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

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SUMMARY

Background

In the research of schizophrenia, which is heterogeneous at different system levels, efforts to reveal connections between the levels and to determine relevant etiological subgroups are stalling because the given levels are examined separately.

Aims

To investigate whether schizophrenia could be divided into subgroups with a series of systematic studies.

Method

The employed methodology included a vertical, robust cognitive neuropsychiatric analysis on a group of 50 patients with schizophrenia spectrum disorder, and a fuzzy cluster analysis.

Results

Distribution of the patients within the group was continuous, with two distinct clusters identifiable. There was a great correspondence between the clusters and the Deficit-Nondeficit subgroups.

Conclusions

The patterns of cognitive dysfunctions and neurological developmental anomalies equally indicate that in cluster ‘Z’ there is 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.

Declaration of interest

None.

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. Kraepelin, Bleuler, Kleist, Schneider and Leonhard were some of the significant researchers of this era. In the 1970s the model of positive and negative symptoms began to evolve by the attempt of integrating some different aspects of the disease (symptoms, pathophysiology, outcome). The powerful and heuristic hypothesis of Crow (1980) catalysed the multilevel conception and the neurobiological research process of the disease. According to recent observations, the dimensions describing the symptoms of schizophrenia are supposedly not specific to the disease (Peralta *et al*, 1997). Currently, the description of the heterogenic nature of the disease is under way, at the phenomenological, pathophysiological, and etiological levels (Tsuang *et al*, 1990). However, the relations between heterogeneity-levels are still unclear.

In the very beginning of the research Kraepelin and Bleuler supposed, and nowadays Andreasen (2000) supposes a unified morbidity process in the background of the disease, the phenomenological manifestations of which – eg. 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. According to the original concept of Crow (1980) schizophrenia has two types: Type I, which is mainly characterized by positive symptoms, has a more favourable prognosis, and may be associated with a neurochemical disorder; and Type II, which is chronic, characterized by negative symptoms, and may be of structural origin. While Type I can be followed by Type II,

the latter can occur without a previous Type I as well. Similarly to the types of Crow, the Deficit syndrome was also defined as a possible subtype of schizophrenia by the developers of the concept. According to the definition of the researchers having developed this model (Carpenter *et al*, 1988), the syndrome is characterized by primary, idiopathic, and negative symptoms, which are emphasized and can be observed even during periods of clinical stability as personal traits. These latter concepts suppose the possibility and effect of more than one morbidity processes (and their possible interactions) in the background.

Our research group performed a so-called vertical pattern or, in other words, a robust cross-sectional research, which gives an insight to various levels of phenomenological mental, pathophysiological and etiological cerebral processes - simultaneously. (1) Can schizophrenia be divided into subgroups with a series of systematic cross-sectional cognitive neuropsychiatric studies? (2) If so, what depths of the systems can their divergence be followed to? (3) If such diverging subgroups exist, are they suggesting a unified morbidity, or multiple ones?

METHODS

Participants

Fifty patients (27 male, 23 female) were selected from the outpatient clinic of the Department of Psychiatry, University of Szeged. All patients had a diagnosis of schizophrenia - with the nowadays widely used, tight sense - DSM-IV (American Psychiatric Association, 1994) and ICD-10 criteria for research (World Health Organization, 1993), and they were further diagnosed based on clinical subtype and course characteristics. All of them were outpatients in stable interepisodic state under antipsychotic medication. Due to the variety in drug types and doses, the analysis of the relationship between the pharmacological effects of all drugs was not possible, therefore, pharmacotherapy applied to patients was divided into 3 categories in the first approach: therapy with first generation antipsychotics, with second generation antipsychotics, and with first-second or second-second generation combinations. All substances were prescribed usually in medium doses according to their medication protocol.

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. 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 minutes, or any medical illness that could significantly constrain neurocognitive functions. 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 informations.

Clinical symptoms

Clinical symptoms were assessed using the Positive and Negative Syndrome Scale (PANSS) (Kay *et al*, 1991), the Scale for the Assessment of Negative Symptoms (SANS) (Andreasen, 1982), the Schedule for the Deficit Syndrome (SDS) (Kirkpatrick *et al*, 1989).

Neurosomatic alterations

The neurological developmental signs were assessed using the Neurological Evaluation Scale (NES) (Buchanan & Heinrichs, 1989). Fourteen of the 26 items of the NES scale assess neurological signs independently on the two sides, which gives an opportunity to analyse laterality. Besides, one item of the scale analyses handedness in detail.

