Psychopathologic and cognitive investigations in schizophrenia

On the basis of “Budapest 2000”

Master’s Thesis

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Introduction

Some experts anticipate a revolution in psychiatric nosology, on the basis of emerging data from genetics and genomics. There are, however, good empirical and conceptual reasons to dispute such points of view. In 2006 a conference entitled as “Deconstructing Psychosis” was organized by the American Psychiatric Association (APA) to establish a new conceptual framework for the classification of psychosis in the DSM-V. A lot of clinicians agree that changing an invalid classification into another invalid one would be faulty. The debate about the Kraepelinian dichotomy illustrates the lack of evidence-based diagnostic classification in psychiatry as a discipline, and results from genetic studies are contradictory and only partly support the dichotomy.

The recent psychiatric research, including the search for predisposing genes, follows the Kraepelinian dichotomy: both schizophrenia and affective disorders are considered as discrete disease entities with distinct etiology and pathogenesis and these disease entities can be identified by current diagnostic conventions. However, recent findings emerging from genetic studies show increasing evidence for an overlap in genetic susceptibility across the traditional binary classification of psychosis. Moreover, the emerging evidence suggests the possibility of a relatively specific relationship between genotype and psychopathology. On the other hand, the association of endophenotypes, e.g. neuropsychological and neurophysiological markers, to the genetic variations are closer than psychopathology of schizophrenia.

The psychiatric research described the cognitive deficit among patients with schizophrenia in last fifty years; this phenomenon characterizes the 60-80 % of the patients. The cognitive deficit, which shows less association with the positive symptoms than negative symptoms, and has a strong correlation with the social functioning, is a stable trait marker in the course of illness. On the basis of these findings, Carpenter and colleagues (1988) proposed a putative schizophrenia subtype defined by negative symptoms. Patients with primary (idiopathic), enduring negative symptoms meet the criteria of deficit schizophrenia. Deficit schizophrenia can be distinguished from non-deficit schizophrenia on the basis of endophenotypes. The neurocognitive character of deficit subgroup has not been clarified yet, and the current findings contain some contradictions.
The most unfavorable feature of schizophrenia is the psychosis with hallucinations and delusions. Both symptoms emerge in many types of psychoses with different etiology: these are ubiquitous. The two prominent symptoms of positive dimension may appear in different times of the illness course: in the prodromal, psychotic, post psychotic and residual phase as well.

Moreover, the emerging of hallucination and delusion in affective disorders indicates the severity of the illness phase. The cycloid psychosis concept has a long tradition in the European psychiatry; the elaborated delusion or the hallucination do not belong to its core features (ecstatic happiness, serious anxiety, excitation-confusion, inhibition-confusion, hypermotility-hypomotility), they are usually presented in the psychopathological picture.

In contrast to the numerous studies focusing on the general prognosis and outcome of psychotic disorders, surprisingly few studies were designed to investigate the long-term course of hallucinations and delusions. These symptoms determine not only the life course, but the social functioning, suicidal risk (its rate is 10 times acc. to some studies) and the violent behavior of the patients.

Aims

The aim of this work was to compare the results of a traditional categorical classification with the new neurocognitive (dimensional model) approaches.

The longitudinal changes of the basic symptoms of positive dimension were studied focused on schizophrenia in the frame of a 21-33-year prospective follow-up period, conducted in Budapest; the cross-sectional study focused on the cognitive dimension in deficit and non-deficit patients.

1. study: The changes of hallucination and delusion over time, on the basis of 21-33-year follow-up („Budapest 2000”)

1.) To study the longitudinal change of severity of delusion and hallucination in affective, cycloid, and schizophrenia patients.
2.a) To monitor the content of delusion and its changes at the index and two follow-up phases in affective, cycloid and schizophrenia patients.
2.b) To monitor the modality of hallucinations and its changes at the index and two follow-up phases in affective, cycloid and schizophrenia patients.
3.) To test the relationships of longitudinal changes of delusion and hallucination in affective, cycloid and schizophrenia patients.

