Two subgroups of schizophrenia identified by systematic cognitive neuropsychiatric mapping

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Abstract

Description of the heterogenous nature of the schizophrenia in the phenomenological, pathophysiological, and etiological areas is under way, however, the relations between heterogeneity-levels are still unclear. We performed a robust cross-sectional study: a systematic neuropsychological battery; assessment of clinical symptoms, neurological soft signs, morphogenetic anomalies and smell identification; and measurement of event related potentials were performed on 50 outpatients with schizophrenia in their compensated states. An explorative fuzzy cluster analysis revealed two subgroups in this sample, which had separated from each-other on symptomatological, cognitive and neurological levels. The patterns of cognitive dysfunctions and neurological developmental anomalies equally indicate that there maybe some hemispherial differences between the patients belonging to the different clusters.

Key words: Schizophrenia, Heterogeneity, Clusters, Neurocognitive, Hemispherial

Introduction

During the first decades of the systematic research the phenotype of schizophrenia was tried to be determined mainly by describing the cross-sectional constellations of the clinical symptoms and the longitudinal peculiarities in their course. We can regard this as the phenomenological, horizontal surface analysis of the range of phenomena. The powerful and heuristic hypothesis of Crow [1] catalysed the multilevel conception and the neurobiological research process of the disease. According to recent observations, the dimensions describing nowadays the symptoms of schizophrenia (disorganization, psychosis, negative factors; or deficit-nondeficit) are supposedly not specific to the disease [2, 3]. Currently, the description of the heterogenous nature of the disease is under way, in the phenomenological, pathophysiological, and etiological areas, as well [4]. However, the relations between heterogeneity-levels are still unclear.

In the very beginning of the research Kraepelin and Bleuler supposed, and nowadays Andreasen [5] and Saugstad [6] assumes, a unified morbidity process in the background of the disease, the phenomenological manifestations of which – e.g., at the level of clinical features - are reflecting a diverse distribution within a uniform dimension. Contrarily, others see the heterogeneity of the disease as the distinct manifestations of different morbidity processes. The two-type concept of Crow, and the most popular and widespread partition in our days, the deficit-nondeficit division [7] equally suppose the possibility and effect of more than one morbidity processes (and their possible interactions) in the background.

Research results of last decades caused a shift from the categorical approach toward the dimensional one both in understanding of the illness [8], and in its taxonomic concepts [see for review 9]: this approach has been reflected in the teoretical design of this research also. A robust cross-sectional study was performed. According to Wimsatt [10] robustness means multiple determination: different features of objects of reality can be apprehended, measured, understood, and defined in a variety of independent ways. This study gives (’vertical’) insights to 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) stand in its background. In our work-hypothesis we presuppose, that (1) schizophrenia (or schizophrenias) forms (or form) a so-called ’natural category’ from the scientific philosophical point of view; (2) the category is heterogenous genetically, neurobiologically, on both cognitive and clinical levels, and the heterogeneities have dimensional nature; (3) subgroups can be separated within the category, and partly different morbidity processes stand in their background; (4) the expression of the morbidity processes characterizing the subgroups weakens as we move away from the center of the subgroups: they have prototypical nature; (5) one patient can belong to several subgroups at the same time, its location within the multidimensional space of subgroups of the category can be characterized with the distances from the subgroup centroids, that is with the measures of the expressions of morbidity processes typical in the different subgroups.

Main question of our study was whether the schizophrenia could be divided into subgroups with a series of systematic cross-sectional cognitive neuropsychiatric studies? We had two accessory questions as well: If subgroups would separated from each-other, what depths of the systems could their divergence be traced back to? And, if such diverging subgroups existed, were they suggesting a unified morbidity, or multiple ones? The manuscript summarises our results.

