Subtyping Schizophrenia According to Outcome or Severity: A Search for Homogeneous Subgroups

by Marc-André Roy, Chantal Mérette, and Michel Maziaude

Abstract

There is a growing consensus that current definitions of schizophrenia (SZ) include different disorders, or else different dimensions underlain by different pathophysologies. This article reviews the evidence for the validity of three novel strategies to subtype SZ according to outcome or severity (deficit vs. nondeficit, Kraepelinian vs. non-Kraepelinian, congenital vs. adult-onset). Medline and bibliographies were used to locate articles. The methodology of the studies was reviewed, and their results were grouped according to seven validating criteria. Several differences were found between subtypes, particularly for the deficit/nondeficit subtypes. However, for most of these differences, replications have yet to be undertaken. Important indicators of etiology from the environmental risk factors and genetic domains have received very little attention. These three subtyping strategies represent promising attempts to address the etiologic heterogeneity of SZ. However, one cannot conclude that these strategies identify etiologically distinct SZ subgroups. We propose ten methodological and conceptual recommendations for future studies aimed at the identification of valid SZ subtypes according to outcome or severity.

Keywords: Schizophrenia, genetics, etiology, subtypes, deficit syndrome, congenital schizophrenia, Kraepelinian, nosology.


SZ probably includes different diseases or reflects several dimensions of psychopathology, each underlain by its own pathophysiology (Tsuang et al. 1990; Andreasen and Carpenter 1993). This etiologic heterogeneity is one of the most likely explanations for the slow progress in the identification of susceptibility genes and consistent biological markers for SZ. In contrast, the identification of liability genes and pathophysiology has progressed more rapidly for other complex disorders such as breast cancer and Alzheimer dementias because epidemiological studies have identified valid subtypes. Therefore, etiologically homogeneous subtypes and/or valid dimensional phenotypes would facilitate the identification of the causes of SZ (Cloninger 1994; Tsuang 1994).

Distinguishing SZ subjects according to outcome or severity may be one strategy for identifying such subtypes, as suggested by the following findings: (1) there is substantial variability in outcome and severity among SZ subjects (Carpenter and Kirkpatrick 1988), which is a prerequisite to using any variable to define subgroups; (2) many predictors of poor social functioning, such as poor premorbid adjustment and severe negative symptoms, correlate with each other (Roy and DeVriendt 1994), suggesting that these aspects may characterize a specific subgroup of very poor outcome (VPO) subjects; and (3) a few studies found that a family history positive for SZ predicted poor outcome and that a family history positive for affective disorders predicted good outcome in SZ probands (McGlashan 1986). This last finding suggests the implication of different familial/genetic factors in VPO vs. non-VPO SZ, although conflicting results and methodological limitations preclude considering these results definitive.

In agreement with the above considerations, three recent strategies to subtype SZ according to outcome or severity (deficit, Kraepelinian, and congenital) have been proposed.

First, deficit SZ (Carpenter et al. 1988; Kirkpatrick et al. 1989) is defined by the presence of at least two of six negative symptoms for at least 12 months. These symptoms should not be secondary to anxiety, depression, psychosis, drug side effects, mental retardation, or other causes (see Carpenter et al. 1985 for a detailed discussion of the potential causes of secondary negative symptoms). SZ patients who do not meet these criteria are considered nondeficit.
Second, Kraepelinian SZ (Keefe et al. 1987) is defined by (1) either continuous hospitalization, or if living outside the hospital, complete dependence on others for basic needs; (2) the lack of useful employment; and (3) the absence of a complete remission of symptoms. Patients who do not meet these criteria are considered non-Kraepelinian.

Third, congenital SZ (Murray et al. 1991) is defined by an insidious onset, occurring before age 25, preceded by poor premorbid adjustment. After onset, the course is chronic, with at least some symptoms persisting between episodes, and affective symptoms are typically absent. Optional features include a poor response to neuroleptics, the presence of cognitive impairment, and a history of obstetric complications. Conversely, adult-onset SZ is defined by an onset occurring abruptly, at any age throughout life, without significant premorbid impairment. The course is then characterized by acute psychotic episodes with very few symptoms, if any, between episodes. Optional features include a good response to neuroleptics, an absence of cognitive impairment, and no history of obstetric complications. Congenital SZ is posited to result from aberrant brain development during fetal and neonatal life, because of genetic factors or early environmental brain insults, and adult-onset SZ is posited to be genetically related to affective disorders.

These three subtyping strategies share the assumption that subgroups of SZ differing on various aspects of outcome or severity may also differ on crucial etiologic aspects. However, these three strategies do not use the same aspects of outcome or severity to define subtypes. First, deficit SZ emphasizes diminished motivation and affectivity and is the only one of these three strategies that explicitly focuses on a single domain of psychopathology to define subgroups of patients. Second, Kraepelinian SZ emphasizes severe and persisting symptoms and self-care deficits. Third, congenital SZ is defined by its course and natural history (i.e., age and type of onset, premorbid adjustment, and course).

Demonstrating the validity of any VPO SZ subtypes would dramatically change the design of genetic and biological studies of SZ, because such studies would then focus on more homogeneous subgroups within SZ. The goal of the present paper is to review the studies testing the validity of these three subtyping strategies.

Methods

Fifty-one articles comparing SZ subgroups defined according to any of these three subtyping strategies were identified through Medline searches, bibliographies of published articles, and contacts with some of the developers of these subtypes. These reports were grouped according to seven validators of psychiatric syndromes on which SZ subgroups can be compared (Robins and Guze 1970; see table 4). Within each of these seven validators, we assessed the consistency of findings across reports.

