A Separate Disease Within the Syndrome of Schizophrenia

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If schizophrenia is a clinical syndrome rather than a single disease, the identification of specific diseases within the syndrome would facilitate the advance of knowledge and the development of more specific treatments. We propose that deficit psychopathology (ie, enduring, idiopathic negative symptoms) defines a group of patients with a disease different from schizophrenia without deficit features, as the deficit and nondeficit groups differ in their signs and symptoms, course, biological correlates, treatment response, and etiologic factors. These differences cannot be attributed to more severe positive psychotic symptoms or a greater duration of illness in the deficit group. The alternative interpretation that patients with deficit schizophrenia are at the severe end of a single disease continuum is not supported by risk factor and biological features data, but there is a need for independent replication of these findings. We suggest a series of studies designed to falsify one of these hypotheses, ie, multiple diseases vs a single disease.

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Individuals with schizophrenia vary substantially relative to their symptoms, response to treatment, disease impact on function, and biological correlates. There is a long-standing debate as to whether this heterogeneity reflects multiple diseases within a clinical syndrome or individual variation in the effects of a single disease.

In his 1919 description of schizophrenia, Kraepelin[1] noted that some patients with schizophrenia exhibit "a weakening of those emotional activities which permanently form the mainsprings of volition. . . . The result . . . is emotional dullness, failure of mental activities, loss of mastery over volition, of endeavor, and of ability for independent action. The essence of personality is thereby destroyed, the best and most precious part of its being . . . torn from her." This domain of psychopathology, more recently termed *negative symptoms*, was reported to have cross-sectional and longitudinal independence from the psychotic symptoms used to define schizophrenia, an observation that led to a theoretical model in which the syndrome of schizophrenia has 3 main symptom complexes: positive psychotic symptoms, negative symptoms, and interpersonal difficulties.[2,3] A number of subsequent statistical studies, most using factor analysis, have largely confirmed the existence of (at least) 3 domains of psychopathology, but psychotic symptoms have usually separated into factors corresponding to reality distortion (hallucinations and delusions) and the disorganization of thought and behavior,[4-7] whereas the third factor consists of negative symptoms.

On the basis of these findings, Carpenter and colleagues[8] proposed a putative schizophrenia subtype defined by negative symptoms. This 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 to the exclusion of developing relationships and participating

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Criteria for Deficit Schizophrenia

1. At least 2 of the following 6 features must be present and of clinically significant severity:
   - Restricted affect
   - Diminished emotional range
   - Poverty of speech
   - Curbing of interests
   - Diminished sense of purpose
   - Diminished social drive
2. Two or more of these features must have been present for the preceding 12 months, and always have been present during periods of clinical stability (including chronic psychotic states). These symptoms may or may not be detectable during transient episodes of acute psychotic disorganization or decompensation.
3. Two or more of these enduring features are also idiopathic, ie, not secondary to factors other than the disease process. Such factors include:
   - Anxiety
   - Drug effect
   - Suspiciousness
   - Formal thought disorder
   - Hallucinations or delusions
   - Mental retardation
   - Depression
4. The patient meets *DSM* criteria for schizophrenia.

normally in other activities. Patients with primary, enduring negative symptoms meet criteria[8,9] for deficit schizophrenia (**Table**). This group is smaller than the group of patients with clinically significant negative symptoms defined by such rating scales as the Scale for the Assessment of Negative Symptoms,[10] which rate both primary and secondary negative symptoms. In contrast to these rating scales, the intent of the deficit criteria is to classify patients with enduring or trait manifestations of the disease, whether present early in life or after the onset of psychosis.

The construct validity of a subgroup of schizophrenic persons with deficit features is supported by the cohesiveness of the symptoms used to define the group.[9] (A similar cluster of features is sometimes observed in neurologic conditions such as closed head injury, but this article is focused on these features within schizophrenia.) Interrater reliability for the categorization of patients with chronic schizophrenia into deficit and nondeficit groups is good,[9,11-13] although training is required.[14] Longitudinal studies have shown that the deficit/nondeficit categorization itself is highly stable,[11,12] and that the 2 groups have stable differences in symptoms such as depressive mood and anxiety.[15,16] Current estimates of the prevalence of the deficit group within schizophrenia are about 15% of first-episode patients, and 25% to 30% of more chronic schizophrenia populations.

