Cognitive differences between deficit and non-deficit schizophrenia

Thesis

Dr. Patrícia Polgár

Semmelweis Egyetem

Mentális Egészségtudományok Doktori Iskola

Supervisor: Dr. István Bitter

Dr. Szabolcs Kéri

Opponents: Dr. Tamás Tényi

Dr. György Purebl

President of examination committee: Dr. Dániel Bereczki

Members of examination committee: Dr. Zsuzsanna Aszalós

Dr. Anna Géczy

Dr. József Kovács

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Introduction

Abnormal cognitive performance has been reported widely in schizophrenia. Cognitive symptoms are a core feature of the illness, and they affect 40-80 % of the patients. The issue is of great practical and clinical significance, as the cognitive dysfunction also play a major role in the long-term prognosis and psychosocial function. Cognitive dysfunction can be present at an early age, before the first psychotic episode, and can also be detected at healthy biological relatives of schizophrenia patients. The significance of the cognitive dysfunction is well established, however, it is not easy to define its specific nature. One of the difficulties arise from the limitations of classic neuropsychological test methods: the tests used in the last decades were originally developed to examine localised neurological diseases – stroke, brain trauma - and they have limited ability to registrate more subtle differences.

Another difficulty arises from the heterogenity of schizophrenia. A particularly important progress in the field was the introduction of the deficit syndrome. Deficit syndrome refers to a subtype of schizophrenia which is characterized by primary, enduring negative symptoms: flattened affect, anhedonia, poverty of speech, curbing of interest, lack of sense of purpose and diminished social drive. The deficit group manifests persistent, rather than transitory negative symptoms, which were primary or idiopathic to the illness, rather than due to such secondary factors as neuroleptic akinesia, depressive anhedonia, paranoid social withdrawal, or preoccupation with psychotic symptoms. Since the first publication of the original concept a substantial body of clinical, pharmacologic, neuropsychological, and epidemiologic evidence has accumulated supporting the construct validity of the deficit syndrome as a pathophysiologically distinct subgroup within schizophrenia.

Several neuropsychological studies suggested that deficit schizophrenia patients show a more serious cognitive deficit in comparison to non-deficit schizophrenia patients. The exact nature of the difference concerning neuropsychological performance, however, still remains unclear. Some studies suggest that the deficit subgroup only differs from the nondeficit group in general cognitive functioning, while other studies resulted in a variety of specific differences. Classic neuropsychological methods are not likely to uncover circumscribed cognitive impairments in the deficit syndrome. The use of new test methods are also needed, which are based on the results of cognitive neuroscience. This way the description of cognitive dysfunction can help to define schizophrenia phenotypes.

Aims

The aim of my thesis was to investigate, if there is a specific, qualitative difference between deficit (SZ-D) and nondeficit schizophrenia (SZ-ND) regarding cognitive function.
Earlier studies using classic neuropsychological methods resulted in a global, quantitative difference between the to groups, therefore we chose a different approach: in the first study we used a classic, well-documented test on executive functioning, but in order to obtain more refined results, we implemented a factor analytic approach. The second study includes a new test method based on the latest results of cognitive neuroscience. The common aim of both studies was to decide if deficit schizophrenia is characterized by a general, globally more severe cognitive dysfunction in comparison to nondeficit schizophrenia, or qualitative differences are present in specific fields. To investigate this question, we performed the following studies on schizophrenia patients.

1. Executive function in deficit and nondeficit schizophrenia on the Wisconsin Card Sorting Test

The aim of this study was to investigate executive function differences in the two diagnostic subgroups. We used a classic, well-documented test on executive functioning, the WCST (Wisconsin Card Sorting Test). In order to obtain more refined results, we implemented a factor analytic approach.

2. Interactive memory systems in deficit and nondeficit schizophrenia on the Kilroy chain association test

The aim of this study was to investigate interactive memory systems in the two diagnostic subgroups. To achieve this aim, we used a "chaining" association task, the Kilroy test. The task is motivated by evidence suggesting that the medial temporal lobe (MTL) and the basal ganglia (BG) play a distinct role in learning and memory: the MTL, including the hippocampus, is important in declarative memory functions, whereas the BG is essential for learning habits and skills, such as associations between stimuli and responses. The Kilroy test examines the two memory function within one test.