While assessing the seven validators, the following methodological issues were taken into account, as they were in a previous paper on familial versus sporadic SZ (Roy and Crowe 1994): (1) sample size, which affects statistical power; (2) verification of the reliability of the variables used; (3) blindness of the assessment of the dependent variables to subtype assignment; (4) use of an appropriate control group, when needed to determine which subgroup differed from normality; (5) control for pertinent confounding factors; (6) sampling strategy (e.g., observation during acute relapse vs. stabilized stage); and (7) other methodological factors specific to each type of study (e.g., methods used to diagnose relatives in a family study).

Results

This section reviews the evidence for the validity of these three subtyping strategies according to our seven validators. Table 1 summarizes studies on deficit SZ; table 2, studies on Kraepelinian SZ; and table 3, studies on congenital SZ. Table 4 summarizes the main results for these three strategies.

Reliability of the Subtyping Strategies. The Maryland Psychiatric Research Center (MPRC) group (Kirkpatrick et al. 1989) and other investigators (Harris et al. 1991; Fenton and McGlashan 1992; Ribeyre et al. 1994a; Fenton et al. 1997) achieved very good interrater reliability in distinguishing between deficit and nondeficit SZ with the Schedule for the Deficit Syndrome (SDS; Kirkpatrick et al. 1989) or based on a detailed review of extensive clinical information. In addition, the MPRC group has documented very good reliability with another research group (Amador et al. 1999). On the other hand, although the DSM–IV Field Trial did not assess the reliability of the deficit versus nondeficit subtypes, it has yielded poor reliability of a critical step in the identification of these subtypes: the distinction between primary and secondary negative symptoms (Flaum and Andreasen 1995). Three characteristics of the Field Trial may explain this poorer reliability (Flaum et al. 1997): (1) information from relatives, clinicians, and medical records is often critical for the primary/secondary distinction, but the collection of such additional information was not emphasized in the Field Trial; (2) the Field Trial raters did not receive detailed...
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<th>Authors</th>
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<td>Dollfus et al. (1999)</td>
<td>DSM-IV patients</td>
<td>SDS</td>
<td>Environmental risk factors: season of birth</td>
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<td>No difference in month of birth</td>
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<td>Kirkpatrick et al. (1999)</td>
<td>SDS</td>
<td>Postmortem: Density of interstitial cells of the white matter in the inferior parietal cortex</td>
<td>3 deficit</td>
<td>Higher cell density in deficit than in nondeficit and in normal controls</td>
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<td>Buchanan et al. (1998)</td>
<td>DSM-III-R SZ or schizoaffective treatment-resistant MPRC outpatients</td>
<td>SDS</td>
<td>Response to treatment: changes in positive, negative, and extrapyramidal symptoms, and social functioning, during a randomized comparison of clozapine and haloperidol</td>
<td>21 deficit</td>
<td>Better response of positive symptoms and better improvement in social functioning with clozapine vs. haloperidol in both deficit and nondeficit SZ; no differences between deficit and nondeficit SZ</td>
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<td>Turestky et al. (1998)</td>
<td>Baseline, followup research interviews</td>
<td>Auditory evoked potentials: P300 in frontal, parietal, and temporal areas</td>
<td>21 deficit</td>
<td>Longer right parietal latency in deficit and nondeficit SZ vs. controls; longer left temporal and frontal latencies in nondeficit SZ vs. controls; no comparison of deficit and nondeficit SZ</td>
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<td>Buchanan et al. (1997)</td>
<td>DSM-III-R SZ MPRC outpatients</td>
<td>SDS</td>
<td>Neuropsychology: attention (continuous performance and span of apprehension tests)</td>
<td>20 deficit</td>
<td>Poorer performance in deficit vs. nondeficit SZ and controls on both tasks; poorer performance in nondeficit SZ vs. controls on the Span of Apprehension task Lesser education in deficit SZ</td>
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<tr>
<td></td>
<td>Same as above</td>
<td>SDS</td>
<td>Neuropsychology: visual information processing</td>
<td>17 deficit</td>
<td>Slower reaction time in deficit vs. nondeficit SZ and controls, and in nondeficit SZ vs. controls; abnormal asymmetry in nondeficit vs. deficit SZ and controls More severe negative, less severe positive symptoms in deficit SZ</td>
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<td></td>
<td>Kopelowicz et al. (1997)</td>
<td>SDS</td>
<td>Response to treatment: changes in social skills and negative symptoms after social skills training</td>
<td>3 deficit</td>
<td>More improvement in social skills and negative symptoms in nondeficit SZ</td>
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<td>Authors</td>
<td>Population studied</td>
<td>Information used to subtype</td>
<td>Dependent variables</td>
<td>Sample size</td>
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<td>Spalleta et al.</td>
<td><em>DSM-III-R</em> SZ acutely psychotic inpatients</td>
<td>SDS</td>
<td>Clinical: positive, disorganized, negative, depressive symptoms</td>
<td>18 deficit</td>
<td>More severe negative symptoms in deficit SZ</td>
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<td></td>
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<td></td>
<td>Extrapyramidal symptoms</td>
<td>40 nondeficit</td>
<td>Lesser education in deficit SZ</td>
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<td>Waltrip et al.</td>
<td><em>DSM-III-R</em> SZ MPRC outpatients</td>
<td>SDS</td>
<td>Environmental risk factors: presence of anti-Borna disease antibodies</td>
<td>15 deficit</td>
<td>More frequent anti-Borna disease antibodies in deficit and nondeficit SZ vs. controls, and in deficit vs. nondeficit SZ</td>