4.) To determine the odds of delusion and hallucination in the follow-up period in cycloid and schizophrenia patients.

5.) To demonstrate that the features of studied symptoms separate each traditional diagnostic group through the 21-33-year follow-up period.

II. study: cognitive dimension in schizophrenia

1.) The main hypothesis was that deficit patients are less able to use feedback and they show more severe impairment during the learning of associations compared with non-deficit patients.

2.) A battery of classic neuropsychological tests sensitive for frontal lobe functioning was also administered in order to investigate the potential contribution of this brain region to associative learning.

Methods

In the “Budapest 2000” study, participants were 222 female patients who were recruited between 1967-1973 at the Semmelweis University, Department of Psychiatry and Psychotherapy, Budapest, Hungary. As it was earlier published, patients originally were classified according to Leonhard’s criteria. The original diagnostic groups included manic-depressive psychosis, unipolar depression, cycloid psychosis, affect-laden paraphrenia, periodic catatonia, systematic paraphrenia, systematic catatonia, and hebephrenia. Because today these diagnostic groups are less frequently used and some groups contained only a few patients, in the present report we condensed the sample into the groups of cycloid psychosis, paranoid schizophrenia, catatonia, and hebephrenia (Table 1). Patients were assessed at three visits: baseline (index) assessment during the acute phase of the illness, 5-year follow-up, and 21 to 33 year follow-up. At the final follow-up visit, patients were re-diagnosed according to the DSM-IV criteria using the Structured Clinical Interview for DSM-IV (SCID-IV).
Table 1. Basic descriptive and demographic data

<table>
<thead>
<tr>
<th></th>
<th>Cycloid</th>
<th>Hebephrenic</th>
<th>Paranoid</th>
<th>Catatonic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients (index/5-year/21-33-year)</td>
<td>28/28/15</td>
<td>31/31/23</td>
<td>56/56/25</td>
<td>53/53/35</td>
</tr>
<tr>
<td>Age at onset (years)</td>
<td>25.8 (8.7)</td>
<td>19.9 (3.7)</td>
<td>30.3 (6.4)</td>
<td>28.9 (8.2)</td>
</tr>
<tr>
<td>Education (year)</td>
<td>12.6 (2.5)</td>
<td>11.6 (2.3)</td>
<td>13.6 (3.8)</td>
<td>11.9 (3.2)</td>
</tr>
<tr>
<td>Duration of psychiatric inpatient treatment (month)</td>
<td>12.4 (13.3)</td>
<td>39.8 (34.6)</td>
<td>21.5 (16.2)</td>
<td>27.3 (23.4)</td>
</tr>
<tr>
<td>Number of inpatient treatments</td>
<td>6.7 (6.6)</td>
<td>12.9 (9.8)</td>
<td>8.0 (3.9)</td>
<td>8.8 (5.8)</td>
</tr>
<tr>
<td>Family status at the final visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never married</td>
<td>13%</td>
<td>57%</td>
<td>26%</td>
<td>31%</td>
</tr>
<tr>
<td>Widow</td>
<td>13%</td>
<td>13%</td>
<td>31%</td>
<td>13%</td>
</tr>
<tr>
<td>Divorced</td>
<td>20%</td>
<td>4%</td>
<td>31%</td>
<td>23%</td>
</tr>
<tr>
<td>Married</td>
<td>54%</td>
<td>26%</td>
<td>12%</td>
<td>33%</td>
</tr>
<tr>
<td>Functioning at the 21-33-year follow-up</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pensioner</td>
<td>33%</td>
<td>0%</td>
<td>16%</td>
<td>2%</td>
</tr>
<tr>
<td>Disability pensioner</td>
<td>33%</td>
<td>100%</td>
<td>84%</td>
<td>92%</td>
</tr>
<tr>
<td>Unemployed</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Employed</td>
<td>33%</td>
<td>0%</td>
<td>0%</td>
<td>6%</td>
</tr>
</tbody>
</table>

Data are provided as means (standard deviations) and percentages.