The potential pharmacogenic extrapyramidal symptoms were assessed with the help of the Simpson-Angus Scale (SAS) (Simpson & Angus, 1970), the Abnormal Involuntary Movement Scale (AIMS) (Guy, 1976), and the Barnes Akathisia Rating Scale (BAS) (Barnes, 1989).

The minor physical anomalies (MPAs) have two types (Spranger *et al*, 1982; Opitz, 1985): minor malformations (MM), which are pathological and qualitative defects developing during the organogenesis; and phenogenetic variants (PV), which are not pathological, develop during the final morphogenesis after the organogenesis, and differ quantitatively from normal variants. Three examiners investigated the patients using a list of MPAs containing 57 minor signs collected by Méhes (Méhes, 1988; Trixler *et al*, 1997; 2001), the interrater reliability (the kappa coefficient) was >75%.

The B-SIT test was used for assessing smell identification, which is a standardized multiple choice scratch-and-sniff test of odor identification (Doty *et al*, 1996). Compared to the age-related values, which were given by the authors and were based on a relatively small number of cases, all of our subjects had a high olfactory threshold assessed by phenyl ethyl alcohol (mean = -2.875, SD= 0.802, and the normal range between 20-49 years being about -6.55 (CI

99% = from -5.88 to -7.12)). This can indicate a technological problem, since performance in the smell identification task was high at the same time (patients identified 9–10 out of 12 substances on average).

Neuropsychological mapping of the working memory system

Widely used neuropsychological tasks were employed to measure working memory and executive functions. We measured verbal working memory capacity with the Digit Span Task (Racsmány *et al*, 2005), and the Hungarian Nonword Repetition Task (Racsmány *et al*, 2005). We used the Corsi Blocks Task (DeRenzi *et al*, 1975), and the Visual Patterns Test (VPT, Della Sala *et al*, 1997) for measuring visuo-spatial working memory capacity. We assessed executive functions with the Wisconsin Card Sorting Test (WCST, Berg, 1948; Heaton *et al*, 1993), with the Tower of Hanoi Task (Simon, 1975), and with the Letter Fluency (Benton & Hamsher, 1976) and Category Fluency Tasks (Spreen & Strauss, 1991).

For measuring inhibitory control of memory we used the so called *directed forgetting* (DF) procedure to analyse individual differences in inhibitory abilities (see Bjork 1989, Bjork and Bjork 1996 for a review of the DF procedure, and MacLeod 1998 for a more general review of DF). The specific procedure used was DF by lists. In order to differenciate components of the executive system, following Miyake and his colleagues (2000), we aimed at investigating three components of the executive system in individuals living with schizophrenia. We used the perseverative errors on WCST as a score of „Shifting". We used two working memory tasks as measures of the „Updating" function in two modalities, the Hungarian Digit Span Task (Racsmány et al.2005) and the Visual Patterns Test (VPT). We have used the DF task to analyse individual differences in inhibitory abilities of activated memory representation („Inhibition") (see Bjork et al.1998; Conway and Fthenaki 2003). We calculated an inhibitory index by comparing the List 1 performances in "Forget" and "Remember" conditions of the

directed forgetting procedure (see Racsmány and Conway 2006). As for mentalisation the present study adapted the method of Tényi et al. (2002) 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. 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

Gath-Geva Clustering Algorithm

Since we found that the distribution of variables among patients - in accordance with literature data (van Os *et al*, 1998) – was dimensional, and we supposed that the distribution of patients within a group was dimensional as well, we were using the appropriate statistical methods during the analysis. Fuzzy clustering methods allow objects to belong to several clusters simultaneously, with different degrees of membership. The fuzzy maximum likelihood estimates clustering algorithm is able to detect clusters of varying shapes, sizes and densities. This is because the cluster covariance matrix is used in conjunction with an "exponential" distance, and the clusters are not constrained in volume. The partition with the best validity measure value will be chosen as the partition of the data set. Gath-Geva validity index (P_D) is based on criteria for hyper volume and density.

The following approach is widely used to substitute the missing values with computed ones: for each element with missing value, the distances (most often the Euclidean distance is used) from the elements with no missing values are computed. From these elements the n closest elements are selected. The missing value is substituted by a weighted average of the corresponding value of the selected elements. The weights are inversely proportional to the distance between the selected elements and the element with the missing value. The following normalization steps were carried out before clustering was performed: normalization, mean normalization, variance normalization.

