The Neuroanatomies of Schizophrenia
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Abstract

Schizophrenia is a brain disease whose pathophysiology has escaped detection despite intensive investigation. The failure to delineate the neuroanatomy of schizophrenia is related in part to both the subtle nature of the neuropathological abnormalities and to the failure to address adequately the pathophysiological heterogeneity of schizophrenia. The symptoms of schizophrenia aggregate into relatively independent symptom complexes, which suggests that there may be a distinct neural substrate for each complex. If this is true, then the neuroanatomy of schizophrenia is better addressed as the separate neuroanatomies of symptom complexes. However, the use of symptom complexes to guide future neuroanatomical investigations raises crucial methodological issues, including the differentiation of primary versus secondary symptoms, trait versus state characteristics, and continuous versus categorical variables. Decisive hypothesis testing requires that these issues be addressed in study design.


Schizophrenia is a disease of the brain in which various pathophysiological processes result in highly variable clinical manifestations. However, despite a century of study, what is wrong with the brain (and where) is not known with exactitude. Although there are numerous reports of cohort differences between patients with schizophrenia and those without the disease, the most consistent findings (e.g., reduced hippocampal volume, ventricular enlargement, and hypofrontality) have unknown physiological significance, and the findings with the most compelling pathological significance, such as hippocampal pyramidal cell disarray and gliosis, are difficult to replicate. No anatomical or pathological finding is pathognomonic of schizophrenia, and none has sufficient sensitivity and specificity to apply to the diagnosis of schizophrenia. Although schizophrenia may be associated with decreased hippocampal volume, it is also the case that most patients with schizophrenia do not have abnormally small hippocampi. In addition, differences between schizophrenia and normal comparison groups, regardless of the disease correlate being investigated, are usually not very robust because of the considerable variance within the schizophrenia cohort and the extensive overlap of data points between the schizophrenia and normal comparison groups. Moreover, if a finding is argued to relate to brain pathophysiology, then the question of heterogeneity arises immediately; that is, which subgroup of patients is afflicted with the particular pathological feature? Yet, the field has been uneasy in approaching heterogeneity reduction, and virtually all studies are conducted using a design that assumes that schizophrenia is a single disease entity.

In this article, we review the three major pathophysiological models of schizophrenia and the use of domains of psychopathology (or symptom complexes) for heterogeneity reduction and then discuss several methodological issues related to the use of symptom complexes to define patient subgroups and to guide neuroanatomical investigations of schizophrenia.

Pathophysiological Models of Schizophrenia

Three pathophysiological models of schizophrenia can be described: (1) schizophrenia is a single disease entity in which one pathophysiology causes the several symptom complexes; (2) schizophrenia is a syndrome comprising several disease entities, with each etiopathophysiology causing the several symptom complexes; and (3) schizophrenia comprises several symptom complexes, with each complex having its own distinctive etiopathophysiology (Zubin et al. 1985; Carpenter et al. 1988; Kirkpatrick and ...
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In general, there are three approaches to defining schizophrenia subgroups (Carpenter et al. 1993): (1) risk factors (e.g., family history positive vs. negative); (2) physiological markers (e.g., smooth pursuit eye movement or P50 wave); and (3) symptom clusters (e.g., primary, enduring negative, or deficit symptoms). Each approach has its limitations. Risk factors have limited applicability for defining subgroups, since they are population- rather than individual-sensitive. A positive history of familial schizophrenia, birth and pregnancy complications, or winter birth does not ensure that the individual actually has the pathological factor that is associated with the risk variable, nor does a negative history ensure the absence of the pathological factor. Risk factors are probabilistic and weak; for example, an 8 to 12 percent excess in winter birth. Therefore, a subgroup with a risk factor differs to only a modest degree from a subgroup without the factor. Moreover, very large study samples are required for statistical power, making this approach impractical for imaging and postmortem studies. However, this situation changes radically when a risk factor (e.g., a genetic marker with high probabilistic relation to pathogenesis) can be used to assess individuals with high sensitivity and specificity.