Studies comparing the deficit schizophrenia subgroup with the nondeficit schizophrenia subgroup support the hypothesis that deficit schizophrenia is a separate disease. The differences between the deficit and nondeficit groups are not accounted for by a greater severity of psychosis in the deficit group, or by differences in sex, racial composition, or duration of illness. If the deficit disease hypothesis is valid, the implications are profound. For example, (1) the genetic heterogeneity of a clinical syndrome will be reduced if specific diseases are defined; (2) neuropathological studies will be more robust if the study cohort does not consist of patients with different diseases; and (3) neuroimaging studies could address disease hypotheses rather than syndrome hypotheses. We now summarize evidence that deficit schizophrenia is a separate disease, and consider the implications of this evidence for future research.

REVIEW OF DATA SUPPORTING THE SEPARATE DISEASE HYPOTHESIS

Using schizophrenia as an example, Robins and Guze[17] suggested that after a disorder has been described and diagnostic criteria have been established, family, follow-up, and laboratory studies are of particular importance in testing the validity of the diagnosis. A subsequent consideration of the boundaries between schizophrenia and affective disorder[18] organized the relevant studies into symptoms, outcome, family history, treatment response, and cross-national and historical diagnostic comparisons. To include new technologies such as neuroimaging, we have organized our review of the studies of deficit/nondeficit comparisons into 5 areas: signs and symptoms, course of illness, etiologic or risk factors, biological correlates, and treatment response.

Signs and Symptoms

Categorization of a patient into the deficit schizophrenia group is based on the presence of idiopathic (or primary), trait (or enduring) negative symptoms. Patients with schizophrenia who do not meet criteria for deficit schizophrenia are classified as *nondeficit*. The construct validity of this distinction is supported by studies showing that deficit schizophrenia, compared with nondeficit schizophrenia, is associated with (1) greater social and physical anhedonia,[19] (2) less depression on self-report and by clinicians' ratings,[16] (3) less suicidal ideation,[20] and (4) less severe delusions with an exclusively social content, such as delusions of jealousy.[21] As for clinical differences not directly related to construct validity, patients with deficit schizophrenia have less severe suspiciousness[21,22] and less substance abuse,[23] as well as less awareness of dyskinetic movements.[24] The relationship of substance abuse to scores on negative symptom rating scales, which combine primary and secondary as well as state and trait negative symptoms, was weaker than the relationship to the deficit/nondeficit categorization.[23] These deficit/nondeficit differences are observed despite similarity in the severity of all delusions (using measures that included persecutory delusions, delusions with an exclusively social content, plus all other delusions), hallucinations, formal thought disorder, or global measures of positive symptoms.[22,23]

Course of Illness

Patients with deficit schizophrenia have poorer function than patients with nondeficit schizophrenia before the appearance of positive psychotic symptoms.[20,22,23,25] In the Chestnut Lodge study, patients with deficit schizophrenia were less likely to marry before their first hospitalization than were patients with nondeficit schizophrenia, a difference that was not confounded by age of onset; more frequently had an insidi-

ous onset; and more frequently exhibited dyskinetic movements before drug treatment.[12,26] During early and middle adulthood, patients with deficit schizophrenia continue to exhibit poorer social and occupational function than do other patients with chronic schizophrenia,[20,22,23] and in light of the evidence above, this difference cannot be attributed to more severe psychotic symptoms or substance abuse in the deficit group. At long-term follow-up, patients with deficit schizophrenia continue to have poor function compared with patients with nondeficit schizophrenia.[12,20] Despite their poorer function, follow-up studies show the deficit group continues to have a decreased severity of depressive mood and other dysphoric affect[15,16] and less frequent suicidal thoughts.[20] They may also have a decreased risk for suicide.[20]