Comparing the groups

The two clusters were compared by Mann-Whitney *U* test and by chi-square test in case of continuous and categorical variables, respectively. Frequencies of 2x2 tables were compared by Fisher's exact test. The relations of the three types of pharmacotherapy were compared by Kruskal-Wallis test. To avoid the problem of multiple testing which increases the probability of declaring false significances, p-values were adjusted by False Discovery Rate, using the SAS system for Windows version 9.1.

RESULTS

Cluster analysis

The data set contained 50 elements, and 60 attributes, and 6.27 per cent missing attribute values. Gath-Geva 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. The analysis identified the separation of two clusters. 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. (For the time being, we named these cluster ‘S’ and cluster ‘Z’ based on the abbreviations of schizophrenia literature (S: more Serious).)

Comparing the clusters

Demographic features of the clusters

There were no significant differences between the clusters with regard to most of the demographic and course features: the age of the patients at the time of the study, the ratio of genders, the age at onset of disease, the duration of disease, and the number of relapses were essentially the same in the two groups (Table 1). 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 help of the NES: mixed-handedness was significantly more frequent in cluster ‘S’ (Table 1). It is notable that there was not a single left-handed person among the 50 patients participating in the study.

Table 1 Demographic characteristics of the clusters of participants

	Cluster 'S' (n=21)	Cluster 'Z' (n=29)	*P*
Age, years	35.33 (9.45)	32.72 (12.69)	0.251
Gender ratio, male/female %	57/43 %	52/48 %	* 0.718
Education, years	9.71 (1.74)	11.93 (1.98)	**0.00067**
Full scale IQ	89.29 (12.81)	107.56 (12.45)	**0.00055**
Age at onset, years	24.91 (7.75)	24.55 (8.03)	0.671
Duration of illness, years	10.38 (9.01)	8.17 (7.67)	0.344
Relapse	5.55 (4.25)	4.35 (4.86)	0.211
Handedness, by NES	Right 75.0 % Left 0.0% Mixed 25.0 %	Right 100.0 % Left 0.0% Mixed 0.0 %	* **0.017**
Antipsychotic therapy	Atypical 76.2 % Typical 14.3 % Combination 9.5 %	Atypical 65.5 % Typical 13.8 % Combination 20.7 %	* 0.599

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

Clusters and DSM/ICD diagnoses

In the study, the patients were selected from and were diagnosed according to a part of the schizophrenia spectrum which was defined and categorized by combining the diagnoses and subtypes of the DSM-IV and the research version of the ICD-10. Though the distribution of the diagnoses in the two clusters was not significant, it indicated a tendency to dissimilarity (Table 2), which partly originated from the difference between the diagnoses of the residual type.

Table 2 DSM and ICD diagnoses in the clusters of participants

Clusters	Catatonic	Disorganized	Paranoid	Residual	Undifferen-tiated	Schizo-affective	Schizotyp
S (n=21)	0.0 %	9.5 %	52.4 %	23.8 %	4.8 %	4.8 %	4.8 %
Z (n=29)	3.5 %	7.1 %	65.5 %	0.0 %	14.3 %	10.7 %	0.0 %
P (χ^2)				0.104			

The *P* value is based on chi-square test and adjusted by False Discovery Rate.

Clusters and DSM/ICD course patterns

In the study, the patients were sorted - based on the course of their disease - into groups defined by combining the longitudinal course patterns of the DSM-IV and the research version of the ICD-10. The distribution of course patterns in the two clusters was highly significant (Table 3). The diagnostic symptoms were persistent in one fifth of cluster ‘S’

patients, and two thirds had stabile deficits between the episodes. In cluster 'Z', however, there were no deficits in two thirds of the patients, they were in remission.

Table 3 DSM and ICD longitudinal course patterns in the clusters of participants

Clusters	Single episode, full remission	Episodic, interepisodic remission	Episodic, interepisodic stable deficit	Episodic, interepisodic progressive deficit	Persistent
S (n=21)	5.3 %	5.3 %	63.2 %	5.3 %	21.1 %
Z (n=29)	25.9 %	48.1 %	22.2 %	0.0 %	3.7 %
P (χ^2)			**0.0028**		

The *P* value is based on chi-square test and adjusted by False Discovery Rate.

