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Abstract

The concept that there are at least three clinical syndromes within schizophrenia has been influential, and the significance of these syndromes is supported by a growing number of studies. However, the meaning of these syndromes is not clear. The yield of research studies could be increased by the application of a "default" data analysis, in which the differential association—if any—of the three syndromes with the dependent variable(s) of a study is determined.

Keywords: Schizophrenia, psychometrics, statistical models, negative symptoms, research methods.


Factor analysis studies of the symptoms of schizophrenia have led to the concept that there are three clinical syndromes or dimensions within schizophrenia—reality distortion (hallucinations and delusions), disorganization (inappropriate affect, formal thought disorder, and disorganized behavior), and negative symptoms (Buchanan and Carpenter 1994; Andreasen et al. 1995). There is evidence that these three may maintain a significant degree of independence over time (Arndt et al. 1995), but they have been differentially associated with regional brain activation and anatomy (Liddle et al. 1992a, 1992b; Tamminga et al. 1992; Buchanan et al. 1993; Kaplan et al. 1993; Carpenter et al. 1996); plasma homovanillic acid (Ribeyre et al. 1994); neuropsychological and cognitive impairments (Liddle et al. 1989; Liddle and Morris 1991; Buchanan et al. 1994; Cuesta and Peralta 1995; Cuesta et al. 1995); clinical signs on neurological examination (Liddle 1987; Liddle et al. 1989; Buchanan et al. 1990); risk factors (Dollfus et al. 1996); treatment response (Breier et al. 1994; Cuesta et al. 1994; Kopelowicz et al. 1997); associated symptoms (Kirkpatrick et al. 1994, 1996b); and course variables, including age of onset, long-term outcome, and risk of spontaneous movement disorders and drug abuse (Kirkpatrick et al. 1993, 1994, 1996a; Castle et al. 1994; Fenton and McGlashan 1994; Fenton et al. 1994).

Despite these interesting findings, there are important gaps in our understanding of the three putative syndromes. Not every study has found the same factors, and the three-factor structure may also apply more generally to psychosis, and not just to schizophrenia (Kitamura et al. 1995; Maziade et al. 1995; Peralta et al. 1997). Moreover, it is not clear if these clinical dimensions represent individual variation in the anatomical distribution of a single pathophysiological process that affects all patients with schizophrenia. Alternatively, do these continuous dimensions reflect categorical differences among individuals? Do any of the factors reflect in part a separate disease within the syndrome of schizophrenia?

The differences among these possible interpretations of the data are profound, but we will not be able to distinguish between them, or reach some other and perhaps better conclusion, unless appropriate research methods are applied. As a consequence, the field would be well served by adopting, for the foreseeable future, a "default" analysis: in any study in which doing so is practical, it would be profitable to analyze the data in such a way that the differential association—if any—of the three syndromes with the dependent variable(s) of the study can be determined. This default analysis could also supplement another, primary, analysis.

Reprint requests should be sent to Dr. B. Kirkpatrick, Maryland Psychiatric Research Center, P.O. Box 21247, Baltimore, MD 21228; e-mail: bkirkpatr@aol.com.
This would be a “default” approach; in some instances it would not be possible or desirable. For instance, in large epidemiological studies, it is often not possible to distinguish among the three syndromes, and there will be many other studies with sample sizes that are too small, or too homogeneous, for such an analysis. Other studies will be designed to test an a priori hypothesis about one of the syndromes, and the default would not be appropriate.

There would also be uncertainties about the best application of such an approach, but with time these uncertainties might be resolved, or at least clarified, by comparing different approaches, ideally within the same sample. For instance, do symptoms that are present during relative remission, or those associated with relapse, offer the best window to the underlying biology? In the case of disorganization, for example, using enduring features would mean that patients who exhibit marked formal thought disorder during exacerbations, but respond well to treatment and do not exhibit thought disorder between episodes, could not be classified as disorganized. Chronicity of illness presents another ambiguity, because the factor structure found early in the course of illness may differ from that of chronic samples.

Negative symptoms present particular difficulties. There is considerable controversy about the most appropriate definition of this syndrome, although blunted affect and poverty of speech have been included as part of most of the constructs that have been proposed, including negative schizophrenia (Andreasen and Olsen 1982), psychomotor poverty (Liddle et al. 1989), type II schizophrenia (Crow 1985), and the deficit syndrome (Carpenter et al. 1988). Negative symptoms are usually operationalized with rating instruments such as the Scale for the Assessment of Negative Symptoms (SANS; Andreasen 1984), but such instruments as the SANS have proven to be poor predictors of course and biological correlates. In contrast, two other approaches to this area of psychopathology have proven to be powerful in terms of uncovering correlates: the differential diagnosis of negative symptoms, as exemplified by the deficit syndrome criteria (Carpenter et al. 1988; Kirkpatrick et al. 1988), and the analytic approach of Liddle and colleagues (Liddle and Morris 1991; Liddle et al. 1992a, 1992b). In both instances, the focus has been on enduring negative symptoms. In the case of the deficit syndrome, a differential diagnosis of the causes of negative symptoms is made, and those with negative symptoms from such factors as depression, medication, or suspiciousness are eliminated (Carpenter et al. 1988; Kirkpatrick et al. 1989). The validity of the deficit syndrome has been demonstrated in studies of signs and symptoms, course, treatment response, risk factors, and biological correlates (Buchanan et al. 1993, 1994, 1997; Kirkpatrick et al. 1993, 1994, 1996a, 1996b, this issue; Fenton and McGlashan 1994; Ribeyre et al. 1994; Carpenter et al. 1996; Dollfus et al. 1996; Ross et al. 1996; Bustillo et al. 1997; Kopelowicz et al. 1997; Waltrip et al. 1997; Thibaut et al. 1998). In contrast, Liddle et al. (1992b) defined psychomotor poverty on the basis of factor analytic studies, using only those symptoms identified by such studies, namely poverty of speech, flattened affect, and decreased movement. Unfortunately, there has been little overlap in the validators studied by researchers using these two approaches, so at present a direct comparison of the results of these two approaches is, by and large, not possible. Application of both approaches in the same study groups could resolve some of these questions.

