of the population treated by our department. We succeeded in enrolling patients with both the most favorable and unfavorable courses. All patients had a DSM-IV diagnosis of schizophrenia [11] and met ICD-10 criteria

for research [12]. All subjects were 18 to 69 years of age, with a minimum of 8 years of education (primary school), and were able to provide informed consent. The average number of years of education was 11.00 (SD=2.17), and the average full-scale IQ (WAIS, Hungarian version [13]) was 100.17 (SD=15.40). All patients understood and carried out all instructions. All of them were outpatients in stable interepisodic states under antipsychotic medication. Due to the variety of drug types and doses, for statistical purposes the pharmacotherapy applied to the patients was divided into three categories in the first approach: first generation antipsychotics, second generation medicines, and combinations of antipsychotics. All substances were usually prescribed in moderate doses according to their medication protocols. Since identifying mental diseases in the family histories of most of the patients was unreliable (due to the lack of medical documentation), we could not statistically analyze this information. The investigation was approved by the Human Investigation Review Board, University of Szeged, Albert Szent-Györgyi Medical and Pharmaceutical Centre, and it was carried out in accordance with the latest version of the Declaration of Helsinki.

**Clinical symptoms**

Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) [14], the Scale for the Assessment of Negative Symptoms (SANS) [15], and the Schedule for the Deficit Syndrome (SDS) [16].

**Neurosomatic alterations**

Neurological developmental signs were assessed using the Neurological Evaluation Scale (NES) [17]. Fourteen of the 26 items of the NES scale assess neurological signs independently on the two sides, which provide an opportunity to analyze laterality. The potential pharmacogenic extrapyramidal symptoms were assessed with the Simpson-Angus Scale (SAS) [18], the Abnormal Involuntary Movement Scale (AIMS) [19], and the Barnes Akathisia Rating Scale (BAS) [20]. A list of minor physical anomalies (MPAs), including 57 minor signs collected by Mehes, was used for mapping the malformations [21-23]. Three examiners investigated the patients, and the interrater reliability was >75% (kappa coefficient). The cross-cultural smell identification test (CC-SIT) was used for assessing smell identification [24].

**Neuropsychological mapping**

Verbal working memory capacity was measured with the Hungarian Digit Span Task [25] and the Hungarian Nonword Repetition Task [25]. The Corsi Blocks Task [26] and the Visual Patterns Test (VPT) [27] were used to measure visuo-spatial working memory capacity. Executive functions were assessed with the Wisconsin Card Sorting Test (WCST) [28,29], the Tower of Hanoi Task [30], and the Letter Fluency [31] and Category Fluency Tasks [32]. To measure inhibitory control of memory, we used the so-called directed forgetting (DF) procedure [33-35] with lists. Following Miyake and his colleagues [36], we sought to investigate three components of the executive system. Perseverative errors on the WCST were used as a measure of „Shifting". Two working memory tasks were used as measures of the „Updating" function in two modalities, the Hungarian Digit Span Task and the Visual Patterns Test (VPT). We have used the DF task to analyze individual differences in the ability to inhibit activated memory representations („Inhibition") [37,38]. An inhibitory index was calculated by comparing the List 1 performances in the "Forget" and "Remember" conditions of the directed forgetting procedure [39,40]. As for mentalization, the present study adapted the method of Tenyi et al. [41] to unveil any deficit in subjects' mentalization abilities. Subjects were given first-order and second-order mentalization tasks as well as metaphor and irony tasks to test their mentalization skills.

**Electrophysiology**

Recordings were done with a Nicolet Bravo Multimodality System (EMS Co, Korneuburg, Austria) using the Pegasus software (EMS Co, Korneuburg, Austria). The EEG signal was amplified 20,000 times with a sampling frequency of 1024 Hz and a band pass filter setting of 0.1-100 Hz. We performed three auditory evoked potential paradigms that have been extensively investigated in schizophrenia and abnormalities associated with the disease. We measured the habituation of the P50 auditory evoked potential (AEP) in a double click paradigm, the auditory mismatch negativity (MMN) and the auditory P300 wave. The three paradigms were measured in one 1.5-hour session. Subjects were seated comfortably in a chair, asked to keep their eyes open, and given headphones for auditory stimulus presentation. The stimuli were generated with a Helios II System (EMS Co, Korneuburg, Austria). All tones were sinusoidal tones with 5 msec rise/fall time presented binaurally with an intensity of

80 dB sound pressure level (SPL). EEG data were recorded with 19 Zn electrodes, which were placed according to the international 10-20 system with predefined caps (ElectroCap International, Inc., USA). The left earlobe (A1) was used as a reference, and the ground was placed at position FCz. We kept electrode impedances below 7 kΩ. The data was stored on a hard disc and analyzed off-line with the BrainVision Analyzer software (Brain Products GmbH, Munich, Germany).

## Statistical analysis

### Clustering

The goal of clustering is to determine the intrinsic grouping in a set of unlabeled data. Fuzzy clustering methods allow objects to belong to several clusters simultaneously, with different degrees of membership. 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 between 0 and 1 indicating their partial memberships. One of the most widely used algorithms is the Fuzzy c-Means algorithm [42-44]. 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.

At first, the missing values were substituted with values computed by a weighted average of the corresponding values of the three closest elements based on the (most often Euclidean) distances between the selected elements and the element with the missing value. Then, the following normalization steps were carried out: normalization, centralization and variance normalization. After normalization, the ratio of the smallest and the largest value intervals was 2.19. We then applied the Fuzzy C-Means algorithm to attribute cluster membership values to patients.