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 was not restrictive, the only enrollment criteria were relative stable clinical state and cooperation with the study. The exclusion criteria were related to the 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), which could significantly constrain the neurocognitive performances. So the selected patients represented the population looked after at our department. We succeeded in enrolling patients from the ones both with the most favourable and unfavourable courses. All patients had a diagnosis of schizophrenia DSM-IV [11] and 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 able to give informed consent. The average years in education was 11.00 (SD=2.17), the average full-scale IQ (WAIS) was 100.17 (SD=15.40). All patients comprehended and carried out all instructions. All of them were outpatients in stable interepisodic state under antipsychotic medication. Due to the variety in drug types and doses, for statistical purposes the pharmacotherapy applied to patients was divided into 3 categories in the first approach: first generation antipsychotic, second generation medicine, and combinations of antipsychotics. All substances were prescribed usually in medium doses according to their medication protocol. Since identifying mental diseases in the family history of most of the patients was unreliable (due to the lack of medical documentation), we could not analyze statistically these pieces of 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) [13], the Scale for the Assessment of Negative Symptoms (SANS) [14], the Schedule for the Deficit Syndrome (SDS) [15].

Neurosomatic alterations

The neurological developmental signs were assessed using the Neurological Evaluation Scale (NES) [16]. Fourteen of the 26 items of the NES scale assess neurological signs independently on the two sides, which gives an opportunity to analyse laterality. The potential pharmacogenic extrapyramidal symptoms were assessed with the Simpson-Angus Scale (SAS) [17], the Abnormal Involuntary Movement Scale (AIMS) [18], and the Barnes Akathisia Rating Scale (BAS) [19]. A list of minor physical anomalies (MPAs) containing 57 minor signs collected by Mehes was used for mapping the malformations [20, 21, 22]. Three examiners investigated the patients, the interrater reliability was >75% (kappa coefficient). The cross-cultural smell identification test (CC-SIT) was used for assessing smell identification [23].

Neuropsychological mapping

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]. For measuring inhibitory control of memory we used the so called directed forgetting (DF) procedure [32, 33, 34] by lists. Following Miyake and his colleagues [35], we aimed at investigating three components of the executive system. The perseverative errors on WCST were used as scores 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 analyse individual differences in inhibitory abilities of activated memory representation („Inhibition") [36, 37]. An inhibitory index was calculated by comparing the List 1 performances in "Forget" and "Remember" conditions of the directed forgetting procedure [38, 39]. As for mentalisation the present study adapted the method of Tenyi et al. [40] to unveil any deficit in subjects' mentalization abilities. Following the authors, subjects were given first-order and second-order mentalization tasks, and also metaphor and irony tasks to test their mentalization skills.

Electrophysiology

The recordings were done with a Nicolet Bravo Mulimodality System (EMS Co, Korneuburg, Austria) using the Pegasus software (EMS Co, Korneuburg, Austria). The EEG signal was amplified 20,000 times with the sampling frequency of 1024 Hz and a band pass filter setting of 0.1-100 Hz. We performed three auditory evoked potential paradigms which are extensively investigated in schizophrenia and the abnormailites of which were 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 hours long session. Subjects were seated comfortably in a chair, asked to keep their eyes opened, and were 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 and presented binaurally with the intensity of 80 dB sound pressure level (SPL). EEG data was 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 reference and the ground was placed at position FCz. Additionally, we recorded vertical eye movements of the left eye from above and below the eye. We kept electrode impedances below 7 kOhm. 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 rather are assigned membership degrees between 0 and 1 indicating their partial memberships. One of the most widely used algorithms is the Fuzzy c-Means algorithm [41, 42, 43]. By this approach clusters are determined by the use of cluster prototypes. The prototype is in most cases a point in the n-dimensional space. The similarity is measured by calculating the distance from this point.