In contrast to risk factors, physiological markers can be used to assign individual cases to a subgroup (Zubin et al. 1985). However, these measures are usually continuous variables with arbitrary cut-off points for categorical assignment. Between-group differences may not result in good sensitivity or specificity in individual case assessment. Statistical power is difficult to achieve in most neuroanatomical studies with small sample sizes. Unlike risk factors and symptom complexes, postmortem studies cannot be based on physiologically distinct subgroups unless antemortem testing is available.

The use of symptoms to define subgroups of patients with schizophrenia originated with Kraepelin (1919/1971) and Bleuler (1911/1950) and remains the most common approach for defining more homogeneous patient subgroups. Multiple factor analytic studies have been conducted to examine the structure of schizophrenia symptoms. Although the manifestations of schizophrenia are many and varied, the majority of these studies have demonstrated that the symptoms of schizophrenia typically aggregate into three relatively independent complexes: (1) hallucinations and delusions; (2) negative symptoms, including blunted affect, anhedonia, poverty of speech, curbing of interests, avolition, and diminished social drive; and (3) disorganized behavior, including positive formal thought disorder, inappropriate affect, and bizarre behavior (Buchanan and Carpenter 1994; Andreasen et al. 1995).

The repeated demonstration that the symptoms of schizophrenia aggregate into three independent complexes suggests that these complexes may be the manifestation of independent pathophysiological processes that are characterized by abnormalities in unique neural circuits. If this is true, the relative independence of schizophrenia symptom complexes has profound consequences for the investigation of the neuroanatomy of schizophrenia. The focus of the investigation of the neuroanatomy of schizophrenia should therefore shift from the disease entity level to the level of symptom complexes: The neuroanatomy of schizophrenia then becomes the neuroanatomies of hallucinations and delusions, of negative symptoms, and of disorganized behavior.
At the level of brain-behavioral relationships, the hypothesis that different symptom complexes involve different neural circuits is intuitively compelling. One would not expect the brain structures involved in the production of auditory hallucinations to be the same as those associated with avolition. Indeed, recent studies have implicated both the anterior cingulate basal ganglia-thalamocortical (Tamminga et al. 1992; Silbersweig et al. 1995) and language (Cleghorn et al. 1992; McGuire et al. 1993) circuits in the production of hallucinations and delusions and the dorsolateral prefrontal basal ganglia-thalamocortical circuit in the production of deficit symptoms (Liddle et al. 1992; Tamminga et al. 1992). These observations further support the proposition that the neuroanatomy of schizophrenia is better addressed at the level of symptom complexes.

**Design Issues**

Most postmortem and many imaging studies necessarily report on a relatively small number of cases. Statistical power must be maximized through the use of more methodologically rigorous study designs, rather than attempting to accommodate for experimental noise with larger cohorts. Three methodological issues—primary versus secondary psychopathology, state versus trait variables, and continuous versus categorical variables—are crucial in the use of symptom complexes in neuroanatomical investigations of schizophrenia. The failure to address these issues in study design so substantially undermines experiments that negative findings are rarely definitive.

**Primary Versus Secondary Psychopathology.** We have advocated using domains of psychopathology to reduce the heterogeneity of schizophrenia. However, a problem immediately arises when assessing symptoms: Is the symptom a direct manifestation of schizophrenia pathophysiology, or is it a secondary manifestation of some associated feature of schizophrenia? Study designs are usually adequate when dealing with hallucinations and delusions or disorganized behavior, since the differential diagnosis of schizophrenia requires distinguishing symptom manifestations of the disease from alternative causes of these phenomena. For example, an effort is typically made to determine whether a paranoid delusion or auditory hallucination is a primary manifestation of schizophrenia or is caused secondarily by comorbid substance abuse or some other medical condition affecting brain function.