Clusters and Deficit-Nondeficit syndromes

There was a remarkable overlap between the clusters and the Deficit/Nondeficit categorization, which was revealed by using the SDS (Table 4). Besides the remarkable statistical analogy between the results of the two groupings, from the more favourable groups the Nondeficit group seemed to be broader than the cluster Z, while from the less favourable groups the cluster S was seemingly broader than the Deficit group.

Table 4 Correspondence between the clusters and the Deficit syndrome in the participants

Clusters	Schedule for the Deficit syndrome (SDS)	
	Deficit	Nondeficit
S (n=21)	61.90 %	38.10 %
Z (n=29)	3.45 %	96.55 %
P (χ^2)	**0.00006**	

The *P* value is based on chi-square test and adjusted by False Discovery Rate.

Symptomatologic differences between the clusters

Obvious symptomatologic differences could be demonstrated between the patients of the two clusters, who were all in a compensated, interepisodic period, and were treated ambulatorily. Cluster 'S' patients in their compensated state had more emphasized symptoms in every aspect of the examined dimensions of clinical symptoms. Though the differences were marked statistically, they actually indicated a moderate difference clinically: they mainly originated from the slight/moderate occurrence (of every examined aspect) of the negative symptoms, which were demonstrable even during the interepisodic period (Table 5).

Table 5 Symptomatologic characteristics of the clusters of participants

	Cluster 'S' (n=21)	'Z' cluster (n=29)	*P*
PANSS, Positive	13.57 (5.30)	10.11 (3.69)	**0.018**
PANSS, Negative	21.19 (5.87)	12.50 (4.67)	**0.00006**
PANSS, General	35.48 (10.76)	25.50 (7.71)	**0.0015**

PANSS, Total	70.24 (19.14)	47.68 (14.04)	**0.00036**
SANS, Affective flattening	2.33 (1.11)	0.96 (0.98)	**0.00057**
SANS, Alogia	2.24 (0.10)	0.67 (79)	**0.00006**
SANS, Avolition	2.29 (1.15)	0.82 (88)	**0.00036**
SANS, Anhedonia	2.95 (1.20)	1.37 (1.08)	**0.0005**
SANS, Inattention	1.86 (1.11)	0.67 (83)	**0.00055**

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 slightly, but significantly poorer performance in the mentalization tasks and on the two fluency tasks, and robustly worse WCST (see Table 6).

Table 6 Secondary cognitive characteristics of the clusters of participants

	Cluster 'S' (n=21)	Cluster 'Z' (n=29)	*P*
Digit Span, forward	5.43 (0.98)	5.90 (1.24)	0.220
Digit Span, backward	3.57 (0.75)	4.10 (1.01)	0.089

Hungarian Nonword Repetition Task	6.32 (1.29)	6.35 (1.08)	0.826
Corsi blocks, forward	4.19 (1.21)	5.14 (1.19)	**0.013**
Corsi blocks, backward	4.19 (1.21)	5.14 (1.19)	**0.013**
Visual Patterns Test	5.60 (1.39)	7.00 (1.85)	**0.017**
Letter fluency, words	7.13 (2.34)	8.89 (2.48)	**0.031**
Letter fluency, errors	0.64 (80)	0.86 (81)	0.282
Semantic fluency, words	12.56 (3.15)	15.79 (3.78)	**0.013**
Semantic fluency, errors	0.38 (43)	0.61 (66)	0.278
Towers of Hanoi, movements	13.25 (5.82)	10.48 (3.92)	0.154
Towers of Hanoi, errors	0.42 (77)	0.17 (47)	0.278
WCST, completed categories	0.90 (1.20)	4.29 (1.82)	**0.00003**
WCST, perseverative errors (%)	38.32 (20.56)	17.89 (9.96)	**0.00057**
WCST, conceptual level responses (%)	19.47 (16.16)	55.79 (22.18)	**0.00006**
Theory of Mind, first order	0.84 (38)	0.97 (57)	0.474
Metaphor comprehension	2.11 (1.20)	2.93 (0.88)	0.066
Theory of Mind, second order	1.16 (0.60)	0.83 (60)	0.104
Irony comprehension	1.74 (1.41)	2.66 (1.52)	**0.00057**

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 investigated the level of modality dependent (verbal or visual) updating and rehearsing functions, and components of the executive system, such as shifting and inhibiting. 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 7 shows, we found strongly significant differences in tasks measuring shifting and in visual working memory functions, and moderately significant difference in inhibition function.