Treatment Response

Antipsychotic drugs are effective treatments for the positive symptoms of both deficit and nondeficit groups,[27,28] a finding that is consistent with the evidence that psychosis is a psychopathological domain separate from deficit features, and that antipsychotic drugs are superior to placebo in the treatment of psychosis regardless of etiology (eg, affective disorder, Huntington disease, or Alzheimer disease). Antipsychotic drugs are also effective for negative symptoms, when defined by such measures as the Brief Psychiatric Rating Scale anergia factor, the Schedule for the Assessment of Negative Symptoms, or the Positive and Negative Syndrome Scale to include primary and secondary negative symptoms.[29-31] In studies that have examined the efficacy of antipsychotics for such broadly defined negative symptoms, the therapeutic effect on negative symptoms has been observed in the context of concurrent improvement of positive, depressive, and/or extrapyramidal symptoms,[32-40] which are major sources of secondary negative symptoms. There have been relatively few studies that have attempted to examine whether the observed negative symptom improvement includes primary negative symptoms, or if it is restricted to secondary negative symptoms. In a clinical trial that used the Schedule for the Deficit Syndrome (SDS) to distinguish deficit and nondeficit groups, the positive symptoms of patients with deficit schizophrenia showed the same therapeutic response to clozapine as patients with nondeficit schizophrenia, but there was no improvement in the negative symptoms of patients with deficit schizophrenia.[27,28] In other studies of new-generation antipsychotics, there is little direct evidence that any of these agents have a clinically meaningful effect on primary negative symptoms, despite their efficacy for positive psychotic symptoms and broadly defined negative symptoms.[36-40]

In a psychosocial treatment study, patients with deficit and nondeficit schizophrenia received social skills training. Improvement in negative symptoms was found in the patients with nondeficit schizophrenia but not the patients with deficit schizophrenia.[41]

Risk and Etiologic Factors

Deficit and nondeficit groups have been shown to differ relative to 3 risk factors: family history, the presence of Borna disease virus antibodies, and season of birth. As is traditional in epidemiology, the segregation of populations on the basis of risk factors suggests the existence of different etiopathophysiological pathways to disease, even when the pathologic mechanism is not known. For example, family history and genetic risk have been used to validate other diagnostic groups in neuropsychiatry before researchers had knowledge of a specific gene, protein, or histological abnormality.

Compared with the relatives of probands with nondeficit schizophrenia, the relatives of patients with deficit schizophrenia appear to have an increased risk of schizophrenia.[42-44] In addition, the nonpsychotic relatives of probands with deficit schizophrenia also show significantly more severe social withdrawal than the relatives of probands with nondeficit schizophrenia. The greater social withdrawal could not be explained by more severe depression or other dysphoria, or by more severe subclinical psychotic-like experiences, as the severity of these potentially confounding features was significantly less in the families of subjects with deficit schizophrenia.[13] The deficit/nondeficit categorization also has a significant concordance within families: the presence of a sibling with deficit schizophrenia is associated with a 3-fold increase in risk that a sibling with schizophrenia will have the deficit rather than nondeficit subtype.[45]

There is a small increase in the prevalence of Borna disease virus antibodies in schizophrenia. Waltrip et al[46] reported a significantly greater prevalence of antibodies to Borna disease virus in deficit compared with nondefict schizophrenia. This preliminary finding received support from a subsequent finding that Borna disease virus antibodies were associated with the severity of negative but not positive symptoms in a group of patients with schizophrenia.[47] Whether the deficit group also has an increased prevalence of antibodies to other viruses has not been tested.

A winter birth excess repeatedly has been associated with schizophrenia,[48] although the physiological underpinnings of this relationship are not known. It is particularly interesting, therefore, that summer birth appears to be a risk factor for the deficit form of schizophrenia. A summer birth excess was observed in 2 hypothesis-generating studies and replicated in 2 population-based studies of incident cases of psychosis.[44,49] We have also replicated the association in a study of incident cases from the Cantabria First Episode Study (B.K., S. Herrera Castanedo, MD, J. Vazquez-Barquero, MD, unpublished data, April 2000), an incidence study from Dumfries and Galloway in Scotland (B.K., C. Tek, MD, J. Allardyce, MB, G. Morrison, MB, R. McCreadie, DSc, MD, unpublished data, March 2000), and 2 studies of prevalent cases: the Nithsdale Survey (B.K., R. McCreadie, DSc, MD, C. Kelly, MB, unpublished data, May 1999) and the Epidemiological Catchment Area study (E. De Messias, MD, B.K., unpublished data, September 1999) (all of these were population-based studies). There has been

a failure to replicate this association in a study group that was not a population-based sample and did not consist of incident cases,[50] as well as in a population-based study (the Roscommon Family Study) (B.K., D. Ross, MD, D. Walsh, MB, K. Kendler, MD, unpublished data, April 1999).