The variables used during the explorative clustering were as follows (48): Age; Education; Full scale IQ; Age at onset; Relapse-duration ratio; Digit span, forward and backward; Corsi blocks, forward and backward; Letter fluency, correct words, errors; Category fluency, correct words, errors; Tower of Hanoi, steps, errors; Nonword repetition; Visual Patterns Test;

Theory of Mind, first-order and second-order; Metaphor comprehension; Irony comprehension; Wisconsin Card Sorting Test, perseverative errors (%), conceptual level responses (%), completed categories, failure to maintain set; Directed forgetting; PANSS, positive subscale, negative subscale, general subscale, and total; SANS, Affective flattening subscale; Alogia subscale, Avolition subscale, Anhedonia subscale, Inattention subscale; NES, sensory inhibition subscale, motor coordination subscale, motor sequencing subscale, the 'other' subscale, and total; P50 wave, latency, amplitude; MMN frequency deviant stimuli, latency, amplitude; MMN duration deviant stimuli, latency, amplitude; P300 wave, latency, amplitude.

Excluded variables were those that had either nominal values (DSM diagnostic subgroups, remission types, deficit-nondeficit categorization, gender, handedness by NES, type of therapy) or relatively numerous (>20%) missing cases (minor malformations, phenogenetic variants, smell threshold, smell identification test).

**Comparing the groups**

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. Pairwise p-values from univariate tests are commonly reported with a Bonferroni correction for multiple tests. While the Bonferroni correction controls the experiment-wise α, this correction is very conservative (this means that the method does not reject hypotheses as often as it should) and therefore lacks power. An alternative is to control the false discovery rate (FDR), which is less conservative than the Bonferroni procedure, and as a result yields more power to detect genuine positive effects. 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.

**Sample size**

The analysed sample size was reliably sufficient for the explorative, cluster-searching mathematical methodology used according to the dimensional approach constituting the theoretical background of our study. 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.

## 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. (On the basis of clinical experiences, the subdivisions of currently accepted diagnostic systems and historical divisions, the number of possible subgroups was anticipated to be below six.) 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. Ninety-six percent of the runs produced the same partition. Before every single run, the supposed centroids of the supposed clusters were located by the Monte Carlo method, and the (nondeterministic) FCM algorithm was run again and again from these various optional starting points determined differently in the multidimensional space of the variables. We investigated the stability of the clustering, and

the further increase of the number of runs did not result in any further changes in the results of the clustering.

We reduced the number of analyzed variables by the attribute selection method in the interest of increasing the distance between the cluster centroids – with preservation of the explored groups - so that the membership probabilities could become more interpretable. We eventually reduced the original 48 variables to 10 and obtained practically the same clustering result. Widening the centroids yielded high probability values: the mean membership probability value in the case of patients belonging to cluster S was 0.636, and that of those belonging to cluster Z was 0.629. The ten selected variables were Education; Digit span, backward; Corsi blocks, backward; Theory of Mind, second-order; Wisconsin Card Sorting Test, conceptual level responses (%), completed categories; Directed forgetting; PANSS, positive subscale, negative subscale, general subscale, and total; SANS, Alogia subscale, Anhedonia subscale; MMN frequency deviant stimuli, amplitude; P300 wave, latency.

**Comparing the subgroups**

The algorithm of cluster analysis works well for sets of variables whose coordinates overlap for a few of these variables. The validity of clusters was qualified by high correspondence (96%) of the independent runs of the algorithm and mean values above 60% of the patients' membership probabilities. Statistical tests were applied to find which variables were important in forming clusters.

**Diagnostic features**

The distributions of the clinical DSM/ICD diagnoses in the two clusters were not significantly different ($p$=0.115, chi-square test and False Discovery Rate).

**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 (Table 1.1). In addition,

the two groups differed in handedness as determined by the NES: mixed-handedness was significantly more frequent in cluster S (Table 1.1). The type of pharmacotherapy influenced neither the subgroup formation (analyzed with 2-sided Fisher's exact test) (Table 1.1), nor the neurocognitive performance (analyzed with the Kruskal-Wallis and Chi-square tests) (data not shown).

**Table 1.1** Demographic characteristics of the clusters of participants

| | Cluster S (n=23) | Cluster Z (n=27) | *p* |
|---|---|---|---|
| Age, years | 35.78 (10.40) | 32.15 (12.15) | 0.331 |
| Gender ratio, male/female % | 56.5/43.5 | 51.9/48.1 | 0.782* |
| Education, years | 9.78 (1.68) | 12.04 (2.01) | **0.00038** |
| Full scale IQ | 90.21 (12.42) | 108.39 (12.62) | **0.00038** |
| Age at onset, years | 25.43 (8.07) | 24.07 (7.74) | 0.443 |
| Duration of illness, years | 10.30 (8.89) | 8.07 (7.68) | 0.443 |
| Relapse | 5.32 (4.11) | 4.44 (5.03) | 0.365 |
| Handedness, by NES | | | |
| Right | 77.3% | 100% | |
| Left | 0.0% | 0.0% | **0.045*,**† |
| Mixed | 22.7% | 0.0% | |
| Antipsychotic therapy | | | |
| SGA | 78.3 % | 63.0 % | |
| FGA | 13.0 % | 14.8 % | 0.443* |
| Combination | 8.7 % | 22.2 % | |

Values represent mean values (SD)

*p* values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate

*NES* Neurological Evaluation Scale, *SGA* second generation antipsychotic, *FGA* first generation antipsychotic

**p* value is based on 2-sided Fisher's exact test and adjusted by False Discovery Rate, † This difference would lose its significance with correction of the conservative Bonferroni-method. The corrected p-value by Bonferroni-Holm method: Handedness, by NES: 0.105.