</tr>
<tr>
<td>Dollfus et al.</td>
<td><em>DSM-III-R</em>, Carpenter, Schneider, or Langfeldt SZ</td>
<td>SDS</td>
<td>Genetic: SZ or other disorders in relatives</td>
<td>22 deficit</td>
<td>More frequent family history positive for any psychiatric disorder in nondeficit SZ</td>
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<td>Kirkpatrick et al.</td>
<td><em>DSM-IV</em> field trial: PDS</td>
<td>MPRC: SDS</td>
<td>Clinical: positive and disorganized symptoms, suspiciousness, and depressive episodes</td>
<td>Field trial: 51 deficit, 101 nondeficit</td>
<td>More severe suspiciousness and trend for more frequent depressive episodes in nondeficit SZ</td>
</tr>
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<td>Kirkpatrick et al.</td>
<td><em>DSM-III-R</em> first episode SZ, schizoaffective, or schizophreniform cases</td>
<td>PDS</td>
<td>Natural history: social functioning at admission and followup, longitudinal stability of PDS</td>
<td>32 deficit</td>
<td>Less severe alcohol and drug use in nondeficit SZ and Poorer current and premorbid adjustment in deficit SZ</td>
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<td>Loas et al.</td>
<td><em>DSM-III-R</em> SZ inpatients and outpatients</td>
<td>PDS</td>
<td>Clinical: self-rated physical anhedonia and depressive symptoms</td>
<td>29 deficit</td>
<td>More frequent summer birth in deficit SZ</td>
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<td>Ross et al.</td>
<td><em>DSM-III-R</em> SZ MPRC outpatients</td>
<td>SDS</td>
<td>Eye tracking: position root mean square error during the pursuit of a sinusoidal target; latency to pursuit onset, open-loop acceleration. velocity</td>
<td>12 deficit</td>
<td>More frequent abnormal tracking in deficit vs. nondeficit SZ, in deficit SZ vs. controls, and in nondeficit SZ vs. controls; lessor</td>
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<tr>
<td>Reference</td>
<td>Study Design</td>
<td>Measures</td>
<td>Findings</td>
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<td>Bustillo et al. (1995)</td>
<td>DSM-III-R SZ MPRC outpatients</td>
<td>SDS</td>
<td>Presence of tardive dyskinesia</td>
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<tr>
<td>Nibuya et al. (1995)</td>
<td>DSM-III-R SZ long-term inpatients</td>
<td>SDS</td>
<td>Extrapyramidal symptoms in deficit vs. nondeficit SZ and controls; lesser open-loop velocity in deficit SZ vs. controls</td>
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<tr>
<td>Buchanan et al. (1994)</td>
<td>DSM-III-R SZ MPRC outpatients</td>
<td>SDS</td>
<td>Extrapyramidal symptoms in deficit vs. nondeficit SZ and controls; lesser open-loop velocity in deficit SZ vs. controls</td>
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<tr>
<td>Fenton and al. McGlashan (1994); Fenton et al. (1994, 1997)</td>
<td>SZ subjects from Chestnut Lodge</td>
<td>Medical records and research interview (mean followup = 19 years)</td>
<td>Natural history: premorbid, current functioning; age, type of onset; response to life events</td>
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<tr>
<td>Gur et al. (1994); Mozley et al. (1994); Turetsky et al. (1995)</td>
<td>DSM-III-R SZ cases from University of Pennsylvania</td>
<td>Baseline and follow-up research interview</td>
<td>MRI: brain, cranial, temporal, and frontal volumes; CSF volume: ventricular, sulcal, temporal, and frontal areas</td>
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<td>Authors</td>
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</table>
| Kirkpatrick et al. (1994)    | DSM-III-R SZ MPRC outpatients       | SDS                    | Natural history: age of onset  
Clinical: positive, disorganized, negative symptoms  
Gender ratio  
Clinical: clinician and self-rated depressive symptoms | 24 deficit  
76 nondeficit | More severe clinician and self-rated depressive symptoms in nondeficit SZ  
Greater proportion of males in deficit SZ |
| Mayerhoff et al. (1994)      | First episode RDC SZ cases      | Research interview       | Natural history: premorbid, current functioning; age at onset  
Clinical: positive, negative, and disorganized symptoms | 11 deficit  
36 nondeficit | Earlier onset, poorer premorbid and current functioning in deficit SZ  
More severe formal thought disorder in deficit SZ |
| Ribeyre et al. (1994b); Thibaut et al. (1998) | DSM-III-R SZ inpatients and outpatients | SDS                  | Biochemical pHVA and MHPG  
Clinical: positive, negative symptoms  
Natural history: age of onset | 14 deficit  
20 nondeficit | Lower pHVA and higher MHPG levels in deficit SZ  
More severe negative symptoms in deficit SZ |
| Buchanan et al. (1993)       | DSM-III-R SZ MPRC outpatients   | SDS                    | MRI: prefrontal, caudate, amygdala/hippocampus, and cranial volumes  
Natural history: age of onset, education | 17 deficit  
24 nondeficit  
30 controls | Smaller prefrontal volume in nondeficit vs. deficit SZ and controls; larger left caudate and smaller amygdala-hippocampus in deficit and nondeficit SZ vs. controls  
Lesser education in deficit SZ |
| Tamminga et al. (1992)       | DSM-III SZ MPRC drug-free inpatients | SDS                 | PET scan: glucose use in temporal, occipital, parietal, frontal lobes; cingulum; hippocampus; caudate; pallidum; substantia nigra; thalamus | 4 deficit  
7 nondeficit  
11 controls | Trends for lower thalamic, frontal, and parietal metabolism in deficit SZ vs. nondeficit SZ and normal controls |
| Harris et al. (1991)         | DSM-III-R SZ stable outpatients age ≥ 46 | SDS                  | Clinical: positive, negative, depressive symptoms  
Neuropsychology: IQ; Halstead-Reitan global scores  
Natural history: age of onset, education | 17 deficit  
20 nondeficit | More severe negative symptoms in deficit SZ  
More severe impairment on the Halstead Impairment Index and lower IQ in deficit SZ |
| Buchanan et al. (1990)       | DSM-III-R SZ MPRC outpatients   | SDS                    | Natural history: premorbid adjustment, age of onset | 17 deficit  
17 nondeficit | Poorer premorbid adjustment in deficit SZ |
Neurological soft signs: sequence, motor, and sensory signs and sensory integration