At first the missing values were substituted with computed ones by a weighted average of the corresponding values of the 3 closest elements based on the (most often the 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. Then we applied the Fuzzy C-Means algorithm to attribute cluster membership values to patients.
The variables used during the explorative clustering (51): Age; Education; Full scale IQ; Age at onset; Relapse-duration ratio; Digit span, forward, backward; Corsi blocks, forward, 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, 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, total; SANS, Affective flattening subscale; Alogia subscale, Avolition subscale, Anhedonia subscale, Inattention subsclae; NES, sensory inhibition subscale, motor coordination subscale, motor sequencing subscale, the 'other' subscale, total; Simpson-Angus Scale; Barnes Akathisia Scale; Abnormal Involuntary Movement Scale; P50 wave, latency, amplitude; MMN frequency deviant stimuli, latency, amplitude; MMN duration deviant stimuli, latency, amplitude; P300 wave, latency, amplitude.
The excluded variables either have nominal values (DSM diagnostic subgroups, remission types, deficit-nondeficit categorization, gender, handedness by NES, type of therapy), or in case of them relatively numerous (>20%) values were missing (minor malformations, phenogenetic variants, smell threshold, smell identification test).

Comparing the groups
After the explorative clustering, statistical tests were applied to find which variables are important in forming clusters, that is the explored clusters were compared. Distribuiton of continuous variables was tested by Kolmogorov-Smirnov test with a Lilliefors significance level for testing normality. Continuous variables in the explored clusters were compared by Mann-Whitney U-test, categorical variables were compared by Fisher's exact test. To avoid the problem of multiple testing (which greatly increases the probability of declaring false significances), univariate p-values were adjusted by False Discovery Rate. 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 doesn't depend on the number of elements, beside this, our control examination - done according to the scientific praxis on a weakly reduced sample (in our case by five subjects) - resulted in the same outcome.

Results

Cluster analysis

The data set contained 50 subjects, and 60 variables, and 6.27 percent missing variable values. Fuzzy C-Means (FCM) clustering algorithm was executed for each number of centroids between 2 and 5 picking the one as the true partition with the best validity index. (On the basis of clinical experiences, the subdivisions of currently accepted diagnostic systems and the historical divisions, the number of possible subgroups was anticipated to be below six.) The analysis

identified the separation of two clusters. We named these cluster ‘S’ and cluster ‘Z’ based on the abbreviations of schizophrenia literature (SZ) (S could suggest: more Serious features) not 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. Ninty-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 rise of the number of runs did not result any further changes in the results of clustering.

We reduced the number of analysed 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 reduced the original 51 variables to 10 at last, and we got practically the same clustering result. With widening the centroids we got high probability values: the mean membership probability value in case of patients belonging to the cluster S was 0,636, and those belonging to the Z was 0,629. The 10 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, 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. Statistical tests were applied to find which variables were important in forming clusters. The validity of clusters was qualified by high correspondence (96%) of the independent runs of the algorithm and the mean values above 60% of the patients’ membership probabilities.

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 parameters were significantly lower in cluster S (Table 1). In addition, the two groups were differing in handedness determined with the NES: mixed-handedness was significantly more frequent in cluster S (Table 1). The type of the pharmacotherapy influenced neither the subgroup forming (analysed with 2-sided Fisher’s exact test) (Table 1), nor the neurocognitive performances (analysed with the Kruskal-Wallis and chi-square tests) (data not shown).

Table 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)	0.211
Gender ratio, male/female %	56.5/43.5	51.9/48.1	* 0.782
Education, years	9.78 (1.68)	12.04 (2.01)	**0.00035**
Full scale IQ	90.21 (12.42)	108.39 (12.62)	**0.00035**
Age at onset, years	25.43 (8.07)	24.07 (7.74)	0.453
Duration of illness, years	10.30 (8.89)	8.07 (7.68)	0.408
Relapse	5.32 (4.11)	4.44 (5.03)	0.275
Handedness, by NES	Right 77.3 % Left 0.0% Mixed 22.7 %	Right 100.0 % Left 0.0% Mixed 0.0 %	* **0.015**
Antipsychotic therapy	SGA 78.3 % FGA 13.0 % Combination 8.7 %	SGA 63.0 % FGA 14.8 % Combination 22.2 %	* 0.394