Clinical symptoms were assessed with the 16-item Rockland-Pollin Rating Scale (RPRS) and with the List of Specific Symptoms. At the final assessment, in addition to the administration of the RPRS, all patients were rated using the Positive and Negative Syndrome Scale (PANSS).

The changes of symptom severity (dependent variables) over time and its association with the independent variables (diagnostic group, relative time, diagnostic
group by time) was analyzed with Hierarchic Longitudinal Model (HLM). First, the analyses were performed in the main diagnostic groups (affective, cycloid and schizophrenia), then in the schizophrenic subgroups (catatonic, paranoid and hebephrenic schizophrenia).

The relationships of longitudinal changes of delusion and hallucination was analyzed with canonical component analysis (CCA).

Differences among the diagnostic groups in the likelihood of the two principal target symptoms (delusions and hallucinations) over time was investigated by generalized linear mixed model (GLIMMIX) analysis, a longitudinal data analysis technique which makes possible the utilization of incomplete data resulting from missing observations. The Type III test for fixed effects assessed the main effects of diagnostic group, time (first, second, and third visit during the follow-up period), and the interaction between diagnostic group and time (differences in the change of the likelihood of delusions and hallucinations over time).

In the second study, schizophrenia patients and healthy control volunteers were recruited. The diagnosis was based on the criteria of the Diagnosis and Statistical Manual of Mental Disorders-IV. All participants received the Mini-International Neuropsychiatric Interview. The deficit syndrome was assessed using the Schedule for the Deficit Syndrome. Clinical symptoms were evaluated with the Positive and Negative Syndrome Scale (PANSS). The two subgroups of patients were matched for age, gender, education, duration of illness, positive and general symptoms, and type and chlorpromazine-equivalent dose of antipsychotic medications (Table 2). The dependent measures were the mean number of errors in the training phase and the proportion of incorrect responses in the transfer phase of the Rutgers Acquired Equivalence Test.

Classic tests sensitive for frontal lobe functioning were administered: Wisconsin Card Sorting Test (WCST), Trail Making B tests (TMB) Controlled Oral Word Association Test (COWAT). Repeated measures analysis of variance (ANOVA) was used with group (controls, deficit and non-deficit patients) as the between-subject factor and with dependent measures of tests as the within-subject factor. Scheffé’s tests were used for post-hoc analysis. Pearson’s correlation coefficients were calculated between clinical measures and test results.
# Table 2. Demographic characteristics and neuropsychological results