Clinical: physical and social anhedonia, magical ideation, perceptual aberration, impulsive nonconformity

Eye tracking: qualitative rating; volitional and reflex saccadic latencies; distractibility score; saccade size

Tardive dyskinesia

Natural history: stability of negative symptoms, age of onset, education, current functioning

Neuropsychology: motor speed, visuomotor, tactile-motor, constructional skills; spatial memory; executive functioning; IQ

Clinical: positive, negative, depressive symptoms

Natural history: current functioning, age of onset, education

More sensory signs, more impaired audiovisual integration, graphesthesia, face-hand test, and left-right confusion in deficit SZ

More severe physical and social anhedonia in deficit SZ

Greater stability of negative symptoms in deficit SZ

More severe negative symptoms in deficit SZ

Greater proportion of males in deficit SZ

Poorer psychomotor performance in deficit and nondeficit SZ vs. controls; poorer general performance in deficit SZ vs. controls

More severe negative symptoms in deficit SZ

Note.—BPRS = Brief Psychiatric Rating Scale; CSF = cerebrospinal fluid; CT = computed tomography; MHPG = 3-methoxy-4-hydroxyphenylglycol; MPRC = Maryland Psychiatric Research Center; MRI = magnetic resonance imaging; PDS = Proxy Deficit Syndrome; PET = positron emission tomography; pHVA = plasma homovanillic acid; RDC = Research Diagnostic Criteria; SDS = Schedule for the Deficit Syndrome; SZ = schizophrenia. For studies published in more than one report, the order is determined by the year of the first report.
### Table 2. Studies comparing Kraepelinian and non-Kraepelinian schizophrenia

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<tr>
<th>Authors</th>
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<tr>
<td>Davis et al.</td>
<td>Male DSM-III-R SZ inpatients or outpatients</td>
<td>Research interviews, medical records, and information from relatives</td>
<td>CT: changes in VBR over a 5-year period</td>
<td>22 Kraepeiinian 31 non-Kraepelinian 13 controls</td>
<td>Greater increase in VBR in Kraepeiinian vs. non-Kraepelinian SZ and controls (no significant differences between groups at baseline)</td>
</tr>
<tr>
<td>Keefe et al.</td>
<td>Male DSM-III-R SZ or schizoaffective inpatients or outpatients</td>
<td>CASH, medical records, and information from relatives</td>
<td>Clinical: positive, negative symptoms; thought disorder; bizarre behavior; frequency of schizoaffective diagnosis Natural history: premorbid functioning, age of onset</td>
<td>61 Kraepeiinian 80 non-Kraepelinian</td>
<td>More severe negative symptoms and thought disorder in Kraepeiinian SZ; more frequent schizoaffective diagnosis in non-Kraepelinian SZ</td>
</tr>
<tr>
<td>Harvey et al.</td>
<td>RDC SZ or schizoaffective (mainly SZ subtype) or Feighner SZ inpatients</td>
<td>Research interviews, medical records, and information from relatives</td>
<td>Response to treatment: response to a 6-week discontinuation of neuroleptic treatment, followed by a 4-week trial of flexible dose of haloperidol</td>
<td>8 Kraepeiinian 16 non-Kraepelinian</td>
<td>More severe increase in severity of symptoms during drug washout, and more important decrease after reintroduction of haloperidol in non-Kraepelinian SZ</td>
</tr>
<tr>
<td>Keefe et al.</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Response to neuroleptic treatment: 6-week flexible-dose trial of haloperidol</td>
<td>21 Kraepeiinian 54 acutely psychotic non-Kraepelinian</td>
<td>Better response to treatment in non-Kraepelinian SZ</td>
</tr>
<tr>
<td>Keefe et al.</td>
<td>Same as above</td>
<td>Same as above</td>
<td>Clinical: positive, negative symptoms; thought disorder; presence of an affective syndrome Natural history: premorbid and current functioning, age of onset Genetic: frequency of SZ spectrum disorders in first and second degree relatives (FHRDC)</td>
<td>26 Kraepeiinian 101 non-Kraepelinian (15 remitted, 86 acutely psychotic)</td>
<td>More severe thought disorder and negative symptoms, and less frequent affective syndrome in Kraepeiinian SZ Poorer current functioning in Kraepeiinian SZ Higher frequency of a positive family history for SZ spectrum disorder, and higher morbid risk for SZ in relatives of Kraepeiinian SZ</td>
</tr>
</tbody>
</table>
Keefe et al. (1987, 1991)  
Same as above  
Same as above  
CT scan: VBR and asymmetry of lateral ventricles  
15 Kraepelinian  
15 non-Kraepelinian  
Higher left-right ventricle ratio in Kraepelinian SZ  

Note.—CASH = Comprehensive Assessment of Symptoms and History; CT = computed tomography; FHRDC = Family History Research Diagnostic Criteria; RDC = Research Diagnostic Criteria; SZ = schizophrenia; VBR = ventricle-to-brain ratio.