Methods

Patients suffering from schizophrenia, treated at the from the Semmelweis University Psychiatry and Psychotherapy Clinic took part in the studies. The diagnosis was based on the DSM-IV (Diagnostic and Statistic Manual of Mental Disorders) criteria. DSM- IV diagnoses were confirmed by the Hungarian translation of the MINI 5.0 diagnostic interview. Symptoms were evaluated with the Positive And Negative Symptom Scale (PANSS). The deficit status of the patients was evaluated with the SDS (Schedule for Deficit Syndrome). Exclusion criteria were severe comorbid neurological disease, head trauma, mental retardation and substance abuse. Healthy controls were recruited from volunteers and examined by the MINI diagnostic interview to exclude psychiatric disorders.

1. Executive function in deficit and nondeficit schizophrenia on the Wisconsin Card Sorting Test

Subjects

154 SZ-D, 121 SZ-ND patients and 130 healthy controls participated the study. The three study groups demonstrated no significant difference in sex distribution. Analyses revealed significant between-group differences in terms of completed education, and the difference approached significance for age, so these variables were added as covariates to the analyses.

Wisconsin Card Sorting Test

The WCST is a widely used test method primarily created to measure frontal lobe dysfunction. The subjects are required to sort a deck of cards according to the color, shape or number of the symbols printed on them. The task is to find the right sorting rule based on the simple „right or wrong" feedback of the examiner. The examiner changes the sorting rule from time to time without warning. The sorting rule changes when the subject found the actual sorting rule and gave 10 right answers in a row.

Statistical analysis

The Statistical Analysis System for Windows (version 9.1; SAS Institute, Cary, NC) was used for all statistical analyses. Differences between the three diagnostic subgroups were tested using the General Linear Model (GLM) analysis. In the GLM model, diagnostic group (deficit, nondeficit, control) was applied as the independent variable. Indices of executive functioning, including scores on the WCST factors, identified by principal component

analysis with varimax rotation were applied as dependent variable. Age and level of education were added as covariates to the analyses.

2. Interactive memory systems in deficit and nondeficit schizophrenia on the Kilroy chain association test

Subjects

Participants were 78 patients with schizophrenia (45 SZ-D, 27 SZ-ND) and 30 healthy volunteers. 6 patients were not able to complete the "chaining" task, these patients were excluded from the analysis. The three study groups demonstrated no significant difference in sex distribution, education or age.

The Kilroy-test

The test has two phases, thus the two interactive memory systems can be examined separately within one test. The task was run on a Macintosh OS9 computer. Participants were requested to navigate a cartoon character through a sequence of 4 rooms by learning to choose the open door from 3 colored doors in each room. The aim of the game was to learn the full sequence of rooms until the character reached the outside. In the *training phase*, each stimulus leading to reward (open door in each room) was trained via feedback until the complete sequence was learned. In the *probe phase*, the context of rewarded stimuli was manipulated: in a given room, in addition to the correct door of that room, there also appeared a door which was open in another room. Whereas the training phase is dominantly related to basal ganglia circuits, the context-dependent probe phase requires intact medial-temporal lobe functioning.

Other neuropsycholoical tests

We used 3 widely applied neuropsychological tests to measure frontal lobe functioning. These included FAS fluency (total number of words recalled), WCST (number of perseverative errors), and Trail Making B (time to completion).

Statistical analysis

The STATISTICA 6.0 package was used for data analysis (StatSoft, inc., Tulsa). First, data were entered into Kolmogorov-Smirnov tests in order to check the normality of distribution. Since data showed normal distribution, analyses of variance (ANOVAs) were used, followed by two-tailed t-tests. Pearson`s correlation coefficients (r) and linear regressions were used to assess the relationship between relevant variables.

Results

1. Executive function in deficit and nondeficit schizophrenia on the Wisconsin Card Sorting Test

Results of the exploratory factor analysis of the whole sample yielded 2 factors which together explained approximately 95 % of the total variance. The distribution of the amount of variance explained across the 2 factors was the following: factor 1 („general executive functioning") = 76 %, and factor 2 („non-perseverative errors") = 19 %. The 2-factor solution remained stable for the three groups.

The composition of Factor 1 was stable in all samples, and consistent with the literature. The variables loaded on this factor were the following: Correct responses, Conceptual responses, Categories completed, Perseverative responses, and Perseverative errors. This factor includes variables which represent concept formation and perseveration, the ability to find a correct sorting principle as well as to switch to a next, different sorting principle, if needed. Since factor loadings were uniformly high for all the above mentioned variables, we interpreted Factor 1 as General executive functioning.

Factor 2 was also quite consistent among the three groups with one exception: Non-perseverative errors loaded specifically on this factor in both schizophrenia samples, and also in the pooled sample of the three groups, but not in the control group. In this group we observed a slightly different structure for Factor 2, with a higher loading of Completed Categories, Perseverative Responses and Perseverative Errors.