These findings of a risk factor specific to the deficit form of schizophrenia are consistent with a review of the season of birth literature that suggested schizophrenic subjects born in the winter have on average a more benign course of illness than those born in the rest of the year.[51] The summer-birth risk factor is theoretically interesting because of the apparent double dissociation vis-à-vis season of birth: compared with the general population, summer birth is associated with an increased risk for the deficit form of schizophrenia, whereas winter birth appears to increase risk for nondeficit schizophrenia.

Biological Correlates

Ribeyre and coworkers[52] reported patients with deficit schizophrenia had lower plasma homovanillic acid (pHVA) concentrations than did patients with nondeficit schizophrenia, but a subsequent study[53] found higher pHVA concentrations in a deficit group. An important methodological issue may account for the contradictory results. The deficit criteria (Table), which are operationalized with the SDS, constitute the only method with established reliability and validity for making the deficit/nondeficit categorization clinically. The clinical features of the deficit group of Nibuya et al[53] differ from those of Ribeyre et al[52] and most others who have used the SDS. A subsequent study[54] in which the SDS was also used replicated the finding of lower pHVA concentrations, as well as higher plasma 3-methoxy-4-hydroxyphenylglycol concentrations in the deficit compared with the nondeficit group.

Results from neurocognitive, functional imaging, and structural imaging studies suggest dysfunction of the dorsolateral prefrontal basal ganglia–thalamocortical circuit (DLPFC) as the neural basis for deficit symptoms. This contrasts with evidence that the anterior cingulate basal ganglia–thalamocortical circuit (AC) is associated with hallucinations and delusions.[55] In humans, the dorsolateral prefrontal and inferior parietal cortices, the head and body of the caudate, and specific thalamic nuclei are part of the DLPFC.[56]

Patients with deficit schizophrenia exhibit selective impairments on a number of neurocognitive measures that are thought to be subserved at least in part by the DLPFC. In a neuropsychological study,[57] the deficit group was significantly more impaired than the nondeficit group on measures sensitive to frontal and parietal lobe dysfunction; these same tests were also the only ones that failed to differentiate the nondeficit group from normal control subjects. There were no significant deficit/nondeficit differences on measures sensitive to temporal lobe dysfunction; on these measures, both groups were impaired compared with normal controls. The greater cognitive impairment in the deficit group probably contributes significantly to their poorer social function, which as noted above does not appear to be due to more severe positive symptoms, depression, or drug abuse. Patients with deficit schizophrenia also perform more poorly than patients with nondeficit schizophrenia or normal controls on the degraded stimulus version of the Continuous Performance Test (CPT), whereas patients with nondeficit schizophrenia and normal controls do not differ from each other.[58] On a structured neurologic examination, the deficit group was found to have an impairment in sensory integration compared with a matched nondeficit group.[25] The two groups did not differ on measures of the sequencing of complex motor acts, motor coordination, or miscellaneous signs. Sensory integration signs are thought to be related to frontal and parietal function. In an extension of this study (with additional subjects), the contributions to variance of disorganization, the deficit/nondeficit categorization, and hallucinations plus delusions were considered simultaneously. Again, the deficit group was impaired exclusively on sensory integration tasks.[59] In contrast, disorganization was associated with impairments of sensory integration and the sequencing of complex motor acts.