**Symptomatologic differences between the clusters**

Obvious symptomatological differences could be distinguished between the two clusters of patients. Cluster S patients, in their compensated state, had more emphasized symptoms in every aspect of the examined dimensions of clinical symptoms (Table 1.2). 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 (without causing relevant dysfunctions) and also obvious, mild negative signs (Table 1.2). In both clusters, anhedonia was pronounced among negative symptoms (Table 1.2).

**Table 1.2** Symptomatologic characteristics of the clusters of participants

| | Cluster S (n=23) | Cluster Z (n=27) | *p* |
|---|---|---|---|
| PANSS, positive | 13.26 (5.19) | 10.12 (3.79) | **0.014** |
| PANSS, negative | 20.57 (6.00) | 12.38 (4.80) | **0.00005** |
| PANSS, general | 34.61 (10.68) | 25.50 (7.98) | **0.0008** |
| PANSS, total | 68.43 (19.22) | 47.54 (14.56) | **0.00014** |
| SANS, affective flattening | 2.22 (1.17) | 0.96 (0.98) | **0.00059** |
| SANS, alogia | 2.17 (0.98) | 0.60 (0.76) | **0.00003** |
| SANS, avolition | 2.22 (1.13) | 0.76 (0.88) | **0.00009** |
| SANS, anhedonia | 2.87 (1.18) | 1.32 (1.11) | **0.00016** |
| SANS, inattention | 1.83 (1.07) | 0.60 (0.82) | **0.00009** |

Values represent mean values (SD)

*p* values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate

*PANSS* Positive and Negative Syndrome Scale, *SANS* Scale for the Assessment of Negative Symptoms

**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 (Table 1.3).

**Table 1.3** Secondary cognitive characteristics of the clusters of participants

| | Cluster S (n=23) | Cluster Z (n=27) | *p* |
|---|---|---|---|
| Digit Span, forward | 5.39 (0.99) | 5.96 (1.22) | 0.157 |
| Digit Span, backward | 3.65 (0.89) | 4.07 (0.96) | 0.157 |
| Hungarian Nonword Repetition Task | 6.29 (1.27) | 6.37 (1.08) | 0.705 |
| Corsi blocks, forward | 5.13 (0.92) | 5.63 (1.15) | 0.191 |
| Corsi blocks, backward | 4.26 (1.21) | 5.15 (1.20) | **0.0424**† |
| Visual Patterns Test | 5.73 (1.52) | 7.00 (1.84) | **0.0292**† |
| Letter fluency, words | 7.36 (2.37) | 8.81 (2.56) | 0.132 |
| Letter fluency, errors | 0.71 (0.80) | 0.81 (0.82) | 0.624 |
| Semantic fluency, words | 12.81 (3.16) | 15.81 (3.90) | **0.0475**† |
| Semantic fluency, errors | 0.43 (0.45) | 0.58 (0.67) | 0.445 |
| Towers of Hanoi, movements | 13.05 (5.71) | 10.44 (3.91) | 0.192 |
| Towers of Hanoi, errors | 0.38 (0.74) | 0.19 (0.48) | 0.445 |
| WCST, completed categories | 0.95 (1.24) | 4.50 (1.66) | **0.000003** |
| WCST, perseverative errors (%) | 37.57 (19.73) | 16.92 (9.54) | **0.00031** |
| WCST, conceptual level responses (%) | 19.76 (16.32) | 58.35 (20.29) | **0.000009** |
| Theory of Mind, first order | 0.86 (0.36) | 0.96 (0.59) | 0.570 |
| Metaphor comprehension | 2.19 (1.21) | 2.93 (0.87) | 0.076 |
| Theory of Mind, second order | 1.10 (0.63) | 0.85 (0.60) | 0.240 |
| Irony comprehension | 1.81 (1.44) | 2.67 (1.52) | 0.126 |

Values represent mean values (SD)

*p* values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate

† These differences would lose their significances with correction of the conservative Bonferroni-method. The corrected p-values by Bonferroni-Holm method: Corsi backward 0.143; Visual Patterns Test: 0.210; Semantic fluency, words: 0.195.

**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, as Table 1.4 shows, we found strongly significant differences in tasks measuring shifting and visual working memory functions and a nearly significant difference in inhibition function.

**Table 1.4** Primary executive function characteristics of the clusters of participants

| | Cluster S (n=23) | Cluster Z (n=27) | *p* |
|---|---|---|---|
| Verbal Updating: Digit Span Task | 5.39 (0.99) | 5.96 (1.22) | 0.157 |
| Visual Updating: Visual Patterns Test | 5.73 (1.52) | 7.00 (1.84) | **0.0292** |
| Inhibition: Directed Forgetting, inhibitory index | -0.67 (1.40) | 0.35 (2.06) | 0.059 |
| Shifting: WCST, percentage of perseverative errors | 37.57 (19.73) | 16.92 (9.54) | **0.00031** |

Values represent mean values (SD)

*p* values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate

**Neurological alterations in the clusters**

The total frequency of signs was notably higher in cluster S, in which sensory integration disorder was remarkably frequent (Table 1.5).

**Table 1.5** Neurological signs in the clusters of participants

| | Cluster S (n=23) | Cluster Z (n=27) | *p* |
|---|---|---|---|
| Sensory integration | 6.32 (2.44) | 3.67 (2.75) | **0.0012** |
| Motor coordination | 2.50 (2.20) | 1.52 (1.65) | 0.153 |
| Motor sequencing | 5.27 (3.43) | 4.37 (3.13) | 0.364 |
| Others | 10.00 (4.08) | 8.96 (4.42) | 0.480 |
| Total | 24.09 (8.30) | 18.52 (8.09) | **0.021** |

Values represent mean values (SD)

*p* values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate

Of the 14 neurological signs that can be assessed by body side, those belonging to sensory integration showed significant differences. Sensory integration at the level of hemispheres is represented by those items of the NES that examine stereognosis and graphesthesia. 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 ($p$=0.023, Mann-Whitney $U$ test and False Discovery Rate).