Comparison of the diagnostic groups on each of the factors revealed that deficit schizophrenia patients suffer from a more severe degree of impairment on the 'General executive function' factor than nondeficit schizophrenia patients.

Significant group differences were detectable among each of the groups on Factor 1 ($p<.05$ for all pairwise comparisons).

As for Factor 2, a significant group ($p=0.0012$) difference was found, indicating poorer functioning in the nondeficit schizophrenia subgroup vs. the controls; a difference between the deficit and nondeficit subgroups approached statistical significance ($p=.073$).

2. Interactive memory systems in deficit and nondeficit schizophrenia on the Kilroy chain association test

In the first ANOVA, the between-subject factor was the group (controls, SZ-D, SZ-ND) and the within subject factor was the number of errors in the training phase (collapsed across the 4 phases) and in the probe phase. This ANOVA revealed significant main effects of group ($F(2,99)=11.21$, $p<0.001$), errors ($F(1,99)=22.18$), and a significant two-way interaction ($F(2,99)=5.62$, $p<0.05$). SZ-ND patients displayed significantly more errors than controls on the probe phase ($t(73)=-3.70$, $p<0.001$), but not on the training phase ($p>0.1$). SZ-D patients were less accurate than controls on both the probe $t(55)=-4.96$, $p<0.001$) and training phases ($t(55)=-4.71$, $p<0.001$). Critically, SZ-D and SZ-ND patients displayed statistically similar performance on the probe phase ($p>0.1$), whereas SZ-D patients committed more errors on the training phase than did SZ-ND patients ($t(70)=-3.01$, $p<0.01$)

In the second ANOVA, we explored the differences between the groups in the 4 training phases of the task (from 1 to 4 rooms). This ANOVA indicated significant main effects of group ($F(2,99)=9.80$, $p<0.001$), task phase ($F(3,297)=38.03$, $p<0.001$), and a two-way interaction ($F(6,297)=4.57$, $p<0.001$). As compared with controls and with SZ-ND patients, SZ-D patients showed significantly more errors in the 3rd and 4th phase of the task ($t>2$, $p<0.05$).

Patients with schizophrenia were impaired on all tests of frontal lobe functioning as compared with controls. In addition, patients with deficit syndrome performed worse than SZ-ND patients.

None of the measures of frontal tests correlated with the number of errors in the training and probe phase of the “chaining” task ($r<0.1$).

Conclusions

Our resuts reveal that not only a generalized, but a specific cognitive dysfuncion can be described in deficit-syndrome in comparison to nondeficit schizophrenia.

1. In Study 1., results revealed that both schizophrenia groups showed executive function impairment in comparison to controls. SZ-D patients suffer from a more severe degree of impairment on the 'General executive function' factor (conceptualization, flexibility, set shifting) than SZ-ND patients. On the other hand, only SZ-ND patients and healthy controls showed a significant difference on Factor 2. The WCST is a widely used neuropsychological test, designed to examine localized neurological diseases. Our results show that with refined statistical analysis, WCST is able to detect more subtle differences: deficit-syndrome has a different profile concerning executive function in comparison to SZ-ND.
2. Another significance of this study is the description of the cognitive processes behind the WCST with a factor analyic method. Most of the earlier factor analytic studies examined small, mixed groups. To our knowledge, this is the first WCST factor analysis carried out on a large, Hungarian sample of schizophrenia patients.
3. The results of Study 2. revealed that while context-dependent, MTL-mediated learning is uniformly impaired in schizophrenia, BG-mediated procedural learning remains relatively intact in SZ-ND patients. However, deficit syndrome is associated with prominently impaired BG-mediated stimulus–response reinforcement learning.

In conclusion, the two diagnostic subgroups seem to differ not only in the degree of cognitive impairment, but in the characteristics as well. The deficit-syndrome can be characterized by a specific profile regarding executive function, and shows greater impairment in procedural learning. We found a compelling and specific difference between the neurocognitive profile of deficit and non-deficit schizophrenia, which may strengthen construct validity and may shed new light on the pathophysiology of the deficit syndrome. Separating deficit-syndrome from nondeficit schizophrenia has clinical significance as well. Deficit-syndrome has a worse prognosis and quality of life, deficit patients has a more psychosocial and occupational dysfunction compared to nondeficit schizophrenia. Treatment of primary enduring negative symptoms with antipsychotic medication also raises difficulties.

With appropriate test methods, a diagnostic subgroup can be identified within schizophrenia with specific symptoms, cognitive profile and prognosis. These should be taken into consideration while planning treatment, antipsychotic medication and psychosocial interventions.

Publications

Publications related to the thesis

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