Table 3. Studies comparing congenital and adult-onset schizophrenia

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<th>Authors</th>
<th>Population studied</th>
<th>Information used to subtype</th>
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<td>Corrigall and Maudsley (1994)</td>
<td>Maudsley twin sample</td>
<td>Case summaries</td>
<td>Genetic: frequency of congenital and adult-onset psychoses and of nonpsychotic depression in co-twin</td>
<td>18 congenital psychotic, 34 adult-onset psychotic, 4 nonpsychotic depression</td>
<td>Trends for more frequent adult-onset psychosis and nonpsychotic depression in co-twin of adult-onset psychotic probands, and for more frequent congenital psychoses in co-twin of congenital psychotic proband</td>
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### Table 4. Summary of results

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<td>Hallucinations and delusions</td>
<td>Good to very good (RF)</td>
<td>Good to very good (RF)</td>
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<td>Disorganized symptoms</td>
<td>Equal or lesser severity in nondeficit (RF)</td>
<td>No differences during stabilized stage (RF)</td>
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<td>Negative symptoms</td>
<td>More severe in deficit SZ (IF)</td>
<td>More severe in Kraepelinian (RF)</td>
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<td>Depressive symptoms</td>
<td>More severe in deficit SZ (RF)</td>
<td>More severe in Kraepelinian (RF)</td>
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<td><strong>Natural history</strong></td>
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<td>Premorbid adjustment</td>
<td>Poorer in deficit SZ (RF)</td>
<td>No differences (RF)</td>
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<td>Age of onset</td>
<td>No differences (RF)</td>
<td>No differences (RF)</td>
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<td>Type of onset</td>
<td>More insidious in deficit SZ (UF)</td>
<td>Not tested</td>
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<td>Social functioning</td>
<td>Poorer in deficit SZ (RF)</td>
<td>Poorer in Kraepelinian (RF)</td>
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<td>Temporal stability</td>
<td>High degree (RF)</td>
<td>High degree (UF)</td>
</tr>
<tr>
<td><strong>Gender ratio</strong></td>
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<td>Possible association between male gender and deficit SZ (RF)</td>
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<td><strong>Response to treatment</strong></td>
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<td>Social skills training</td>
<td>Poorer response in deficit SZ (UF)</td>
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<td>Neuroleptics</td>
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<td><strong>Biological markers</strong></td>
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<td>Structural imaging</td>
<td>Increased temporal spinal fluid volume in deficit SZ (UF)</td>
<td>Abnormal lateral ventricles asymmetry and higher degree of progressive ventricular enlargement in Kraepelinian SZ (UF)</td>
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<td>Functional imaging</td>
<td>Greater degree of ventricular enlargement in deficit SZ (UF)</td>
<td>Not tested</td>
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<tr>
<td>Postmortem brain study</td>
<td>Smaller brain frontal volume in nondeficit SZ (UF)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Neuropsychology</td>
<td>Decreased thalamic, frontal, and parietal metabolism in deficit SZ (UF)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Eye tracking</td>
<td>Higher density of interstitial cells of the white matter of the inferior parietal lobe in deficit SZ (UF)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Auditory evoked potentials</td>
<td>Poorer performance in deficit SZ in several domains (UF)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Biochemical markers</td>
<td>Abnormal asymmetry of visual processing in nondeficit (UF)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Neurological soft signs</td>
<td>Poorer tracking in deficit SZ (UF)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Spontaneous dyskinesias</td>
<td>No differences (OF)</td>
<td>Not tested</td>
</tr>
<tr>
<td>Tardive dyskinesias</td>
<td>Lower level of 3 MHPG in deficit SZ (UF)</td>
<td>Not tested</td>
</tr>
<tr>
<td><strong>Twin and family studies</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Environmental risk factors</td>
<td>More frequent Borna virus antibodies in deficit SZ (UF)</td>
<td>Higher risk for SZ in Kraepelinian</td>
</tr>
<tr>
<td></td>
<td>More frequent summer birth in deficit SZ (RF)</td>
<td>Not tested</td>
</tr>
</tbody>
</table>

**Note:** IF = inconsistent finding (a minority of studies reporting this finding, with a predominance of negative results); MHPG = 3-methoxy-4-hydroxyphenylethanol; OF = opposite finding (a single study with at least one other study reporting opposite results); pHVA = plasma homovanillic acid; RF = replicated finding (at least two studies that present concordant results; if there are some inconsistent results, they can be easily accounted for by methodological factors); SZ = schizophrenia; UF = unreplicated finding (a single study without any attempt at replicating results or with a single negative study). We did not include a separate column on congenital and adult-onset SZ because its validity was tested in a single study. This study revealed that co-twins of probands with congenital psychoses had a higher risk for congenital psychoses, and that co-twins of probands with adult-onset psychoses had a higher risk for adult-onset psychoses and nonpsychotic depression. In addition, that study revealed very good interrater reliability of these subtypes. These results have not been replicated.
training on the primary/secondary distinction of negative symptoms; and (3) 93.4 percent of the patients were undergoing a psychotic relapse at the time of the assessment, and the primary/secondary distinction is easier to perform during a stabilized stage between psychotic episodes (Spalletta et al. 1997). To overcome these difficulties, which are often encountered in large-scale studies, the Proxy Deficit Syndrome (PDS) was developed (Kirkpatrick et al. 1993). The PDS classifies SZ subjects into deficit or nondeficit subgroups based on a specific profile on the Brief Psychiatric Rating Scale (BPRS): that is, low scores on anxiety, guilt feelings, depressive mood, and hostility, and high scores on affective blunting, which were found to predict a deficit syndrome on the SDS.

The developers of the Kraepelinian versus non-Kraepelinian dichotomy have documented very good interrater reliability for this distinction (kappa = 0.96) (Keefe et al. 1996), which was confirmed by the DSM–IV Field Trial (Amador, personal communication cited in Keefe et al. 1996).

The developers of the congenital versus adult-onset SZ achieved very good interrater reliability (Corrigall and Murray 1994) (kappa = 0.80), but this reliability was not tested by other groups.

Clinical Differences Outside the Subtype Definition. Finding that subtypes differ according to symptoms not included in their definition may add support to their validity. Congenital and adult-onset SZ could not be compared on such symptoms, because most of them were included in their definition.