One aim of the analysis we are proposing would be to help resolve some of these uncertainties. At present such an analysis is uncommon, although there is now a basis for the hypothesis that the three syndromes will differ relative to many of the variables we study. We would be well served to determine how common these differences are and to attempt to understand their significance.

Addendum: A Reply to Dr. van Os

In his accompanying commentary, Dr. van Os uses this article to discuss some of the most difficult and controversial methodological questions in schizophrenia research. More than one of these questions merits a lengthy discussion, but we believe it is most appropriate to respond briefly.

Categorical Versus Continuous Measures. Dr. van Os suggests that the dimensional or continuous approach to investigating heterogeneity is superior for the following reasons: (1) the dimensions have been derived empirically rather than a priori; (2) the dimensions reflect the varying psychopathology found in patients; and (3) the dimensional approach has been more logical when considering heterogeneity.

We do not see how these arguments are compelling. Diagnostic groups can also have an empirical basis; examples include a “neurodevelopmental” group of patients (Castle et al. 1994), groups derived by Kendler et al. (1998) on the basis of familial aggregation, and the deficit syndrome group (mentioned in our article). Nor is the existence of continuous clinical variables necessarily a reliable guide. Although blood glucose is a continuous variable, in the study of diabetes one is frequently best served by a comparison of patients with the categorical diagnosis of diabetes to control subjects. Body temperature is also a continuous variable, but we consider its causes, such as cholera, malaria, or familial Mediterranean fever, to be categorical. Psychotic symptoms are also found in Huntington’s disease, temporal...
lobe epilepsy, and other conditions; is it therefore inaccurate to consider these separate diseases?

It is uncommon for both continuous and categorical analyses to be conducted in the same data set, but doing so may contribute to resolving the issue of which is more useful, a continuous or categorical analysis. In one study, we found that the deficit/nondeficit categorization, but not a continuous measure of negative symptoms, was associated with summer birth (Kirkpatrick et al. 1998). We have subsequently replicated the association between the deficit/nondeficit categorization and summer birth (Kirkpatrick et al., this issue).

We would conclude that the issue of dimensional versus categorical analyses is not settled. However, our view is that the power of a categorical approach has been shown by the last century and a half of medical research. Not only has the concept of categorical diseases proven to be a powerful one for heuristic purposes, but the nature of interventions, which are fundamentally categorical, makes categorical concepts nearly unavoidable. Be that as it may, if our article leads more researchers to consider this problem, it will have served a useful purpose.

The Meaning of the Factor Analytic Studies in Psychosis Broadly Defined. Dr. van Os cites the studies of the factor structure of psychosis that have been conducted in groups other than schizophrenia. This is an interesting observation, but its meaning is unclear and we do not see how it should change the recommendation we made in our article. There may be instances in which it will be illuminating to combine schizophrenia and other psychotic groups in analyses, but most schizophrenia researchers are unlikely to abandon the distinction between affective and nonaffective psychosis, and differences in such variables as family aggregation, genetic linkage, neurocognitive variables, treatment response, long-term course, and anatomical differences in postmortem tissue support this distinction.

Validity of the Deficit Syndrome. The original intent of the deficit syndrome criteria was to decrease the noise caused by sources of impairment other than the illness itself, such as medication side effects, depression, and so on (Carpenter et al. 1988). Some of the evidence for the success of this effort is mentioned in our article. Dr. van Os is not quite correct in stating that there are a priori diagnostic rules concerning suspiciousness and medication (Kirkpatrick et al. 1989). We have used suspiciousness as one element in a proxy approach to distinguishing deficit and nondeficit groups (Kirkpatrick et al., this issue), but this was an exception. In most studies from our group, the deficit and nondeficit groups have not differed relative to the severity of hallucinations, delusions, or formal thought disorder, or relative to medication treatment (Kirkpatrick et al. 1989, 1993, 1994, 1996a, 1996b, 1996c; Kirkpatrick and Buchanan 1990; Buchanan et al. 1993, 1994; Tamminga et al. 1992; Ross et al. 1996). It is therefore not true that “nothing is known about the distribution of positive, disorganization, and other symptoms in deficit and nondeficit patients.” We believe that one of the advantages of the analysis we outlined—simultaneously varying for all three syndromes—is that the relationship of each to the dependent variable of interest should be clarified.

Debate about the issues Dr. van Os has raised no doubt will—and should—continue. We appreciate his thoughtful comments.

References


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The Authors

Brian Kirkpatrick, M.D., M.S.P.H., is Research Professor, Maryland Psychiatric Research Center, University of Maryland, Baltimore, MD; William G. Ryan, M.D., is Associate Professor, Department of Psychiatry, University of Alabama, Birmingham, AL.