Basic underlying structure of psychopathological symptoms in schizophrenia and its change over time during pharmacological treatment

Doktori tézisek

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INTRODUCTION

Identification of basic underlying dimensions of manifest psychopathology displayed by patients with schizophrenia has been the focus of ongoing research for over fifty years. Although various models have been proposed and countless empirical studies were conducted in order to address this issue, the true intrinsic dimensionality of the observed clinical manifestations remains elusive. We identified several major methodological problem areas that may underlie the continuing uncertainties regarding the factor structure of psychopathological symptoms observed in schizophrenia as indexed by widely used comprehensive psychopathological scales, including the BPRS (Brief Psychiatric Rating Scale) and the PANSS (Positive and Negative Syndrome Scale). These problems consist of (1) various methodological shortcomings (e.g., small sample size in factor analyses, various ad hoc decisions with regard to the identification of factors), (2) conceptual problems (ignoring the hierarchical structure of symptoms), and (3) the lack of longitudinal view in the analyses of data. In this dissertation, while dealing with problem areas 1 and 2, we were placing a particular emphasis on problem area 3, i.e., the longitudinal view in the analyses of data.

From a practical standpoint, it is important to note that because the total scores of the more comprehensive scales (which provide a broad item coverage for manifest clinical symptoms) were shown to be insensitive to measure specific changes of psychopathology, individual symptoms factors are increasingly used in studies for longitudinal comparisons, including psychopharmacological treatment in clinical trials (e.g., factors of BPRS or PANSS). The implicit assumption of the use of individual factors in these comparisons is that the factors represent an instrument of measurement which is invariant with time; it is assumed that the factor structure and the underlying dimensionality remains unaffected by treatment. Clearly, it is undesirable if changes detected during drug treatment are attributable to changes in the measuring instrument per se. The broad general goal of the investigations that we summarize in this dissertation was to examine whether the same
factor structure can provide an adequate representation of symptoms at different time points during psychopharmacological treatment.

**SPECIFIC OBJECTIVES**

Based on the aforementioned conceptual background the dissertation had the following three specific aims.

1/ First, in view of the **time-varying associations** among clinical symptoms, our principal purpose was to investigate whether **time invariant** latent variables (factors) can describe the psychometric data at different time points in a clinical trial, including a lead-in placebo washout period. The specific goals in this regard were to

- examine the replicability of previously published factor structures of psychopathological symptoms,
  - applying exploratory factor analysis techniques analogous to those published in the literature.
  - formulating confirmatory factor models in order to test various theoretically postulated models of latent structures of psychopathological symptoms

- Investigate the change in factor structure over time during psychopharmacological treatment with the prototype typical antipsychotic haloperidol

- Considering the multidimensional nature of psychopathological variables in patients with schizophrenia, test hierarchical latent structure (factor) models to examine whether higher (second) order factor structures would be more suitable than first order factors to describe the psychopathological data.
2/ Second, in order to gain additional insight about the structure and relationship of basic symptoms in schizophrenia, and in view of the conflicting views of their association or independence, in a second ancillary substudy investigate the longitudinal covariation between positive and negative symptoms during haloperidol treatment.

3/ Third, in view of the considerable support for the observation that atypical antipsychotics have a broader range of therapeutic effects than traditional antipsychotics (in particular, they have been shown to be superior in terms of improvement of negative, cognitive and affective symptoms in patients with schizophrenia), examine whether atypical antipsychotics change the underlying syndromal structure of schizophrenic phenomenology as a result of treatment.

METHODS

The data for the analyses that we describe in this dissertation were collected in three separate clinical trials that examined the relationship between clinical effects and doses and types of typical and atypical antipsychotic medications in the treatment of patients with schizophrenia or schizoaffective disorder. The studies (‘parent studies’) have previously been published in the literature.