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Non-deficit</th>
<th>Deficit</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=</td>
<td>20</td>
<td>26</td>
<td>23</td>
</tr>
<tr>
<td>Male/female</td>
<td>14/6</td>
<td>18/8</td>
<td>15/8</td>
</tr>
<tr>
<td>Age (years)</td>
<td>35.4 (7.5)</td>
<td>36.1 (9.6)</td>
<td>37.1 (10.0)</td>
</tr>
<tr>
<td>Education (years)</td>
<td>10.9 (3.8)</td>
<td>10.6 (7.3)</td>
<td>10.1 (5.6)</td>
</tr>
<tr>
<td>Duration of illness (years)</td>
<td>-</td>
<td>12.0 (5.1)</td>
<td>13.4 (6.2)</td>
</tr>
<tr>
<td>Type of antipsychotic medication (second-generation/first generation/both)</td>
<td>-</td>
<td>20/3/3</td>
<td>19/4/0</td>
</tr>
<tr>
<td>Chlorpromazine-equivalent dose of antipsychotics (mg/day)</td>
<td>-</td>
<td>375.6 (192.7)</td>
<td>360.0 (194.5)</td>
</tr>
<tr>
<td>PANSS-P</td>
<td>-</td>
<td>13.1 (5.2)</td>
<td>14.9 (6.9)</td>
</tr>
<tr>
<td>PANSS-N</td>
<td>-</td>
<td>15.4 (5.4)</td>
<td>24.4 (3.4)</td>
</tr>
<tr>
<td>PANSS-G</td>
<td>-</td>
<td>36.0 (14.0)</td>
<td>36.5 (11.2)</td>
</tr>
<tr>
<td>WCST*</td>
<td>9.9 (6.0)</td>
<td>14.9 (3.6)</td>
<td>23.3 (14.0)</td>
</tr>
<tr>
<td>TMB**</td>
<td>55.6 (19.3)</td>
<td>90.0 (27.5)</td>
<td>113.6 (46.8)</td>
</tr>
<tr>
<td>COWAT***</td>
<td>39.4 (10.7)</td>
<td>28.4 (12.1)</td>
<td>22.1 (12.6)</td>
</tr>
<tr>
<td>RAET – errors in the training phase+</td>
<td>7.2 (9.1)</td>
<td>9.0 (15.6)</td>
<td>22.5 (23.4)</td>
</tr>
<tr>
<td>RAET – proportion of errors, old associations++</td>
<td>0.12 (0.15)</td>
<td>0.08 (0.11)</td>
<td>0.11 (0.11)</td>
</tr>
<tr>
<td>RAET – proportion of errors, new associations+++</td>
<td>0.17 (0.22)</td>
<td>0.39 (0.27)</td>
<td>0.37 (0.24)</td>
</tr>
</tbody>
</table>
Results

Bearing in mind the limitations of the first study (e.g. diagnostic criteria, rating scales, inclusion criteria (female), the high attrition rate, medication), our results can be summarized as follows:

1.) On the whole, the severity and the number of symptoms, the rate of patients exhibiting the symptoms, indicate reduction in the case of delusion, as well as hallucination, through the 21-33-year follow-up. This result concurs with the known data in the literature. Nevertheless, the change of severity of hallucination is significant over time: the symptom severity reduction significant at the 5-year follow-up, and from this time point the severity shows significant worsening to the 21-33-year follow-up. This temporal breaking was not seen in the case of delusions.

In contrast, the affective and cycloid patients were symptom free at the first follow-up, and remained at the second follow-up too.

2.) The number of delusions decreased in each diagnostic group of patients; it was typical also for the schizophrenia subgroups through the whole follow-up (80%).
Albeit, 72% of the schizophrenic population showed “any” delusion (mild symptom) while 29% “definite” delusion (severe symptoms) at the 21-33-year follow-up.

The hallucination events, as well as delusional thinking, decreased through the first five years (70% reduction). After this time point, the number of the hallucination, that can make uncover, mildly increased. In the index (acute) phase, especially acoustic and somaesthetic hallucinations appeared; the minimal relevant literature emphasizes that, in the acute phase of schizophrenic and non-schizophrenic psychoses there are more often in the first row, the acoustic, in the second row, the visual hallucination than other ones. The various modalities exist, at most the number of hallucination in given modality decreases.

We were not able to identify psychotic symptoms in patients with cycloid psychosis at both second (5 years) and third (21-33 years) visits.

3.) The proportion of patients with hallucination and delusion decreased significant in each diagnostic group over time.

4.) The relationship of longitudinal change of delusion and hallucination separated three subgroups in schizophrenic group: paranoid, catatonic and hebephrenic schizophrenia.

5.) The odds of appearing of delusion and hallucination trough the 21-33-year follow-up: separation of diagnostic groups.

The most striking finding was the difference between cycloid psychosis and subtypes of the schizophrenic psychosis. Odds ratios indicated that psychotic symptoms were observed with different probabilities in the diagnostic groups, and this probability changed during the follow-up period. Cycloid psychosis is characterized by frequent psychotic symptoms, which have transient features and vanish during the long-term-course of the illness. Cycloid psychosis is a stab, separate entity between the two Kraepelinian psychoses.