Although only a minority of patients with schizophrenia have the trait of avolitional pathology captured by the deficit syndrome concept (Carpenter et al. 1988), almost all experience negative symptoms at some point during the course of their illness. However, the differentiation of primary and secondary negative symptoms is rarely addressed in study designs. Commonly used assessment approaches, such as the Scale for the Assessment of Negative Symptoms (Andreasen and Olsen 1982), do not distinguish primary from secondary sources of negative symptoms, and the behavioral items (e.g., impersistence at work or school) used to indicate negative symptoms may be influenced by a wide range of phenomena in patients with schizophrenia, including a drug-induced diminished drive, demoralization, inward withdrawal in the face of psychosis, and paranoid guardedness. If a neuroanatomically based hypothesis regarding avolitional pathology is to be tested, then it is essential that the experimental group exclude patients with schizophrenia who do not exhibit this pathology and that the ascertainment instrument differentiate primary from secondary negative symptoms. If one postulates that dorsolateral prefrontal cortical circuitry is involved in deficit psychopathology, then it is of little use to test this hypothesis in a patient group whose negative symptom ratings are substantially based on psychotic withdrawal, antipsychotic drug side effects, or depression. The importance of this issue has been underscored in a series of recent studies that have documented differential associations between deficit symptoms and negative symptoms broadly defined to include both primary and secondary negative symptoms. These findings include frontal and parietal cortical hypofrontality, a summer birth excess, less social content to delusions, the prevalence of comorbid substance abuse, and psychological insight into symptom manifestation (Tamminga et al. 1992; Kirkpatrick et al. 1996, and submitted for publication; Amador et al., in preparation).

**State Versus Trait Variables.** Any study that examines the relationship between structural measures of brain tissue (either postmortem or structural brain imaging) and a psychopathological aspect of schizophrenia must necessarily derive its hypothesis from a theory that distinguishes trait from state phenomena. Most antemortem and postmortem studies of brain morphology are necessarily related to clinical trait hypotheses, and therefore study design must differentiate trait from state characteristics and ascertain enduring trait features. However, a common mistake, which often makes its way into the literature, is to select a morphological measure based on a neurodevelopmental theory of schizophrenia and then to examine the relationship of the structural measure and the severity of a symptom rating obtained at the time of the morphological assessment. This use of a cross-sectional assessment of symptom severity confuses the state variable of severity with the trait variable of the vulnerability to develop the
symptom and ignores the historical course of the expression of the symptom. A structural trait-variable hypothesis should contrast patients with and without a history of the trait variable of interest. For example, if morphological abnormalities of the medial temporal lobe are hypothesized to be associated with the trait of vulnerability to develop auditory hallucinations, then patients with a history of auditory hallucinations should be contrasted with those without a history of auditory hallucinations. A functional trait-variable hypothesis, which relates trait functional brain characteristics to trait clinical phenomena, is best conducted with patients in remission to reduce state-dependent artifacts. In contrast, a functional state-variable hypothesis would select subjects with a history of auditory hallucinations who vary in the severity of their hallucinations at the time the functional measures are obtained. The potential power achieved with designs that properly address state versus trait issues is illustrated in recent studies using small sample sizes (Tamminen et al. 1992; Silbersweig et al. 1995).

The expression of the trait vulnerability of a symptom complex varies with the phase of illness. In addition to the marked variability among patients with schizophrenia in the type of illness course (Angst 1988; Carpenter and Kirkpatrick 1988; Harding 1988; McGlashan 1988), which may be used to reduce heterogeneity (Stevens 1997, this issue), followup studies suggest that the course of illness can be subdivided into three major phases (Carpenter and Kirkpatrick 1988; Breier et al. 1991). The first phase is often characterized by frequent positive symptom exacerbations. It is followed by a plateau phase, in which the severity of positive symptoms stabilizes and the number of symptom exacerbations decreases. In the late phase, symptoms, particularly those of the hallucination and delusion and disorganized behavior symptom complexes, may remit in a substantial proportion of patients (McGlashan 1988). The relationship between the presence of these symptoms and the phase of illness supports the importance of conducting longitudinal assessments of symptoms. For example, a patient may have had marked symptoms during the early phase of illness, but these symptoms may have remitted during the late phase. However, the absence of symptoms during the late phase does not mean that the patient no longer has the trait characteristic of the vulnerability for developing these symptoms. The failure to conduct a longitudinal assessment of the patient's symptom history could result in the erroneous exclusion of the patient from a subgroup defined by these symptoms. This issue is particularly relevant for postmortem studies in which subject samples are characterized by broad age ranges that would be expected to span multiple course of illness epochs.