Using the scales that assess extrapyramidal symptoms, we did not find differences between the two groups with regard to the occurrence of parkinsonism, akathisia and tardive dyskinesia. Neither the occurrence of the developmental neurological signs nor that of the (most likely pharmacogenic) extrapyramidal symptoms correlated to the type of pharmacotherapy applied (first vs. second generation vs. combination) in any of the groups ($p$>0.05 in all cases, Kruskal-Wallis test).

**Morphogenetic 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. In addition, we found no regional difference by side in the occurrence of anomalies either within the whole group of patients (in agreement with the literature) [45] or between the two groups.

**Smell identification alterations in the clusters**

We found no significant difference between the two groups' performances on the smell identification task.

**Electrophysiological alterations in the clusters**

We found no difference in the early, preattentive phase of acoustic information processing between the two groups. There was no demonstrable variance in the latency and amplitude differences, the P50 waves, the MMN waves (in terms of both frequency- and duration-deviant stimuli), or the P300 waves. In addition, there were no demonstrable differences

between the latency and amplitude characteristics of the signals measured on the bilateral electrodes (C3-C4, P3-P4, F3-F4) in the two subgroups.

## Discussion

In a group of 50 patients diagnosed with schizophrenia according to DSM and ICD criteria, the distribution of the patients within the groups was dimensional, and two distinct grouping zones were identifiable within this distribution. The analysis credibly identified two separate clusters. The analyses demonstrated that cluster Z had more favorable and cluster S had more unfavorable (more serious) characteristics.

Based on earlier results in the literature, we selected tasks and procedures from existing batteries that seem to separate patients with schizophrenia not only from healthy controls, but from other groups with mental disorders. In our opinion, one of the significant aspects of our results was that we could demonstrate that performance on these tasks could also draw distinctions within the group of schizophrenic patients. Differences within the group could be detected with only a subset of the methods used. Similar performances of the functions tested with other techniques might indicate common features of the group of patients as a whole, which might reflect a common, overlapping morbidity that characterizes both of the clusters equally. 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 (>15th percentile) [see 27 and 29 for normative data], and, as the positive value of the inhibitory

index shows, they produced some inhibition in the Directed Forgetting task as well [25,40]. On the contrary, S cluster patients exhibited impaired performance on the VPT and WCST (<15th percentile) and, as the negative value of the inhibitory index indicates, they did not produce inhibition in the Directed Forgetting task, although they performed normally on the Digit Span task.

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 [46-48]. 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 neural substrates underlying the discriminative tactile, kinesthetic, and proprioceptive information processing needed to perform the functions of stereognosis and graphesthesia are well known (the cardinal regions are the contralateral thalamus and the primary (SI) and secondary sensory cortex (SII)). Since the patients did not completely lack stereognosis and graphesthesia, and other accompanying drop-out symptoms were missing as well, the dysfunction of this distributed (thalamo-) cortical network was presumably present in the background, influencing only the left hemisphere in cluster Z and both hemispheres in cluster S.

Although this study is only the first phase of an overall investigation and it is preliminary to draw any broader theoretical conclusion from the results, it may be useful to speculate on possible explanations of the pattern of differences. 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 [see for reviews 49]. Conway and Fthenaki [38] showed that right frontal lobe injury can abolish inhibition in the Directed Forgetting task, while Anderson et al. [50], using different procedures, produced evidence that inhibitory control of memory retrieval is associated with the activation of the right cerebral cortex. Above all, updating and rehearsing visual and spatial information is associated with the activation of the right fronto-parietal and fronto-temporal circuits [see 50 for a detailed

review]. 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.

Another possible interpretation of the results is that patients belonging to cluster S show more profound deficits of frontal lobe functions, and as a consequence they exhibit worse performance on tasks sensitive to functions of executive working memory. It may be the case that visuo-spatial working memory tasks load on storage and updating functions more strongly than do verbal tasks. This difference in frontal functions would account for the differences in education and IQ level strongly associated with executive functions. However, this interpretation would not explain the difference in handedness and disorder of sensory integration. We are aware that further studies are necessary to find a solid explanation for the core differences between the clusters.

The peripheries of the spectrum were not examined by the present study, which sheds only a dim light on the structure of the internal diversity of the spectrum. One of the limitations of our study is the exclusive use of the narrow diagnostic concept of schizophrenia (DSM/ICD), which is presumably insensitive when approaching the outer boundaries of the disease. The sample size is reliably manageable for the explorative cluster-searching methodology, but in the comparing of clusters we tried to decrease the false positive results using the False Discovery Rate method. So – after adjusting by FDR - a part of the differences have significance level cca. 0.0001, the other differences have significance level below 0.04. These latter results of the comparisons should be interpreted with care.

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

## Introduction

From a research point of view, schizophrenia is widely accepted to be a heterogeneous illness. This follows from the presumed dimensional nature of the disease characteristics, and from the fact that both the outer borders within the group of psychotic disorders, and the inner borders of the assumed subgroups of schizophrenia are evenly uncertain and fuzzy. Allowing heterogeneity, the obviously non-overlapping clinical, pathophysiological and etiological diversity can be substantially decreased by the determination of etiologically valid subgroups. The deficit syndrome was defined as a putative subtype of schizophrenia by Carpenter et al. [7]. According to their definition, the syndrome is characterised by primary, idiopathic and enduring negative symptoms, which are marked and present as traits in clinically stable periods as well. Currently the diagnosis of the syndrome is based on clinical symptoms applied by scales such as the Schedule for the Deficit Syndrome (SDS) [16] or the Proxy for the Deficit Syndrome (PDS) [53]. The validity of the deficit syndrome construct is underlined by the results of a fifteen-year-long research [54] which differentiated the two subgroups by demographic [55], neurocognitive [56-61] and emotional features [62], and by structural [63, 64], and functional brain imaging differences [65], and by therapeutic characteristics [66,67]. According to the authors, this distinction is not only a reliable and valid construct, but it also unfolds categorically distinct subgroups [68].