Some measures of oculomotor function in schizophrenic patients and their family members appear to have a bimodal distribution, and mixture analyses of oculomotor data strongly suggest the existence of 2 distinct subgroups in schizophrenia.[60-65] Oculomotor dysfunction is significantly associated with deficit schizophrenia.[66,67] As the oculomotor data suggest the existence of distinct groups, this association provides some evidence against the interpretation that the deficit group is on one end of a severity spectrum. Functional imaging studies also suggest that deficit features and eye tracking dysfunction are due to abnormal function in overlapping brain regions.[68-70] The deficit group may also have a generalized increase in visual reaction time.[71,72]

Positron emission tomography functional imaging studies have examined glucose and regional cerebral blood flow differences in patients with deficit and nondeficit schizophrenia, and provide data implicating DLPFC dysfunction in the production of deficit symptoms. In one study,[68] when compared with a nondeficit group and normal controls, the deficit group showed decreased glucose use in 3 components of the DLPFC: the thalamus and the dorsolateral prefrontal and inferior parietal cortices. Both patient groups had decreased glucose use in the anterior cingulate and hippocampus. In a study of activation during the performance of memory tasks, Heckers and colleagues[73] also found that patients with deficit schizophrenia were characterized by decreased blood flow in these 2 components of the DLPFC (the dorsolateral prefrontal and inferior parietal cortices) compared with the nondeficit group and normal controls. In that study, both patient groups had decreased hippocampal blood flow. Carpenter et al[69] have also reported decreased prefrontal and parietal cortical blood flow in the deficit group, whereas Liddle and coworkers[74,75] observed that patients characterized by persistent nega-

tive symptoms had decreased resting regional cerebral blood flow in the dorsolateral and inferior parietal cortices, and increased regional cerebral blood flow in the caudate nuclei.

There have been fewer structural imaging studies in which the deficit/nondeficit categorization was used. In one study, deficit and nondeficit groups differed significantly in prefrontal white matter volume, with the nondeficit group having smaller volumes whereas the deficit group was similar to normal controls.[76] This finding is incompatible with the interpretation that the deficit group is at the more impaired end of a single severity continuum. In contrast, Turetsky et al[77] found patients with deficit schizophrenia had smaller prefrontal total volumes, but they did not examine prefrontal gray and white matter volumes separately, and did not use the Schedule for the Deficit Syndrome to make the deficit/nondeficit diagnosis.

In a postmortem study,[78] patients with deficit schizophrenia have been found to have an increased density of interstitial cells of the white matter in the inferior parietal cortex (Brodmann area 39) compared with normal controls. The nondeficit group was not significantly different from the controls, but more cases are required to judge if this abnormality is restricted to the deficit group.

In summary, the anatomically related evidence suggests that deficit and nondeficit groups share AC behavioral and functional abnormalities (ie, positive psychotic symptoms and abnormal function in that neural substrate), but differ relative to DLPFC involvement. Within the DLPFC, the evidence of a specific association between anatomy and deficit features is probably stronger for the inferior parietal cortex than for the prefrontal cortex, as other studies that have not made the deficit/nondeficit categorization suggest the prefrontal cortex has abnormal structure and function in nearly all patients with schizophrenia.[79,80]

CONCLUSIONS

The implications of the negative symptom psychopathology have been difficult to grasp, since most investigations use rating scales that fail to distinguish primary from secondary negative symptoms. Criteria for the deficit group were explicitly developed to capture the avolitional psychopathology described by Kraepelin,[1] and can be applied reliably. In doing so, important differences emerge between deficit and nondeficit cases of schizophrenia. These studies have largely come from the Maryland group and their collaborators, but the body of work by Liddle and colleagues,[74,75] the recent report by Heckers and colleagues,[73] the Chestnut Lodge data,[12,20,26] the early dissection of symptom complexes and course data of Strauss, Carpenter, and Bartko,[2,3] and the many factor analysis studies of the symptoms of schizophrenia[4-7] all reinforce the view that enduring, idiopathic negative symptoms provide considerable leverage in the reduction of the heterogeneity of schizophrenia. The following section outlines a plan for further testing of the separate disease hypothesis.