Continuous Versus Categorical Variables. The other major methodological issue associated with the use of clinical variables for reducing heterogeneity is whether these measures should be used as continuous or categorical variables. The answer to this question depends in part on what hypothesis is being tested. As discussed above, continuous measures may be more appropriate for testing hypotheses concerning the relationship between symptom severity and state neuroanatomical correlates. However, there are several advantages to using a symptom complex as a categorical variable to define a hypothesized subgroup of schizophrenia. First, doing so allows the investigator to define a subgroup that is homogeneous for the construct of interest. This design enables the investigator to define a priori the experimental and comparison groups, thereby ensuring that the two groups differ on the independent variable, and to base the size of each group on power calculations. In addition, if the primary determining factor of an abnormality in a specific brain region is the presence and not the severity of the symptom complex, then the use of a symptom complex as a continuous variable would lead to Type II errors, since the patients with both low and high symptom severity will exhibit the same pathophysiology. Even if the neuroanatomical abnormality is related to the severity of the symptom complex, the use of symptom complexes as a categorical variable would be unlikely to preclude observing the relationship because the comparison group would be defined by the absence of the symptom complex. In addition, the relationship between severity and neuroanatomical abnormality could be still observed within the subgroup defined by the presence of the symptom complex. Second, the use of a symptom complex as a categorical variable enables the investigator to match more closely the experimental and comparison groups on other variables that might influence group comparisons. In contrast, the within-group examination of the relationship between a symptom complex and neuroanatomical variable does not take into account the impact of the presence of other symptom complexes or the interaction between the symptom complex of interest and other symptom complexes on the neuroanatomical variable. This problem is especially relevant for negative symptoms, particularly if the negative symptom measure fails to differentiate between primary and secondary negative symptoms.

The argument that statistical power is maximized when analyzing along a continuum needs to be considered carefully in the context of the present discussion. Heterogeneity implies that within a diagnostic cohort some, but not all, patients will share certain features. Categorical distinction allows the investigator to identify the group of interest and to use the group within the fea-
ture of interest as a key comparison group. If severity is relevant to the hypothesis, a continuous analysis within the subgroup having the categorically ascertained variable can be conducted. However, severity is often not a straightforward consideration in schizophrenia research. Take, for example, a 40-year-old patient with schizophrenia who experiences hallucinations. How is severity to be determined? By how much time is spent in hallucinatory experience at present? By the intensity of the hallucinatory experience? By special features of that experience (e.g., third-party hallucinations)? By the age at onset of hallucinations? By the length of time spent in remissions? Or by how many perceptual systems are involved in hallucinations? If the study hypothesizes a correlation between language circuit activation and auditory hallucinations, then the intensity of the hallucinations during imaging defines severity. If the hypothesis requires examination of pedigrees for pathological characteristics of probands with hallucinations, then the categorical presence and perhaps age of onset may be crucial. If a trait vulnerability hypothesis is being tested, then the frequency of exacerbation in hallucinations may be critical. There is no correct design solution for all experiments, but rather each study must carefully relate dependent and independent variables. In science this is a truism, but its practice relevant to the neuroanatomy of schizophrenia is the exception rather than the rule.

Summary

The delineation of the neuroanatomy of the symptom complexes of schizophrenia is a major goal of schizophrenia research. If progress is going to be made in this area, then advances in structural and functional imaging and post-mortem techniques need to be parallel by similar advances in study design and ascertainment methodology. Structural findings are usually conceptualized as trait variables and must necessarily seek trait clinical correlates. In contrast, functional measures may reflect either trait vulnerabilities or state-dependent functions, and investigators must link conceptually dependent and independent variables. In general, trait vulnerability correlates are best examined during periods of clinical remission to reduce state-dependent fluctuations. A state-dependent hypothesis must necessarily measure the degree of hallucinations at the time of testing to correlate with the dependent variable. In postmortem work, study questions almost always need to address trait variables since clinical state at the time of death is unlikely to be known. In all instances, the issue of heterogeneity requires resolution in order to ensure that experimental group subjects have the phenomenon of interest.

References


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