Table 7 Primary executive function characteristics of the clusters of participants

	Cluster 'S' (n=21)	Cluster 'Z' (n=29)	*P*
Verbal Updating: Digit Span Task	5.43 (0.98)	5.90 (1.24)	0.220
Visual Updating: Visual Patterns Test	5.60 (1.39)	7.00 (1.85)	**0.017**
Inhibition: Directed Forgetting inhibitory index	-0.85 (1.28)	0.37 (2.01)	**0.045**
Shifting: WCST, percentage of perseverative errors	38.32 (20.56)	17.89 (9.96)	**0.00057**

Values represent means (SD)

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

Neurological alterations in the clusters

There was a significant difference between the clusters with regard to neurological signs. The summed up frequency of signs was notably higher in cluster 'S', in which the disorder of motor coordination was more marked, and the occurrence of sensory integration disorder was remarkably higher (Table 8).

Table 8 Neurological signs in the clusters of participants

	Cluster ‘S’ (n=21)	’Z’ cluster (n=29)	*P*
Sensory integration	6.40 (2.54)	3.79 (2.69)	**0.00138**
Motor coordination	2.75 (2.15)	1.41 (1.64)	**0.0268**
Motor sequencing	5.45 (3.52)	4.31 (3.01)	0.268
Others	10.45 (3.98)	8.72 (4.37)	0.231
Total	25.05 (8.02)	18.24 (7.92)	**0.0029**

Values represent means (SD)

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

Analysing in detail those items of the NES scale which assess the signs on a side-basis, we found a significant difference in laterality between the two groups. Of the 14 neurological signs assessed by side, those belonging to sensory integration showed a significant difference. 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. While cluster ’Z’ was characterized by the dominance of the right body side in case of sensory integration as well, in cluster ’S’ even more disorders could be detected on the left body side, besides the frequent right-sided symptoms, (Table 9). Sensory integration at level of hemispheres are represented by those items of the NES which examine stereognosis and graphesthesia. Thus, 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.

Table 9 Neurological signs by side in the clusters of participants

	Cluster 'S' (n=21)		Cluster 'Z' (n=29)		*P*
Body-half	right	left	right	left	
Sensory integration	1.56 (0.81)	1.94 (1.24)	1.21 (1.10)	0.63 (0.97)	**0.023**
Motor coordination	1.63 (1.03)	1.31 (1.35)	0.58 (83)	0.42 (58)	0.503
Motor sequencing	2.13 (1.20)	1.56 (1.59)	1.46 (1.50)	1.13 (1.23)	0.633
Others	1.10 (1.10)	1.07 (1.14)	1.02 (0.86)	1.00 (1.45)	0.679
Total	7.50 (2.92)	6.88 (3.32)	5.29 (2.85)	4.17 (1.95)	0.539

Values represent means (SD)

P values are based Mann-Whitney *U* test and adjusted by 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 akathisia (mean value in cluster 'S' 0.39 (SD=1.15), in cluster 'Z' 0.21 (SD=0.68), *P*=0.854, Mann-Whitney *U* test) and tardive dyskinesia (mean value in cluster 'S' 0.28 (SD=0.58), in cluster 'Z' 0.10 (SD=0.31), *P*=0.250, Mann-Whitney *U* test). However, symptoms of parkinsonism were significantly more frequent in cluster 'S' (mean value in cluster 'S' 6.06 (SD=4.73), in cluster 'Z' 2.10 (SD=2.50), *P*=0.002, Mann-Whitney *U* test).

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). The applied pharmacotherapy was basically set up earlier, its drugs had

been taken for a longer period before the time of the study, and the doses were unchanged. (Due to the cross-sectional nature of the study, an analysis of more subtle relationships was not possible.) These observations suggest that cluster ’S’ had an increased neurological vulnerability, developmental neurological signs were more common in this group (especially in sensory integration and motor coordination), and the occurrence of parkinsonism (affecting other than the previous motor modalities) was higher as well during the treatment, maybe partially independently of the actually applied therapy.