The first trial was a clinical trial of haloperidol and explored the relationships between plasma levels in the range of 2-35 ng/ml and clinical effects in 176 acutely exacerbated schizophrenic and schizoaffective patients, and included an initial placebo washout period. The second trial (which also included a lead-in placebo period) examined relationship between clinical effects and haloperidol plasma levels in the range of 2-10 ng/ml, and enrolled 65 patients with acutely exacerbated schizophrenia or schizoaffective disorder. The third trial was a parallel-group, double-blind trial to compare the clinical efficacy and safety of clozapine, olanzapine, risperidone, and haloperidol plus benztropine in 156 chronic treatment-resistant patients with schizophrenia and schizoaffective disorder. A more detailed description of the methods and procedures in the individual trials are available for further reference in the dissertation.
In order to accomplish the principal goal set for the research reported here (i.e., examination of change in the factor structure of psychopathological symptoms over time), a two-step approach was adopted in one (1st substudy) of the 3 principal substudies that we included in the dissertation. In the first step, exploratory factor analyses (EFA) were performed at different time points during treatment. In the second step, confirmatory factor analysis (CFA) was used. We posited and statistically tested specific relationships between the individual symptoms and factors (measurement model), and between the factors themselves (structural model).

The first substudy was based on the BPRS scale, and used data from the first trial mentioned above. As we were interested in the invariance of the traditional clinical BPRS factors over time, our null hypothesis was that at each time point the relationship between the individual items and the extracted factors (measurement model) was the same as in the clinical factors (i.e., we hypothesized the same item composition as in the clinical factors at each time point). Because relationship between the factors (structural model) may change over time, at each time point we investigated which of the possible alternative theoretical models, positing different types of overlap between the factors, can best describe the data.

As an ancillary exploratory investigation (2nd substudy), we also investigated the longitudinal covariance between positive and negative symptoms over time using pooled data from two clinical trials (the first and 2nd trials described above). Finally, as mentioned in the objectives, in an additional study (3rd substudy for the dissertation) we investigated the invariance of the factor structure of the PANSS scale before and after neuroleptic treatment using typical and atypical antipsychotics in a group of patients with schizophrenia or schizoaffective disorder.

RESULTS

A consistent finding across studies was that, at study baseline and end point, the exploratory factor analyses were able to replicate the factor structures that have been published in the literature and used in clinical practice. In particular at study baseline (i.e.,
pre-placebo baseline in the Study 1 [i.e., 1st substudy], and at pretreatment in Study 3 [i.e., 3rd substudy]) five factor solutions for the BPRS and PANSS, respectively, emerged, which were similar to published ‘gold-standards’ from the literature in terms of their item composition.

For BPRS, the 5 factors included (with items in parentheses) the Anxiety/Depression (anxiety, guilt, depression, somatic concerns); Thought Disturbance (unusual thought content, conceptual disorganization, hallucinatory behavior, grandiosity); Anergia (blunted affect, emotional withdrawal, motor retardation); Hostile-Suspiciousness (hostility, uncooperativeness, suspiciousness); and Activation (excitement, tension, mannerisms–posturing). For PANSS, the five factors included Excitement (excitement, hostility, uncooperativeness, poor impulse control); Negative symptoms (blunted affect, emotional withdrawal, poor rapport, passive/apathetic social withdrawal, lack of spontaneity, active social avoidance); Positive symptoms (delusions, hallucinatory behavior, grandiosity, unusual thought content, suspiciousness/persecution); Cognitive symptoms (conceptual disorganization, difficulty in abstract thinking, disorientation, poor attention, preoccupation); and Anxiety/Depression (anxiety, guilt feelings, tension, depression).

In terms of invariance of factor structures over time, a consistent finding from the exploratory factor analyses across studies was that certain items loaded on different factors at different time points. This finding supports the view that the latent structure of psychopathological factors can not be conceived as consisting of time invariant and "pure" (non-overlapping) constructs. The confirmatory factor analysis in the first study provided further support for this conclusion.