Hallucinations and delusions. Nine studies found no differences in the severity of hallucinations and delusions between deficit and nondeficit SZ (Wagman et al. 1987; Carpenter et al. 1988; Harris et al. 1991; Fenton and McGlashan 1994; Mayerhoff et al. 1994; Nibuya et al. 1995; Buchanan et al. 1997; Spalletta et al. 1997; Thibaut et al. 1998). Conversely, five studies found lesser severity of these symptoms in deficit SZ (Buchanan et al. 1994; Turetsky et al. 1995; Kirkpatrick et al. 1996b, 1996c; Bustillo et al. 1997). Although we found no methodological features that could explain the discrepant conclusions of these two groups of studies, the studies unequivocally support the finding that people with deficit SZ do not have more severe psychotic symptoms than people with nondeficit SZ.

Non-Kraepelinian SZ subjects, most of whom were undergoing an acute psychotic relapse, were found not to differ from Kraepelinian SZ subjects on the severity of psychotic symptoms in two studies (Keefe et al. 1987, 1991, 1996). However, the severity of psychotic symptoms has not been compared in these subgroups during the stabilized stage.

Disorganized dimension. Three studies (Fenton and McGlashan 1994; Mayerhoff et al. 1994; Nibuya et al. 1995) found more severe disorganized symptoms (i.e., thought disorder and bizarre behavior) in deficit than in nondeficit SZ. However, these differences were not observed in four studies (Turetsky et al. 1995; Kirkpatrick et al. 1996b; Buchanan et al. 1997; Spalletta et al. 1997). We found no methodological explanation for these discrepant results.

Kraepelinian SZ subjects were found to have more severe formal thought disorder than non-Kraepelinian SZ subjects in two independent samples (Keefe et al. 1987, 1991, 1996).

Negative symptoms. Three noteworthy refinements can be found on the severity of negative symptoms in deficit versus nondeficit SZ beyond the obvious observation of more severe negative symptoms in deficit SZ: (1) one study (Spalletta et al. 1997) confirmed that the greater severity of negative symptoms in deficit SZ was also present during acute psychotic relapse; (2) two studies found that the greater severity of negative symptoms in deficit SZ observed by clinicians was concordant with patients’ self-reports (Kirkpatrick and Buchanan 1990; Loas et al. 1996); and (3) one study found no change of negative symptoms in either deficit or nondeficit cases whose psychosis remained stable during a 2-week drug discontinuation (Bustillo et al. 1995). These findings suggest that the greater severity of negative symptoms in deficit SZ does not result from neuroleptic side effects, in agreement with two studies that did not find more severe extrapyramidal symptoms in deficit SZ (Bustillo et al. 1995; Spalletta et al. 1997).

Finally, Kraepelinian SZ was found to display more severe negative symptoms than non-Kraepelinian SZ in two independent studies (Keefe et al. 1987, 1996).

Depressive symptoms. Three studies on stabilized outpatients found more severe depressive symptoms in nondeficit than in deficit SZ probands (Kirkpatrick et al. 1994, 1996b; Loas et al. 1996), consistent with the observation of a higher suicide risk in nondeficit SZ probands (Fenton et al. 1997). On the other hand, three studies did not find such differences (Carpenter et al. 1988; Nibuya et al. 1995; Spalletta et al. 1997). Sampling differences may explain the negative results of one of the three latter studies (Spalletta et al. 1997) because it focused on acutely psychotic patients; depressive symptoms observed within such a context may have a different significance from those observed in stabilized outpatients. In addition, the studies finding differences between deficit and nondeficit SZ used more detailed assessments of depressive symptoms, which may have increased their sensitivity to differences between groups. Indeed, two of the studies finding differences used the Beck Depression Inventory (Kirkpatrick et al. 1994; Loas et al. 1996), and the third
sought diagnoses of previous depressive episodes (Kirkpatrick et al. 1996b) as opposed to the negative studies that relied on a cruder assessment of depressive symptoms (Carpenter et al. 1988; Nibuya et al. 1995; Spalletta et al. 1997), that is, the depressive symptoms assessed by the BPRS. Given these methodological issues, we conclude that there is strong evidence for more severe depressive symptoms in nondeficit SZ.

Comparisons on depressive symptoms have not been reported for Kraepelinian versus non-Kraepelinian SZ. However, a higher proportion of schizoaffective disorder was found in non-Kraepelinian subjects (Keefe et al. 1987, 1996), which is in agreement with previous findings of schizoaffective disorder having a better outcome than SZ (Samson et al. 1988).

Natural History. We examined whether the subtypes differed from each other on several natural history validators. Congenital and adult-onset SZ could not be compared on these aspects, as most of them were included in their definition.

Premorbid adjustment. Poorer premorbid adjustment in deficit SZ can be considered well replicated because it was found in four studies (Buchanan et al. 1990; Fenton and McGlashan 1994; Mayerhoff et al. 1994; Kirkpatrick et al. 1996a) and was confirmed by the observation of a lesser level of education in deficit SZ (Buchanan et al. 1993, 1997; Spalletta et al. 1997), which is an indirect indicator of premorbid problems.

Two studies found no differences in premorbid adjustment between Kraepelinian and non-Kraepelinian SZ (Keefe et al. 1987, 1996).

Age of onset. A single study (Mayerhoff et al. 1994) found that deficit SZ cases had an earlier onset than nondeficit SZ cases, but 14 studies found no differences (Wagman et al. 1987; Carpenter et al. 1988; Buchanan et al. 1990, 1993, 1994, 1997; Harris et al. 1991; Fenton and McGlashan 1994; Nibuya et al. 1995; Turetsky et al. 1995; Kirkpatrick et al. 1996b, 1996c; Bustillo et al. 1997; Spalletta et al. 1997). Therefore, a genuine difference in age of onset between deficit and nondeficit SZ appears unlikely.