Morphogenetic anomalies in the clusters

We did not find a difference in the occurrence of somatic developmental anomalies between the two groups. There was no demonstrable difference between the two groups in the occurrence of either the minor malformations, which reflect the disorder of organogenesis (in cluster ‘S’ 1.46 signs (SD=1.51), in cluster ‘Z’ 1.82 signs (SD=1.91), P=0.666, Mann-Whitney U test), or the phenogenetic variants, which reflect later developmental stages (in cluster ‘S’ 1.31 signs (SD=1.11), in cluster ‘Z’ 1.12 signs (SD=1.62), P=0.356, Mann-Whitney U test). 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, see Weinberg *et al*, 2006) or between the two groups. In the study, these were the most common anomalies by body region: the double posterior hair whorl and the flat occiput on the head; the antimongoloid slant in the orbital region; the small oral opening and the abnormal philtrum in the oral region; the low-set ears in the auricular region; the Sydney line on the hands; the pigmented naevi on the trunk; the sole crease and the hallucal abnormality on the foot. The most frequent minor malformations were the pigmented naevi, the double posterior hair

whorl, the flat occiput and the Sydney line; the most common phenogenetic variants were the antimongoloid slant, the small oral opening and the low-set ears.

Smell identification alterations in the clusters

While the smelling threshold of the patients in the two groups was similarly and remarkably low (in cluster 'S' -2.86 (SD=0.85), in cluster 'Z' -2.89 (SD=0.79), *P*=0.593, Mann-Whitney *U* test), the identification performance was high, which may reflect a technical problem of the applied standardized threshold-determining method. Only a tendencious difference was demonstrable between the two groups during the smell identification task: the performance of cluster 'S' was slightly poorer than that of cluster 'Z' (the number of identified substances in cluster 'S' 9.13 (SD=1.31), in cluster 'Z' 9.91 (SD=1.26), *P*=0.077, Mann-Whitney *U* test).

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 of the P50 waves (difference of wave-pair latencies in cluster 'S' 8.95 msec (SD=17.17), in cluster 'Z' 8.02 msec (SD=13.37), *P*=0.612; difference of wave-pair amplitudes in cluster 'S' 0.09 mV (SD=2.28), in cluster 'Z' 0.63 mV (SD=2.93), *P*=0.268). In addition, there were no differences between the two groups in the latency and amplitude values of the MMN waves, neither in case of frequency deviant, nor in case of duration deviant stimuli (latency in case of frequency deviant stimuli in cluster 'S' 170.18 msec (SD=47.76), in cluster 'Z' 155.10 msec (SD=37.89), *P*=0.408; amplitude in cluster 'S' 3.56 mV (SD=1.90), in cluster 'Z' 4.63 mV (SD=2.12), *P*=0.173; latency in case of duration deviant stimuli in cluster 'S' 225.10 msec (SD=39.74), in cluster 'Z' 238.58 msec (SD=34.25), *P*=0.247; amplitude in cluster 'S' 5.76 mV (SD=2.80), in cluster 'Z' 5.36 mV

(SD=2.85), *P*=0.609). We did not find a difference in the latency and amplitude values of P300 waves between the two groups (latency in cluster 'S' 389.57 msec (SD=74.51), in cluster 'Z' 409.87 msec (SD=59.88), *P*=0.187; amplitude in cluster 'S' 7.45 mV (SD=3.26), in cluster 'Z' 5.82 mV (SD=2.82), *P*=0.087). 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. Measurements available on right and left hemispheres and clusters were compared by two-way repeated-measurements ANOVA: *P*>0.05 for independent, dependent comparisons and for the interaction as well.

DISCUSSION

Subgroups

In a group of 50 patients, who where diagnosed with the schizophrenia spectrum according to DSM and ICD categories the distribution of the patients within the group was dimensional and continuous, with two distinct grouping zones identifiable. The analysis creditably identified the separation of two, already defuzzificated clusters. For the time being, we named these cluster ‘S’ and cluster ‘Z’ based on the abbreviations common in schizophrenia literature. The analyses have demonstrated that cluster ‘Z’ has more favourable, and cluster ‘S’ has more unfavourable (more Serious) characteristics. There was a remarkable overlap between the clusters and the Deficit/Nondeficit categorization, but from the more favourable groups the Nondeficit group seemed to be broader than the cluster Z, while from the less favourable groups the cluster S was seemingly broader than the Deficit group.

Demographic and clinical features

Of the demographic differences, lower education and IQ values indirectly reflect a more pronounced cognitive disorder even during interepisodic periods in cluster ‘S’. While most of the patients in cluster ‘Z’ were in remission during the interepisodic period, residual symptoms were present in the majority of cluster ‘S’ patients, who have more emphasized symptoms in every aspect of the examined symptomatic dimensions.