Like other psychiatric diagnostic categories, the diagnosis of deficit syndrome shows minor, but relevant instability. Irrespectively of the categorical diagnostic constraint, the distribution of the syndrome within schizophrenia could be dimensional, as well. This assumption would explain the practical observation that the diagnosis proves to be unstable in a certain number of patients when followed up longitudinally, even when the diagnostic crtieria of deficit or even nondeficit syndrome are based on thorough longitudinal and cross-sectional considerations. This observation was underlined by the results of a follow-up study of diagnostic validity which found that using a repeated diagnostic process many years later, the initial diagnosis was modified to the opposite in 17% of the cases of the deficit group, and in

12% of the nondeficit group [69]. A recent study using factor analysis verified that the occurrence of negative symptoms were unrelated to other clinical dimensions, and identified two factors (diminished emotional expression and anhedonia-asociality) which point at the multidimensional nature of negative symptoms [70]. Another research using factor analysis on the SDS symptoms revealed two, generally simultaneously occurring factors (avolition and emotional expression) within the deficit syndrome [71]. Furthermore, Möller et al. [72] in a fifteen-year-long follow-up study revealed that although negative symptoms - primary negative or deficit syndrome in a narrower sense - are most pronouncedly present in schizophrenia, they can also be detected in a larger group of functional psychoses and occur rarely in affective psychoses also. This observation was specified by Peralta and Cuesta [3] who studied the distribution of temporary and permanent, and also of primary and secondary negative symptoms in a mixed group of psychotic syndromes, even outside of the diagnostic category of schizophrenia. They found that deficit syndrome was not specific to schizophrenia. Persistent primary symptoms associated with the clinical diagnosis of schizophrenia - depending on the diagnostic method – were present in 14-37% of the cases, while their occurrence was 2-22% in other non-schizophrenic psychoses. According to Peralta and Cuesta [3], the differentiation of negative syndromes as primary/secondary symptoms seemed to be not as critically important as it was assumed by the original concept.

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 (because of its nominal value). Patients could be divided into a more favourable and a more unfavourable group by both of the two different grouping methods. 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). Since the fourth group was monoelemental, i.e. we found only one patient

in the whole test group 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

We performed detailed analyses to explore the nature of the relationship between the two different divisions. To compare the three groups, Kruskal-Wallis test and chi-square test were used for continuous variables and categorical variables, respectively. In case of the 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. SPSS 15.0 for Windows (SPSS Inc., Chicago, IL) was used.

## Results

We analyzed the distributions of changed diagnosis of the deficit syndrome in the three statistical groups. Deficit syndrome was identified in thirteen patients belonging to cluster S (first group) at the end of the research, four of them were classified with nondeficit diagnosis previously. Ten subjects from cluster S were diagnosed as nondeficit patients (second group) at the end of the research, four of them had been classified as subjects with deficit syndrome beforehand. Twenty-six patients of cluster Z were diagnosed as nondeficit subjects at the end of our research (third group), one of them had been diagnosed with deficit syndrome formerly. The category of deficit/nondeficit syndromes was altered in 18.0% of all patients – in accordance with previous research data [69]. It excels from frequency distributions that cluster S was broader than deficit syndrome. Importantly, patients with altered deficit diagnosis in all three groups and the group of nondeficit patients in cluster S (second group) were not identical.

The three statistical groups differed from each-other on several variables. In accordance with the focused aim of the analysis, we compared pairwise Group1 vs. Group2 in order to evaluate whether patients with deficit or nondeficit syndrome had separated from each-other within the cluster S; and also the Group2 vs. Group3 to examine whether patients with nondeficit syndrome from cluster S and Z had separated from each-other (Table 2.1).

**Table 2.1.** Significant differences between the statistical subgroups

| | raw #*p* Groups 1-2-3 | **raw *p* Groups 1 vs 2** | **raw *p* Groups 2 vs 3** | raw *p* Groups 1 vs 3 |
|---|---|---|---|---|
| Education, years | **0.0005**** | 0.7844 | **0.0037*** | **0.0006**** |
| Full scale IQ | **0.0006**** | 0.5999 | **0.0099** | **0.0002**** |
| PANSS, Positive | **0.0219*** | 0.1151 | 0.2253 | **0.0093**** |
| PANSS, Negative | **0.0000***** | **0.0147** | **0.0039*** | **0.0000***** |
| PANSS, General | **0.0015**** | 0.1862 | **0.0376** | **0.0004**** |
| PANSS, Total | **0.0001**** | **0.0493** | **0.0134** | **0.0000***** |
| SANS, Affective flattening | **0.0011**** | 0.3128 | **0.0343** | **0.0004**** |
| SANS, Alogia | **0.0000***** | 0.2316 | **0.0007**** | **0.0000***** |
| SANS, Avolition | **0.0002**** | 0.2839 | **0.0102** | **0.0000***** |
| SANS, Anhedonia | **0.0001**** | 0.1151 | **0.0204** | **0.0000***** |
| SANS, Inattention | **0.0002**** | 0.6049 | **0.0027*** | **0.0003**** |
| WCST, completed categories | **0.0000***** | 0.4679 | **0.0000***** | **0.0000***** |
| WCST, perseverative errors | **0.0002**** | 0.2230 | **0.0009*** | **0.0004**** |
| WCST, conceptual level responses | **0.0000***** | 0.9725 | **0.0001**** | **0.0000***** |
| NES, Sensory integration | **0.0012**** | 0.3575 | **0.0228** | **0.0005**** |