Two studies found no differences in age of onset between Kraepelinian and non-Kraepelinian SZ (Keefe et al. 1987, 1996).

Type of onset. The Chestnut Lodge Study yielded more insidious onset in deficit SZ (Fenton and McGlashan 1994).

Social functioning. Poorer social functioning in deficit SZ was found in seven independent samples, using different sampling methods, different social functioning scales, and either concurrent or prospective assessment of social functioning (Wagman et al. 1987; Carpenter et al. 1988; Fenton and McGlashan 1994; Mayerhoff et al. 1994; Nibuya et al. 1995; Kirkpatrick et al. 1996a, 1996c). One study found less frequent substance abuse in deficit than in nondeficit SZ (Kirkpatrick et al. 1996a), and another study found that deficit SZ subjects were less reactive to difficult life events (Fenton and McGlashan 1994). Therefore, the association between deficit SZ and poorer functional outcome is well replicated, and this association seems to be an inherent consequence of the nature of the disorder rather than an artifact of a difficult living situation or substance abuse.

Social functioning was found to be poorer in Kraepelinian SZ in two studies (Keefe et al. 1987, 1996), which is somewhat tautological because poor social functioning is the main criterion for Kraepelinian SZ.

Temporal stability. One study found that the deficit syndrome became increasingly frequent during the first 5 years of illness and had a high degree of longitudinal stability once established (Fenton and McGlashan 1994). These results are consistent with those of two studies of first-episode SZ patients that found a low prevalence of the deficit syndrome in this population (Mayerhoff et al. 1994) and an increasing severity of the deficit syndrome over the first 2 years of illness (Kirkpatrick et al. 1996c). Moreover, the finding of a high degree of longitudinal stability has been replicated in a recent longitudinal prospective followup (mean duration = 3.8 years) study (Amador et al. 1999).

A high degree of 1-year stability of the Kraepelinian/non-Kraepelinian dichotomy (intraclass correlation coefficient = 0.68) was observed in the DSM-IV Field Trial (Amador, personal communication cited in Keefe et al. 1996). Unfortunately, the methods and the results of this study have not been published in sufficient detail to assess the validity of these findings.

Gender Ratio. The literature on gender differences in SZ suggests an association between male gender and VPO subtypes.

Of 22 published papers examining gender ratio in deficit and nondeficit SZ (Carpenter et al. 1988; Buchanan et al. 1990, 1993, 1994, 1997; Kirkpatrick and Buchanan 1990; Harris et al. 1991; Tamminga et al. 1992; Kirkpatrick et al. 1993, 1994, 1996a, 1996b, 1996c; Fenton and McGlashan 1994; Turetsky et al. 1995, 1998; Dolfhus et al. 1996; Ross et al. 1996; Bustillo et al. 1997; Spalletta et al. 1997; Waltrip et al. 1997; Thibaut et al. 1998), only 3 (Carpenter et al. 1988; Turetsky et al. 1995; Buchanan et al. 1997) found a statistically significant higher proportion of males among deficit SZ patients. On the other hand, all these studies yielded odds ratios for an association between male gender and deficit SZ that were equal to or greater than 1, suggesting a weak association between male gender and deficit SZ. To test this hypothesis, we have undertaken a meta-analysis (Roy et al., in press) that has confirmed a significant association
We found no comparison of congenital and adult-onset SZ biological markers.

Response to Treatment. Despite the modest specificity of psychiatric drugs, finding different response to treatment according to subtypes would add support to their validity. Congenital and adult-onset SZ could not be compared on this aspect because response to treatment is included in their definition. One study found no difference in response to either haloperidol or clozapine between deficit and nondeficit SZ (Buchanan et al. 1998). Another study found poorer response to social skills training in deficit versus nondeficit SZ (Kopelowicz et al. 1997), although the very small sample size (n = 6) made these results preliminary.

Non-Kraepelinian SZ has yielded a more important increase in severity of symptoms during drug washout (Harvey et al. 1991) and a better response to haloperidol (Keefe et al. 1987, 1991; Harvey et al. 1991) than Kraepelinian SZ, suggesting that Kraepelinian SZ may be a form of treatment-resistant SZ.

Biological Markers. We looked for differential patterns of association with biological markers in each subtype. We found no comparison of congenital and adult-onset SZ for any of these aspects.

Structural imaging. Three structural imaging studies compared deficit and nondeficit SZ. One study (Buchanan et al. 1993), using magnetic resonance imaging (MRI), yielded smaller prefrontal brain volumes in nondeficit SZ probands versus normal controls and deficit SZ probands, which was somewhat surprising and contradicted the a priori hypothesis that deficit SZ would be specifically characterized by changes in that area. In a second study using MRI, the only significant difference observed was an abnormal increase in temporal spinal fluid volume that was specific to the left side in deficit SZ patients (Gur et al. 1994; Mozley et al. 1994; Turetsky et al. 1995). A third study, using a computed tomography (CT) scan (Nibuya et al. 1995), found increased ventricular volume in deficit versus nondeficit SZ. Differences among these three studies in terms of imaging method (CT vs. MRI) and the structures measured prevented direct comparisons between them, and therefore, none of the findings can be considered replicated.

Two CT scan studies have compared Kraepelinian and non-Kraepelinian SZ. The first one yielded a greater degree of asymmetry of lateral ventricles (area of left ventricle divided by area of right ventricle) in Kraepelinian SZ (Keefe et al. 1987). However, these asymmetry findings are undermined by the use of area measurements that have been found sensitive to head positioning and to absolute volume of the ventricles (Zipursky et al. 1990). A second CT scan study (Davis et al. 1998) yielded a greater increase in ventricular volume in Kraepelinian SZ over a 5-year followup. However, in the latter study, the Kraepelinian SZ subjects were on average 5 years older than non-Kraepelinian ones, which may partly account for the findings because the Kraepelinian subjects were entering the period that previous studies had found to be characterized by a greater increase in ventricular volume.