Despite the aforementioned changes in the item composition of factors in both studies, Studies 1 and 3 yielded somewhat contradictory findings in terms of factorial invariance over time. In Study 1, exploratory factor analyses demonstrated that the traditionally used clinical factors were reproducible with high fidelity at the pre-placebo time point, but during placebo fundamental changes took place in the factor structure. These changes were indicated both by the coefficients of congruence and by the rotated
factor loadings. In addition, in Study 1, results also indicated a re-emergence of the initial (pre-placebo) factor structure for most of the factors during haloperidol treatment.

However in Study 3, in comparing the PANSS factor structure at baseline and endpoint after 14-week of double-blind treatment, no substantial changes were seen in the PANSS factor structure. We must note, however, that relatively modest changes in symptom severity over time took place in Study 3 as compared to Study 1 (which included a placebo run-in period), which might explain the apparent discrepancy with Study 3 (which did not include an initial placebo phase, and focused on more treatment resistant subjects).

This, in conjunction with the fact that in Study 1 the original (standard) factor structure re-emerged after treatment, may resolve the above mentioned apparent contradiction between the two studies. From a clinical perspective, it is worth noting that in Study 3 chronic patients with a history of treatment resistance were able to show a pattern of modest expanded syndromal response with atypical antipsychotics in the area of negative, excitement, cognitive and affective symptoms, without changing the underlying syndromal structure.

With regard to the hierarchical (second order) latent structure of psychopathological variables, the confirmatory factor analysis results showed that consistently, throughout the entire time period, a model which allowed correlation between the posited theoretical (clinical) factors provided a significantly better description of the data than the independent factor model. This is consistent with a higher order factor model, and indeed such a model provided of the closest fit to the observed data in our study. However, additional studies are needed in order to further examine this issue. Similar to the changes in items composition, the analysis of the intercorrelations among the factors, as shown by the CFA at each time point, revealed a substantial change over time, arguing against the invariance of such a factor model over time following substantial changes in the patient conditions.

Overall, confirmatory factor analysis showed that relationships between the clinical factors and their individual items were significant for most of the items at each time point. However, consistently low values of standardized factor loadings (yielded by the CFA)
indicated a poor reliability for some of the items. In particular, the fact that two items (motor retardation, disorientation) of the anergia factor had low factor loadings suggested a low construct reliability for this factor. This result is in agreement with other reports from the literature. The problem of low reliability suggests that further scale refinement is necessary to improve construct reliability; this work may help attain an increased longitudinal factorial stability.

Examining the longitudinal covariation among symptoms, the principal finding from Study 2 [i.e., 2nd substudy] was that individual positive and negative symptom-change trajectories over time were strongly associated. The finding that negative symptoms improved during haloperidol treatment (although only modestly) contradicts the concept proposed by Crow in his two-syndrome theory of schizophrenia; according to this concept, positive symptoms would be a clinical manifestation of hyperdopaminergia, and therefore neuroleptic responsive; in contrast to positive symptoms, negative symptoms would be due to a structural brain deficit, and therefore immutable to haloperidol treatment.

**CONCLUSION**

Overall, our results suggest that longitudinal applications of the traditional subscales of psychometric rating scales should take the issue of factorial stability over time into consideration. The fact that the congruence of empirically derived factors with the clinical factors was the lowest at placebo can be viewed as a reflection of decreased construct reliability in describing psychopathology at this time point. The lack of the invariance of the factor structure may be the most apparent with "non-Kraepelinian" patients that have the capability to manifest clinically significant changes to a changing pharmacological input. Given the fundamental changes in symptom manifestations on placebo, we believe that a decrease in factorial stability and construct reliability at this time point may not be unique to the BPRS. Because in many clinical trials data from the placebo (wash-out) time point are used as a standard for longitudinal comparisons, we think that replication studies,
testing BPRS, PANSS as well as other major rating instruments, would be of considerable practical use.
Author’s list of publications pertaining for the current dissertation

Published in English:


Published in Hungarian:


Vitrai J, Czobor P: Regression toward the mean. (In Hungarian with English Abstract.). Psychiatria Hungarica 1993; 8:119-124