Cognitive alterations

Instead of an overall difference in working memory functions we found strong differences in tasks measuring inhibitory and shifting functions and in visual working memory functions.

Besides this ‘S’ cluster patients performed significantly worse on the mentalization tasks and robustly worse on the so-called frontal lobe tasks such as the two fluency tasks and WCST. Comparing the level of working memory components to normative data, it is interesting that ‘Z’ cluster patients’ performance is in the lower, but normal range of the population in the updating and shifting tasks (>15 percentile), and, as the positive value of the inhibitory index represents, they produced some inhibition in the directed forgetting task, as well (see Racsmány *et al*, 2005; Della Sala *et al*, 1997; Heaton *et al*, 1993 for normative data). On the contrary, ‘S’ cluster patients produced an injured performance on the VPT and WCST (<15 percentile) and, as the negative value of the inhibitory index indicates, they did not produce inhibition in the directed forgetting task, although they did normally on the digit span task. 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 Aron *et al*, 2004). Conway and Fthenaki (2003) showed that right frontal lobe injury can abolish inhibition in the directed forgetting task, while Anderson *et al* (2004) 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 Shallice, 2004 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 of patients assigned to the ‘S’ and ‘Z’ clusters.

Neurosomatic anomalies

We found a significant difference in the occurrence and in the laterality of neurological signs between the clusters. A more pronounced disorder of sensory integration and motor coordination was demonstrable in cluster ‘S’. 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 (see Crow, 1999; Sommer et al, 2001; Dragovic & Hammond, 2005). Additionally, in cluster ’S’, besides the frequent right-sided stereognosis and graphesthesia (found similar in cluster ’Z’), 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 lateral part of the ventral postreromedial nucleus (VPM) of the contralateral thalamus, in the same contralateral hemisphere the primary sensory cortex (SI), the neighbouring SII area and the broader network system of the so-called vibrotactile working memory (Preuschhof et al, 2006), where the SI, the ventral premotor cortex, the ventrolateral prefrontal cortex and the inferior parietal lobe play prominent roles). 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’.

According to the observations, cluster ’S’ had an increased neurological vulnerability; developmental neurological signs were more common in this group, and the occurrence of parkinsonism was higher as well during the treatment. With regard to the ability of smell identification, cluster ‘Z’ seemingly was the favourable, but the difference was not significant. There was no significant difference in the occurrence of somatic anomalies and in their distribution by body region between the groups.

Electrophysiology

With electrophysiological mapping, we did not find a difference during the early, preattentive phase of acoustic information processing in case of either midline or corresponding hemispherical electrodes.

CONCLUSIONS

In a group of 50 patients with the schizophrenia spectrum diagnosis the distribution of patients seemed to be continuous, and two distinct, already defuzzificated clusters could be identified. 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..

The patterns of the cognitive dysfunctions and of the neurological developmental anomalies equally indicate that there are at least two morbidity domains in the background of the two subgroups: in cluster ‘Z’ there is a dominatingly unilateral, left frontal dysfunctioning, while in the more severe cluster ‘S’, bilateral morbidity processes with left and right frontal neural substrates may be present.

In a pilot study on cerebral structure (Szendi et al, 2006) 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 visuo-spatial working memory performances were at the normal-level in the patients belonged dominantly to the cluster ’Z’- these earlier results may indirectly support our present observations.

One of the limitations of our study is the exclusive use of the narrow diagnostical concept of schizophrenia (DSM/ICD), which is presumably insensitive when approaching the outer

boundaries of the disease. A factor that further limits the value of the data is the small number of cases (50) compared to the high number of the attributes (60) in the robust analysis. The results of the comparisons of the clusters should be interpreted with great care. The expansion and a follow-up of our cross-sectional studies are needed for challenging the results. A further analysis of our results is needed for clarifying the relationship to the Deficit-Nondeficit syndromes. Further targeted studies are needed to approach the identification of the different morbidity processes.

Acknowledgements

We are grateful to Timothy J. Crow for reading, reviewing and commenting our manuscript.

This study was supported by the grants NKFP 50079/2002 (Hungarian National Research Grant for the project 'Cognitive and Neural Plasticity'), OTKA (Hungarian Scientific Research Fund) T 046152/2004, T 034814, 49 840-T53 and K68463, and ETT IV/93/2003 (Hungarian Ministry of Health).

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