*Group1* cluster S and deficit syndrome (n=13); *Group2* cluster S and nondeficit syndrome (n=8); *Group3* cluster Z and nondeficit syndrome (n=28); *PANSS* Positive and Negative Syndrome Scale; *SANS* Scale for the Assessment of Negative Symptoms; *WCST* Wisconsin Card Sorting Test; *NES* Neurological Evaluation Scale; *p* values are based on Mann-Whitney *U* test, #*p* values are based on Kruskal-Wallis test; **p* <0.05 using Step-down Bonferroni correction, ***p* <0.01 using Step-down Bonferroni correction, ****p* <0.001 using Step-down Bonferroni correction

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

Only two significant differences were found between deficit and nondeficit subgroups in raw value within cluster S. The severity of negative symptoms measured by the PANSS subscale and total score of the PANSS-scale were more expressed in patients with deficit syndrome than in patients with nondeficit syndrome, but these differences diminished after correction. That is, 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, a significant difference was found within the nondeficit group between patients of the two clusters. Patients who belonged to cluster S had significantly lower education, even after correction (education, years: Group2: 9.90 (±1.73), Group3: 12.04 (±2.05), $p$ <0.05 based on Mann-Whitney $U$ test and corrected by Step-down Bonferroni method). In these patients the full scale IQ was significantly lower also, but only according to raw significance values. 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 even after correction (PANSS, negative subscore: Group2: 17.30 (±4.14), Group3: 12.36 (±4.90), $p$ <0.05 based on Mann-Whitney $U$ test and corrected by Step-down Bonferroni method). Similarly, we found more pronounced cognitive disturbances indicated by the alogia and inattention dimensions of the SANS-scale in subjects of cluster S (SANS, alogia subscore: Group2: 1.90 (±0.88), Group3: 0.58 (±0.78), $p$ <0.01 based on Mann-Whitney $U$ test and corrected by Step-down Bonferroni method; and SANS, inattention subscore: Group2: 1.70 (±1.06), Group3: 0.58 (±0.83), $p$ <0.05 based on Mann-Whitney $U$ test and corrected by Step-down Bonferroni method). The similar differences were found regarding general symptoms and total score of the PANSS-scale and affective flattening, avolition and anhedonia subscores of the SANS-scale according to raw significance values, but these differences diminished after correction. Differences in neuropsychological parameters between patients belonging to the two clusters within the nondeficit group were the other line of important evidences. The measured scores of WCST indicated a more expressed disturbance in cluster S, a difference which remained significant after correction

(WCST, completed categories: Group2: 1.20 (±1.40), Group3: 4.52 (±1.69), $p$ <0.001 based on Mann-Whitney $U$ test and corrected by Step-down Bonferroni method; WCST, perseverative errors: Group2: 31.90 (±13.55), Group3: 16.64 (±9.62), $p$ <0.05 based on Mann-Whitney $U$ test and corrected by Step-down Bonferroni method; WCST, conceptual level responses: Group2: 20.90 (±19.66), Group3: 58.68 (±20.63), $p$ <0.01 based on Mann-Whitney $U$ test and corrected by Step-down Bonferroni method). As for inhibiting executive function - measured by the inhibitory index of the Directed Forgetting task - 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. While the performance of the cluster S patients within the nondeficit group resulted in an inhibitory index with a negative mean value, that of the cluster Z patients indicated a positive value (Directed forgetting, inhibitory index: Group2: -0.50 (±1.41), Group3: 0.75 (±1.29), $p$ =0.105 based on Mann-Whitney $U$ test and corrected by Step-down Bonferroni method). In contrast to the cluster Z patients whose positive index suggested - in some degree – 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

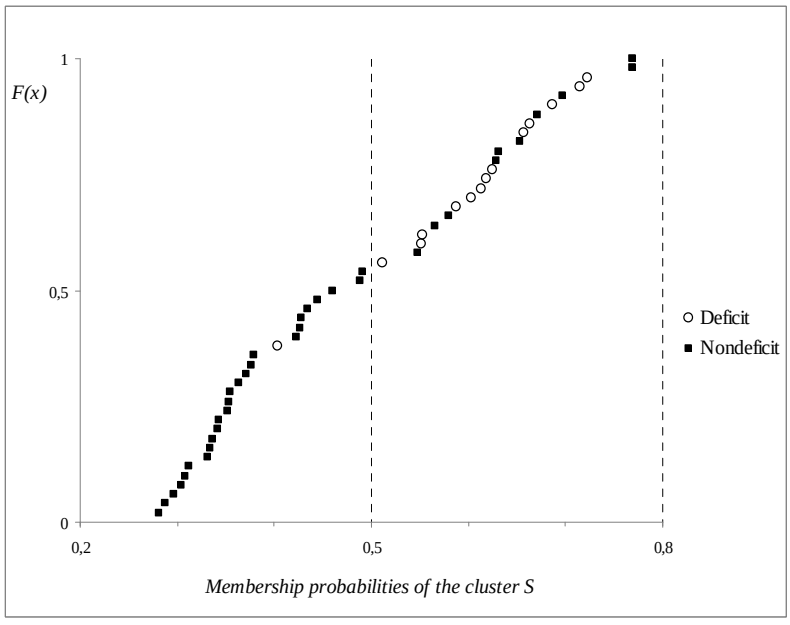
Although we could not perform a full statistical comparative analysis, since we found only a single patient in our subject pool with deficit syndrome belonging to cluster Z, we detected some important differences. According to our results, cluster S proved to be homogeneous, contrary to the nondeficit syndrome. On the grounds of these results it seems to be a feasible conclusion that cluster S is not identical with deficit syndrome, and the more favourable cluster Z is not identical with 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