A second pattern of course was observed in paranoid schizophrenia. Finally, odds ratios indicated a less prominent difference in the probability of psychotic symptoms in patients with hebephrenia and in catatonia. In these patients, hallucinations and delusions were less frequent at the index phase relative to cycloid psychosis and
paranoid schizophrenia, but these symptoms were observable during the follow-up period with some fluctuation.

6.) The severity of psychotic symptoms, which were assessed by the Rockland-Pollin Rating Scale, decreased markedly through the follow-up. The severity of psychosis did not show significant correlation with delusion or hallucination, while the two symptoms were connected.

7.) Positive symptoms and the social functioning:
After 10 hospitalizations, 18% of schizophrenia patients were investigated in psychiatric home care at the second follow-up. Indeed, there are differences in this view: with persistent mild symptoms, the hebephrenic patients are all disability pensioner, 57% of them was never married, and 30% of them lived in psychiatric home care at the 21-33-year follow-up. 66% of catatonic patients were married, but most of them were disability pensioners. Although, the paranoid schizophrenia patients had more severe symptoms, they showed better social functioning: 16% of patient received pension (not disability pension), two-thirds is or was married, as the catatonic one.
The most favorable outcome and excellent social functioning were typical in the cycloid group.

The results of the second study lend further support for the dissociation between feedback-guided learning of association and forming new association on the basis of previous information (acquired equivalence). The former is mediated by the basal ganglia, whereas the latter is related to the medial temporal lobe. This dissociation may be helpful in the definition of the cognitive characteristics of deficit and non-deficit schizophrenia.

1.) Deficit and non-deficit patients showed similar acquired equivalence learning, which was less efficient than that seen in controls. In contrast, deficit patients committed more errors in the feedback-guided training phase than controls, which was not characteristic for non-deficit patients (Table 2.) There was a significant positive relationship between the number of errors in the training phase of the acquired equivalence test and negative symptoms. There was no significant correlation between acquired equivalence test scores and antipsychotic dose.
2.) In general, patients with schizophrenia were impaired on each frontal test, and non-deficit patients outperformed deficit patients. Finally, there was no significant relationship between frontal lobe and acquired equivalence test scores. The lack of any correlation between acquired equivalence test scores and frontal lobe test results may indicate that simple associative learning and acquired equivalence do not depend on higher-level executive functions, similarly to other cognitive skills based on stimulus-response learning.

Conclusions

There is no general agreement whether psychotic symptoms are stable features of schizophrenia or, alternatively, these symptoms appear only temporarily during the course of the illness. Nevertheless, the concept that psychotic symptoms exist in all patients cannot be supported.

The severity and the number of psychotic symptoms decreased through the course of the illness. The severity of hallucination showed significant correlation with the time from the onset of illness. The content of delusions shows an impoverishment, remaining hypersensitivity and thinking of persecution. Both symptoms influence the social functioning of the schizophrenia patients.

The symptoms of the positive dimension clearly separate the Kraepelinian psychoses and cycloid psychosis, as a distinct disease entity.

The relationship of longitudinal changes of two symptoms identified the classical subtypes of schizophrenia: paranoid, catatonic and hebephrenic subtypes.

The second analysis may help elucidate the cognitive character of deficit and non-deficit schizophrenia; it supports the dissociation between feedback-guided learning of associations and forming new association on the basis of previous information (acquired equivalence).

Although the two studies were conducted in different groups of patients, a general conclusion may be that the cognitive dimension distinguishes deficit and non-deficit schizophrenia and the positive dimension separates paranoid, catatonic, and hebephrenic schizophrenia.
The Author’s own publications

**Associating with present work:**

**Book chapters:**


**Publications in Hungarian and foreign periodical:**


12.) Polgár P, Farkas M, Nagy O, Kelemen O, Réthelyi J, Bitter I, Myers CE, Gluck MA, Kéri S. How to find the way out from four rooms? The learning of "chaining" associations may shed light on the neuropsychology of the deficit syndrome of schizophrenia. Schizophr Res 2007 Aug 9 Epub ahead of print


Other publications:


