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ORIGINAL PAPER

Two subgroups of schizophrenia identified by systematic cognitive neuropsychiatric mapping

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Abstract 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 patterns of cognitive dysfunctions and neurological developmental anomalies equally indicate that there may be hemispherical differences between the patients belonging to the different clusters.

Keywords Schizophrenia · Heterogeneity · Clusters · Neurocognitive · Hemispherical

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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, the 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 min) 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 18–69 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) 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) [13], the Scale for the Assessment of Negative Symptoms (SANS) [14], and the Schedule for the Deficit Syndrome (SDS) [15].

Neurosomatic alterations

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 provide an opportunity to analyze 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), including 57 minor signs collected by Mehes, was used for mapping malformations [20–22]. 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 [23].

Neuropsychological mapping

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 to measure visuo-spatial working memory capacity. Executive functions were assessed with the Wisconsin Card Sorting Test (WCST) [27, 28], the Tower of Hanoi Task [29], and the Letter Fluency [30] and Category Fluency Tasks [31]. To measure inhibitory control of memory, we used the so-called directed forgetting (DF) procedure [32–34] with lists. Following Miyake and his colleagues [35], 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") [36, 37]. An inhibitory index was calculated by comparing the List 1 performances in the "Forget" and "Remember" conditions of the directed forgetting procedure [38, 39]. As for mentalization, the present study adapted the method of Tenyi et al. [40] 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 1,024 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-h 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 ms 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 (Electro-Cap 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 were 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 [41–43]. 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. The 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, 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, USA) was used.

Sample size

The analyzed 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 two and five, 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.

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). In addition, the two groups differed in handedness as determined by the NES: mixed-handedness was significantly more frequent in cluster S (Table 1). The type of pharmacotherapy influenced neither the subgroup formation (analyzed with two-sided Fisher's exact test) (Table 1) nor the neurocognitive performance (analyzed 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)	0.331
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%	100.0%	
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 two-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

Diagnostic features and relationship with the deficit/nondeficit division

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).

There was a remarkable correspondence between the clusters and the deficit–nondeficit syndromes, despite the fact that the definition of deficit syndrome is based on clinical symptoms, while our clusters were identified by a complex neuropsychiatric analysis from which the deficit syndrome was excluded as an attribute. In cluster Z ($n = 27$), 96.30% of the patients had nondeficit and 3.70% had deficit diagnoses; while in cluster S ($n = 23$), 56.50% of the patients had deficit and 43.50% nondeficit diagnoses ($p = 0.0003$, Chi-square test and False Discovery Rate). However, despite the marked overlapping, the two divisions were not the same: the relationship of the patients' memberships in cluster S versus Z and the deficit or nondeficit subgroups is illustrated in Fig. 1.

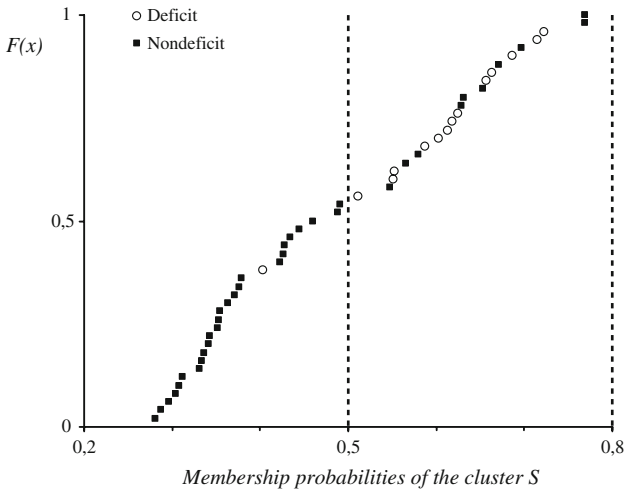

Fig. 1 Distribution function of the membership probabilities. The patients' cluster membership probabilities are represented in this figure. The *symbols* represent patients with or without deficit syndrome. Higher probability values indicate memberships of cluster S, while lower values mark membership 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

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 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

Symptomatological 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 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 2). In both clusters, anhedonia was pronounced among negative symptoms (Table 2).

Secondary cognitive differences between the clusters

Cluster S patients performed significantly worse on visuospatial 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 3).

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 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 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

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 5).

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

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)	0.157
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 means (SD)

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

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)	**0.0012**
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 means (SD)

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

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) [44] 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 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 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 26, 28 for normative data], and, as the positive value of the inhibitory index shows, they produced some inhibition in the Directed Forgetting task as well [24, 39]. 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 [45–47]. A more pronounced disorder of sensory integration was demonstrable in cluster 'S'. In addition, 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 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, 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 hemispherical neural substrates. This explanation is in line with our earlier result from a pilot study on cerebral structure [51], in which we observed the reversal of normal L > R asymmetry to R > L asymmetry of the volumes of straight gyri (BA 11) in 13 young male patients with schizophrenia. This gyrus in part plays a role in the short-term storing of visuo-spatial information. It turned out afterwards that 12 of the 13 examined patients belonged to cluster 'Z'. The volume of the right straight gyrus was greater than the left, and visuo-spatial working memory performance was at the normal level in the patients who belonged dominantly to cluster 'Z'—these earlier results might partly, indirectly support our present observations of hemispherical differences.

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.

Conclusions

In a theory-driven systematic study, we were able to separate patients with schizophrenia into distinct subgroups. Two subgroups were distinguished from each other based on performances on a subset of tests that can separate patients with schizophrenia from both healthy individuals and patient controls with other mental disorders.

Based on the results, it seems that these subgroups represented different types of schizophrenia rather than merely forms of the same type with different severities. Despite 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 favor the explanation that the patterns of cognitive dysfunctions and neurological developmental anomalies equally indicate that there are at least two morbidity domains that underlie the two subgroups: in cluster 'Z', there was a dominant unilateral, left frontal dysfunction, while in the more severe cluster 'S', bilateral morbidity processes with left and right frontal neural substrates might be present. However, as we did not find group differences at more elementary levels of functioning, it is possible that there is a common morbidity root deep in the 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 comparison of clusters we tried to decrease the number of false positive results using the False Discovery Rate method. After adjusting by FDR, some of the differences had significance levels ca. 0.0001, while the other differences had significance levels below 0.04. These latter results should be interpreted with care. Further targeted studies are needed to approach the identification of both common and distinct morbidity processes in schizophrenia.

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