## Introduction

The brain structural changes correlating with mental disorders are usually subtle ones and are not easily revealed with macroscopic volumetric analyses. Schizophrenia is in part a neurodevelopmental disorder based on multifocal brain structure changes with a background of defective neuronal migration, myelinisation and/or cortico-cortical wiring. As a consequence, this disorder is characterised by defective cytoarchitectonical and neurochemical connections within and between certain neuronal networks. Many neocortical areas are affected in schizophrenia, principally the structures of the prefrontal and medial paralimbic regions. Recent imaging studies revealed changes in the middle frontal gyrus, the anterior cingulate gyrus, the paracingulate gyrus, the insula as well as in the frontomedial and orbitofrontal cortical areas [73]. An alteration of the superior temporal gyrus (STG) was also found, more specifically of the planum temporale, the supramarginal gyrus and the Heschl's gyrus [74]. Among subcortical areas the impairment of the amygdala-hippocampus complex [75] and of the thalamus [76] was primarily detected. A significant right>left asymmetry was found in certain areas such as the STG, in which left>right difference is typical among healthy subjects, and also in the amygdala-hippocampus complex [77,78]. Among developmental anomalies, midline deviations are typical in schizophrenia. The dilatation of the third ventricle and the cavum septi pellucidum (CSP) has also been found to be characteristic [79]. In cases with childhood onset, changes are apparent before the onset of psychosis [80].

Research of brain morphology is based on the assumption that macroscopically detectable morphological changes reflect microanatomical changes in certain brain areas and that they are in connection with the functioning of these areas. The difficulty is that there are large-scale neuronal networks in the background of high-level cognitive functions and these could be injured in different nodes and tracks. Disorders of cognitive functions are not simply related to well observable architectural changes as some subtle neurochemical or cythoarchitectural changes can cause functional deficits, too. Hence, correlations of cognitive

dysfunctions and brain architectural changes should be evaluated and interpreted very carefully. Several different brain maps should be assessed in the process of analysis of structure and function, first of all the separate surface maps of convolutions and fissures together with maps of the grey and white matter. Beside these there are some cytoarchitectural maps such as Brodmann's well-known cortical map based on the cell structure of the brain [81]. In addition, maps of cognitive functions have been developed based on the electrophysiological and functional imaging studies of cognitive neuroscience.

There has been a continuous development in the methods of topographical mapping of in vivo magnetic resonance imaging (MRI) data in the past decades. One of the most important innovations was a parcellation method by Rademacher et al. [82] and its revised version published by Caviness et al. [83] which has become widely accepted in research on cognitive brain functions and mental disorders. This method is based on earlier parcellation techniques, especially on that of Jouandet et al. [84], which took into account individual variations and also the relationship of sulci and cytoarchitectonical regions. It also considers the most recent information about cortico-cortical and thalamo-cortical connections. Another valuable parcellation method has recently been developed by Crespo-Facorro et al [85]. Crespo-Facorro et al. [85] realised that landmarks cannot always be identified on each slice as a result of individual variations, therefore they suggested a method by which the continuity of target regions is captured on consecutive slices. They divided the neocortex into 41 regions. Their procedure unites the advantages of the two-dimensional definition of parcels in three orthogonal planes (coronal, sagittal and transaxial) and of the simultaneous visualization of the three-dimensional reconstruction of the brain.

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. In this study, we applied the method of Crespo-Facorro et al., [85] (see also [86]), and we used the method of a French research group for the volumetric measures of the hippocampus [87]. 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 [11] and ICD-10 criteria for research [12]. 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) [88], 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 [13]), had a minimum of 8 years of education (primary school), and were able to give informed consent. Subjects were excluded if they had a lifetime history of neurological illness, any medical illness known to affect brain structure, head injury with loss of consciousness for more than 10 min, psychoactive substance abuse within the last 6 months, or any medical illness that could significantly constrain neurocognitive functions. Patients were excluded if they had previously undergone electroconvulsive therapy.

The demographic and clinical characteristics of the subjects are shown in Table 3.1. Although there was a significant difference between the groups in education and IQ measured by the WAIS, the average of the schizophrenic group was above 100, and the minimum score was 86. All patients comprehended and carried out all instructions. There was no difference between groups in handedness, every subject enrolled in the study was right-handed judged by the Neurological Evaluation Scale (NES) [16]. Because of the low subject number we did not consider the effect of antipsychotics. Three of the patients were treated with conventional neuroleptics, six of them with atypical antipsychotics, and four persons with combination of an atypical oral and a conventional depot injectable neuroleptics. All substances were prescribed in medium dose according to their medication protocol. No one of the patients had any known family history of psychotic disorders.