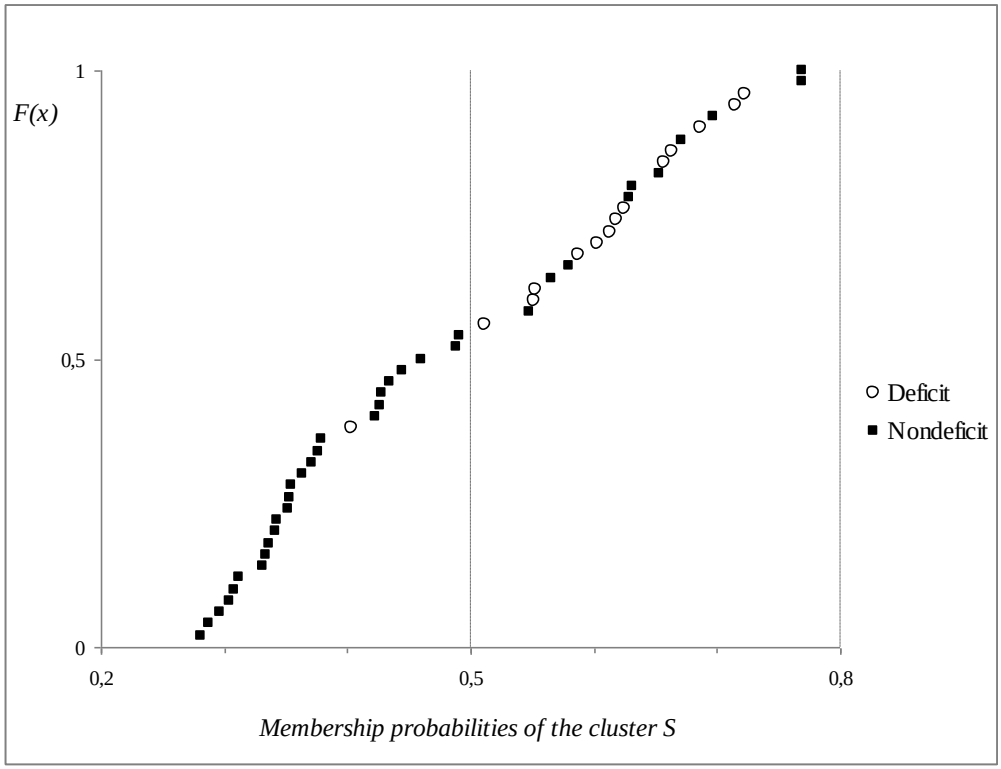
Values represent means (SD)
p values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate
**p* value is based on 2-sided Fisher's exact test and adjusted by False Discovery Rate
NES: Neurological Evaluation Scale
SGA: second generation antipsychotic
FGA: first generation antipsychotic

Diagnostic features and relation with the deficit/nondeficit division

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

There was a remarkable correspondence between the clusters and the deficit-nondeficit syndromes, despite of that the definition of deficit syndrome was based on clinical symptoms, and our clusters were identified by a complex neuropsychiatric analysis from which the deficit syndrome as an attribute was excluded. In the cluster Z (N=27) the 96.30% of the patients had nondeficit, the 3.70% of the patients had deficit diagnose; while in the cluster S (N=23) the 56.50% of the patients had deficit, the 43.50% had nondeficit diagnose (p=0.0003, chi-square test and False Discovery Rate). However, despite of the marked overlapping the two divisions were not the same: the relationship of the patients' memberships to the clusters S versus Z and to the deficit or nondeficit subgroups is illustrated on the 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 or without 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 (96,30%) in the cluster Z had nondeficit diagnosis, only 56,50% of the patients had deficit syndrome diagnosis in the cluster S.

Symptomatologic differences between the clusters

Obvious symptomatologic differences could be demonstrated between the patients of the two clusters. Cluster S patients in their compensated state had more emphasized symptoms in every aspect of the examined dimensions of clinical symptoms (Table 2). While in the interepisodic state the cluster Z patients had - in general - no relevant clinical symptoms (possibly questionable negative signs), the cluster S patients had - commonly - some questionable or existing positive and general symptoms (without causing relevant dysfunctions), and also obvious, mild negative signs (Table 2). In both clusters the anhedonia was pronounced among negative symptoms (Table 2).