TESTING THE HYPOTHESIS OF A SEPARATE DISEASE

We previously proposed that the deficit/nondeficit categorization provided a method and a concept that would advance strong inference research.[55,81] Meaningful and robust differences are observed between deficit and nondeficit cohorts, but some of the data are consistent with both the separate disease hypothesis and the competing hypothesis of a disease severity continuum. However, the hypothesis that deficit schizophrenia represents the severe end of a single schizophrenia continuum is not compatible with the following findings:

- Patients with deficit schizophrenia were reported to have a volume of the frontal lobe white matter that did not differ from that of normal controls, whereas patients with nondeficit schizophrenia had a frontal white matter volume that was significantly smaller than that of the deficit group and controls.[76]
- Although schizophrenia as a whole is associated with winter birth, the deficit group is associated with a robust summer birth excess.[44,49]
- Mixture analyses of eye-tracking variables suggest the existence of 2 discrete populations within schizophrenia, and deficit schizophrenia is associated with eye-tracking dysfunction.[60-67]
- Within schizophrenia, disorganization is significantly associated with an impairment in the sequencing of complex motor acts, whereas deficit schizophrenia is not.[59]
- The relatives of probands with deficit schizophrenia who do not have a psychotic disorder have significantly less severe dysphoria and psychoticlike symptoms compared with the nonpsychotic relatives of probands with nondeficit schizophrenia.[13]
- The deficit group has a decrease in the severity of some measures of positive psychotic symptoms, and has less drug abuse, less risk of suicidal phenomena, and less severe depressive mood, anxiety, guilt, and hostility.[15,16,20,21]

This pattern of findings validates the importance of primary negative symptoms in schizophrenia and provides direct support for the separate disease hypothesis. However, the data must be regarded as preliminary, since most studies have been conducted by the Maryland group. We have discussed the anatomical findings in the context of strong inference in the hope that other groups would also test the deficit hypothesis.[55] About 11 groups have now been trained by one of us (B.K.) in the use of the SDS, and we look forward to new data from other research centers. The recent report by Heckers and colleagues,[73] to name one example, is most welcome in this regard. We would also point out that the data used in risk factor analyses were generated by other investigators.

The central issue in this area of research is now the design of studies with the potential to distinguish between the (categorical) separate disease hypothesis and the (dimensional) unitary disease hypothesis. Approaches that can help lead to refutation of one of these hypotheses in-

clude: (1) replication or refutation of the findings cited above as incompatible with the single disease hypothesis; (2) demonstration of a double dissociation, in which the deficit group would be normal on measure A but abnormal on measure B, whereas the nondeficit group would be abnormal on measure A but normal on measure B (there appears to be a double dissociation in season of birth); and (3) the application of statistical methods designed to test for the existence of separate groups within schizophrenia (eg, taxometrics[82,83] and mixture analyses). Most compelling would be direct evidence of a distinctive etiology. If schizophrenia is a syndrome, then all studies of etiology and pathophysiology will be strengthened by the identification of unique disease entities. The initial work with risk factors and postmortem tissue, as well as the robust effect on imaging data, is encouraging.

In future research in this area, it would be useful to keep 2 methodological points in mind. First, studies of negative symptoms broadly defined are not adequate tests of deficit/nondeficit differences. Not only are negative symptoms and deficit features different conceptually, but their correlates have been shown to differ.[12,15,23,44,49] Second, although the deficit/nondeficit categorization can be made with good interrater reliability, an examination of the clinical features of the deficit and nondeficit groups in published reports suggests some contradictions in the literature may be due to problems in intergroup reliability.[52-54,68,76,77,84] It would be useful to minimize this problem in future studies. Compared with a nondeficit group, an ideal deficit group would have, in addition to primary negative symptoms, (1) positive symptoms (hallucinations, delusions, and formal thought disorder) that are not more severe than those of the nondeficit group; (2) less severe dysphoric symptoms (eg, depressive mood, anxiety, guilt, and hostility); (3) a similar duration of psychotic illness[9,15,16,21-23]; and (4) a prevalence comparable to that in published studies.

In the history of medicine, the categorical approach has proved to be very powerful. Whether or not the deficit group suffers from a separate disease, it is clear that separating deficit and nondeficit groups greatly reduces the heterogeneity of schizophrenia.

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