**Table 3.1** Demographic and clinical characteristics of the subjects

| | | Control (n =13) | Schizophrenia (n =13) | *p* |
|---|---|---|---|---|
| Age (years) | | 29.3 (4.7) | 25.9 (5.4) | 0.139 |
| Education (years) | | 14.4 (2.6) | 11.1 (1.9) | 0.004 |
| Full scale IQ | | 124.3 (12.7) | 101.1 (12.3) | 0.002 |
| Age at onset (years) | | | 21.9 (4.8) | |
| Duration of illness (years) | | | 3.9 (3.0) | |
| Relapses | | | 3.2 (2.1) | |
| PANSS | Positive | | 9.9 (3.8) | |
| | Negative | | 14.0 (5.8) | |
| | Global | | 27.0 (9.0) | |
| | Total | | 50.9 (15.3) | |
| SANS | Affective | | 1.2 (1.1) | |
| | Alogia | | 1.2 (1.1) | |
| | Avolition | | 0.9 (1.0) | |
| | Anhedonia | | 1.6 (1.2) | |
| | Attention | | 0.9 (1.1) | |
| SAS | | | 2.5 (2.3) | |
| BAS | | | 0.2 (0.6) | |
| AIMS | | | 0.2 (0.4) | |
| NES | Sensory integration | 0.1 (0.3) | 4.1 (2.1) | 0.000 |
| | Motor coordination | 0.1 (0.3) | 1.0 (1.0) | 0.026 |
| | Motor sequencing | 0.3 (0.5) | 4.9 (2.6) | 0.000 |
| | Global | 3.6 (2.6) | 19.5 (3.9) | 0.000 |
| SDS | Deficit syndrome | | 2 patients | |
| | Non-deficit | | 11 patients | |

Values represent mean (SD)

*p* values are based on Mann-Whitney *U* test

**Clinical tests**

Clinical symptoms were assessed by psychiatrists using the Positive and Negative Syndrome Scale (PANSS) [13], the Scale for the Assessment of Negative Symptoms (SANS) [14], the Schedule for the Deficit Syndrome (SDS) [15], the Neurological Evaluation Scale (NES) [16], the Simpson–Angus Scale (SAS) [17], the Abnormal Involuntary Movement Scale (AIMS) [18], and the Barnes Akathisia Rating Scale (BAS) [19], with assessment of the demographic and epidemiologic data at the time of the MRI study.

**Working memory tasks**

The verbal working memory capacity was measured with the Hungarian Digit Span Task [24], and the Hungarian Nonword Repetition Task [24]. The Corsi Blocks Task [25], and the Visual Patterns Test (VPT) [26] were used for measuring visuo-spatial working memory capacity. The executive functions were assessed with the Wisconsin Card Sorting Test (WCST) [27,28], with the Tower of Hanoi Task [29], and with the Letter Fluency [30] and also with Category Fluency Tasks [31].

**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 with the following parameters: echo time (TE)=3 fr/ms, repetition time (TR)=33 ms, number of excitations (NEX)=1, rotation angle=458, field of view (FOV)=24_18, slice thickness=1.5 mm, and acquisition matrix of 256_192. Two-dimensional FSE (fast spin echo) T2 sequences were gained as follows: echo time (TE)=91.1 fr/ms, repetition time (TR)=4300 ms, number of excitations (NEX)=3, field of view (FOV)=25_19, acquisition matrix: 384_192. The in plane resolution was 1016_1016 mm in all three planes. 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. The initial step was the identification of the reference anatomical landmarks that served as boundaries on each plane. The second

step was to determine the regions of interest (ROIs) for tracing, and the third step was to trace by hand in each ROI the surface area or grey matter on the appropriate coronal and axial slices. 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 our preliminary report we present 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 ($F(1,24)=4.731$, $p$=0.04) 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. In summary, we found that the asymmetry of the SG was reversed in the patient group with schizophrenia.

A similar tendency toward a hemispheric asymmetry reversal was found in the volume of the anterior cingulate gyri (Group X Side interaction: F(1, 24)=1,282, $p$=0.269; group effect: F(1, 4)=3.057, $p$=0.093). There was a significant main effect of lateralization with left side dominance in the volume of the orbitofrontal cortex for both the absolute (F(1, 21)=5.033, $p$=0.036) and relative values (F(1, 21)=5.137, $p$=0.034). 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 ($p$<0.001), motor coordination ($p$<0.05), and motor sequencing ($p$<0.001) 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 (data not shown).

## 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. One recent study found bilaterally decreased volumes of the SG [89], and another two found a decreased volume and [90], or [91] decreased surface of the right SG in schizophrenia patients. These findings underlie the importance of these regions in the appearance of schizophrenic symptoms. The SG (Brodmann area, BA 11) is situated medially to the

olfactory groove (olfactory sulcus) at the ventromedial edge of the frontal lobe, and is considered to be the frontal extension of the anterior cingulate gyrus. The SG has dense inhibitory connections with the superior temporal gyrus (STG) and the centres of the auditory cortex, and it 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 [92]. 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, - these earlier results might partly and indirectly support the observations of our main study suggesting hemispherical differences. 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. But the performances of subjects did not differ in the visuo-spatial and inhibiting (and planning) executive functions.

# CONCLUSIONS OF THE THESES

Although the MRI-neurocognitive pilot study has a more restricted scope than the main cluster-exploring one, their results may be partly connectable. The group of young male patients with schizophrenia predominantly (92.3%) from cluster Z differed from the group of healthy controls in areas of verbal working memory, verbal fluency and neurological soft signs. Their performances, however, did not differ in the visuo-spatial working memory and inhibiting executive functions. Remarkably, by their perfomance in normal range even in these areas (examined with indentical methods in a wider group of patients) they were separated from their patient partners form cluster S, who performed distinctly worse in these tasks. In addition, these latter patients from cluster S performed badly (similarly to patients from cluster Z) also in those areas where the cluster Z patients had separated from healthy controls. The neurological soft signs could separate the cluster Z patients from healthy subjects, but in the cluster S the disorder of the sensory integration was more pronounced, especially on the left body side.

Thus, we can draw the following conclusions on the basis of our studies:

1. 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.
2. Despite of a remarkable statistical correspondence between the deficit-nondeficit syndromes and these neuropsychiatric clusters, the two divisions were not the same.
3. 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.
4. 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.

5. Based on the results it seemed that these subgroups represented different types, not only forms with different seriousness of the same type.
6. 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.
7. 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.
8. 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.
9. 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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