Table 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 means (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 produced a significantly poorer performance in the semantic fluency task, and robustly worse WCST (Table 3).

Table 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)	0.146
Digit Span, backward	3.65 (0.89)	4.07 (0.96)	0.146
Hungarian Nonword Repetition Task	6.29 (1.27)	6.37 (1.08)	0.737
Corsi blocks, forward	5.13 (0.92)	5.63 (1.15)	0.194
Corsi blocks, backward	4.26 (1.21)	5.15 (1.20)	**0.024**
Visual Patterns Test	5.73 (1.52)	7.00 (1.84)	**0.031**
Letter fluency, words	7.36 (2.37)	8.81 (2.56)	0.115
Letter fluency, errors	0.71 (0.80)	0.81 (0.82)	0.632
Semantic fluency, words	12.81 (3.16)	15.81 (3.90)	**0.031**
Semantic fluency, errors	0.43 (0.45)	0.58 (0.67)	0.453
Towers of Hanoi, movements	13.05 (5.71)	10.44 (3.91)	0.194
Towers of Hanoi, errors	0.38 (0.74)	0.19 (0.48)	0.453
WCST, completed categories	0.95 (1.24)	4.50 (1.66)	**0.000006**
WCST, perseverative errors (%)	37.57 (19.73)	16.92 (9.54)	**0.00028**
WCST, conceptual level responses (%)	19.76 (16.32)	58.35 (20.29)	**0.00002**
Theory of Mind, first order	0.86 (0.36)	0.96 (0.59)	0.559
Metaphor comprehension	2.19 (1.21)	2.93 (0.87)	0.056
Theory of Mind, second order	1.10 (0.63)	0.85 (0.60)	0.247
Irony comprehension	1.81 (1.44)	2.67 (1.52)	0.102

Values represent means (SD)
p values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate

Primary executive functions in the clusters

We have not found an overall difference in working memory functions between the two clusters, as the participants produced in the same range on the verbal memory tasks. However, as Table 4 shows, we found strongly significant differences in tasks measuring shifting and in visual working memory functions, and nearly significant difference in inhibition function.

Table 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)	0.146
Visual Updating: Visual Patterns Test	5.73 (1.52)	7.00 (1.84)	**0.031**
Inhibition: Directed Forgetting inhibitory index	-0.67 (1.40)	0.35 (2.06)	0.058
Shifting: WCST, percentage of perseverative errors	37.57 (19.73)	16.92 (9.54)	**0.00028**

Values represent means (SD)
p values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate

Neurological alterations in the clusters

The summed up frequency of signs was notably higher in cluster S, in which the disorder of sensory integration disorder was remarkably high (Table 5).

Table 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)	**0.0009**
Motor coordination	2.50 (2.20)	1.52 (1.65)	0.146
Motor sequencing	5.27 (3.43)	4.37 (3.13)	0.383
Others	10.00 (4.08)	8.96 (4.42)	0.539
Total	24.09 (8.30)	18.52 (8.09)	**0.024**

Values represent means (SD)
p values are based on Mann-Whitney *U* test and adjusted by False Discovery Rate

Of the 14 neurological signs can be assessed by body side, those belonging to sensory integration showed a significant difference. Sensory integration at level of hemispheres are represented by those items of the NES which 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. But, 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 which 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 did correlate 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 case of minor malformations, or in case of phenogenetic variants. Besides, we did not find a regional difference by side in the occurrence of anomalies either within the whole group of patients (which suits literature data) [44] or between the two groups.

Smell identification alterations in the clusters
We have not found significant difference between the two groups' performances on the smell identification task.

Electrophysiological alterations in the clusters
We did not find a 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 neither of the P50 waves, nor of the MMN waves (neither in case of frequency deviant, nor in case of duration deviant stimuli), nor in case of P300 waves. In addition, there were no demonstrable differences in the latency and amplitude characteristics of the signals measured on the bilateral electrodes (C3-C4, P3-P4, F3-F4), while comparing the two subgroups.

Discussion

In a group of 50 patients diagnosed with the schizophrenia according to DSM and ICD categories the distribution of the patients within the group was dimensional, and within this distribution two distinct grouping zones were identifiable. The analysis creditably identified the separation of two clusters. The analyses have demonstrated that cluster 'Z' had more favourable, and cluster 'S' had more unfavourable (more Serious) characteristics.

Based on earlier results in the literature we selected tasks and procedures from existing batteries seemed to consequently separate patients with schizophrenia not only from healthy controls, but from other groups with mental disorders. In our opinion, one of the significances of our results was that we could demonstrate that performances on these tasks could also draw distinctions within the group of schizophrenic patients. The alterations within the group could be detected with only a part of the set of methods. Similar performances of the functions analysed with other techniques might indicate common features, representing the group of patients collectively, which might reflect common, overlapping morbidity which characterize both of the clusters equally. It seems as if within the group of patients there were fewer differences at the more elementary levels 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 emphasized 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 tendency-like alteration in the inhibitory performance. Besides this '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 (>15 percentile) [see 26 and 28 for normative data], and, as the positive value of the inhibitory index represented, they produced some inhibition in the Directed Forgetting task, as well [24, 39]. On the contrary, 'S' cluster patients produced an impaired performance on the VPT and WCST (<15 percentile) and, as the negative value of the inhibitory index indicated, they did not produce inhibition in the Directed Forgetting task, although they did normally on the Digit Span task. Further, we found a significant difference in the occurrence and in the 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 [45, 46, 47]. 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. Neural substrates in the background of the discriminative tactile, kinesthetic, and proprioceptive information processing needed to the functions of stereognosis and graphesthesia are well known (the cardinal regions are the contralateral thalamus, the primary (SI) and the secondary sensory cortex (SII)). Since the patients did not lack the abilities of stereognosis and graphestesia totally, and the other accompanying drop-out symptoms were missing as well, presumably the dysfunction of this distributed (thalamo-)cortical network was in the background, affecting 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 the differences. One possible interpretation of this pattern of results is that 'S' cluster patients consistently performed worse in tasks measuring right frontal functions than 'Z' cluster patients, which could reflect a lateralized difference between the two patient groups. There is a bulk of evidence that functions of inhibition and shifting are associated to the right frontal lobe [see for reviews 48]. Conway and Fthenaki [37] showed that right frontal lobe injury can abolish inhibition in the Directed Forgetting task, while Anderson et al. [49] using different procedures produced evidence that inhibitory control of memory retrieval is associated with the activation of the right cerebral cortex. Above all of this, updating and rehearsing visual and spatial information is associated to 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 background factor behind the memory differences between the patients assigned to the 'S' and 'Z' clusters. They performed equally weaker on the tasks demanded left hemispherial neural substrates. This explanation is in line with our earlier result as in a pilot study on cerebral structure [51] 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. It turned out afterwards, 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 belonged dominantly to the cluster 'Z'- these earlier results might partly, indirectly supported our present observations on the hemispherial differences.

Another possible interpretation of the results is that patients belonging to cluster 'S' show more profound injuries of frontal lobe functions, and as a consequence they produce worse performance on tasks sensitive to functions of executive working memory. It may be the case that

visuo-spatial working memory tasks load storage and updating functions more strongly than 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 of the clusters.

Conclusions

In schizophrenia with a theory-driven, systematic study we could separate subgroups. Two subgroups 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 also.
Based on the results it seemed these subgroups represented different types, not only forms with different seriousness of the same type. Despite of a remarkable correspondence between the deficit-nondeficit syndromes and our clusters (which were identified by a complex neuropsychiatric analysis from which the deficit syndrome as an attribute was excluded), the two divisions were not the same.
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. But as in the more elementary levels we did find the patient group more solid, it is possible, that there cuold be a common morbidity root in the deep of etiological basement of 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. Further targeted studies are needed also to approach the identification of the different and common morbidity processes.

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