Functional imaging. A positron emission tomography scan study (Tamminga et al. 1992) found lower thalamic, frontal, and parietal resting metabolism in deficit than in nondeficit SZ, but none of these differences achieved statistical significance, probably because of the small sample size, making these results preliminary. Another study (Gur et al. 1995) found no differences on resting brain metabolism between deficit and nondeficit SZ (total n = 42). The latter study was not included in table 1 because it did not focus on the comparisons between deficit and nondeficit SZ and because several important methodological aspects (e.g., the number of deficit versus nondeficit patients, the method used to assess the deficit syndrome) were not reported.

Postmortem brain study. A single postmortem study (Kirkpatrick et al. 1999) has found a higher density of interstitial cells of the white matter of the inferior parietal lobe in deficit than in nondeficit SZ, but none of these differences achieved statistical significance, probably because of the small sample size, making these results preliminary. Warrants caution in the interpretation of these results.

Neuropsychology. Compared to nondeficit SZ subjects and normal controls, deficit SZ subjects were found more impaired on (1) global intellectual functioning (Wagman et al. 1987; Harris et al. 1991; Buchanan et al. 1994; Nibuya et al. 1995); (2) executive functioning and visuospatial tasks (Buchanan et al. 1994); (3) attentional tasks (Buchanan et al. 1997); and (4) visuospatial information processing (Bustillo et al. 1997). Contrasting with the abundance of more abnormal findings in deficit SZ, the right-left asymmetry of visuospatial information processing (Bustillo et al. 1997) was the only task found more impaired in nondeficit SZ. Moreover, a detailed inspection of these studies revealed a systematic ordering of the performance: with very few exceptions, deficit SZ subjects had the poorest performance and normal controls the best, with nondeficit SZ subjects in between.

Eye tracking. Two studies compared deficit and nondeficit SZ on eye tracking, but differences in measures used in these studies precluded comparing their results. First, during an antisaccade task (Thaker et al. 1989),
deficit SZ showed longer latency for volitional saccades and larger saccade size than nondeficit SZ. Second, regarding smooth pursuit movements, deficit SZ subjects showed lesser velocity (Ross et al. 1996) and qualitatively more impaired tracking (Ross et al. 1997) than nondeficit SZ subjects and controls. In the latter study, a systematic ordering of performance could be found, because on average, deficit SZ subjects had the poorest performance and normal controls the best, with nondeficit SZ subjects in between.

Auditory evoked potentials. A single study compared auditory evoked potentials (P300) in deficit and nondeficit SZ subjects and controls (Turetsky et al. 1998). In that study, the electrode location (i.e., frontal, parietal, or temporal) that yielded statistically significant differences between SZ subgroups and controls differed, but no differences between deficit and nondeficit SZ were reported.

Biochemical markers. One study found lower plasma homovanillic acid (pHVA, a metabolite of dopamine) level and higher 3-methoxy-4-hydroxyphenylethylenglycol (MHPG, a metabolite of noradrenaline) levels (Ribeyre et al. 1994b; Thibaut et al. 1998) in deficit versus nondeficit SZ. However, another study yielded opposite findings: that is, a higher level of pHVA in nondeficit SZ than in deficit SZ (Nibuya et al. 1995). Although it is difficult to reconcile such opposite findings, differences in sampling may partly explain these discrepancies, because the second study focused exclusively on long-term SZ patients, while the first study had a broader range of patients.

Neurological soft signs. One study found that deficit SZ cases had more frequent abnormalities in sensory and audiovisual integration than nondeficit cases (Buchanan et al. 1990), suggesting more severe parietal dysfunction in deficit SZ.

Spontaneous and tardive dyskinesias. One study revealed an increased risk for spontaneous dyskinesias in deficit versus nondeficit SZ (Fenton et al. 1994) among neuroleptic-naive SZ patients. While such results suggest that the deficit syndrome is a risk factor for tardive dyskinesia, two studies found no differences in risk for tardive dyskinesias in deficit versus nondeficit neuroleptic-treated SZ patients (Thaker et al. 1989; Ross et al. 1996). However, the modest sample size in the latter studies makes their negative results preliminary.

Twin and Family Studies and Environmental Risk Factors. Given the role of genetic factors in the etiology of SZ, twin and family studies are essential to establishing validate subtypes. Therefore, we looked for evidence of different patterns of psychopathology in relatives according to probands' subtypes. We also looked for differential associations with environmental risk factors.

Five published reports examined these aspects in deficit versus nondeficit SZ. A first study yielded no differences between deficit and nondeficit SZ on the frequency of obstetric complications and psychopathology in relatives (Fenton and McGlashan 1994). However, these aspects were rated from the records of the SZ probands, making these findings inconclusive. A second study (Dollfus et al. 1996) found that nondeficit SZ subjects were more likely to have a family history of any psychiatric disorder than deficit SZ subjects. Given the breadth of the disorders considered (see Roy and Crowe 1994 for a detailed discussion on this issue) and given that diagnoses were based exclusively on the family history (FH; i.e., information from relatives) method, these results should be considered preliminary. Indeed, FH has been shown to agree poorly with best estimate diagnoses (Roy et al. 1996) (i.e., diagnoses based on direct interview with the relatives themselves, FH, and medical records), which are considered more valid (Weissman et al. 1986; Maziaide et al. 1992; Roy et al. 1997). A third study yielded an association between Borna virus antibodies and deficit SZ (Waltrip et al. 1997), which is particularly interesting, given the tropism of Borna viruses in rodents to brain structures likely to be involved in SZ (i.e., the hippocampus and dopaminergic tracts), although the human pathogenic effects of this virus remain uncertain. A fourth report yielded an association between summer birth and deficit SZ in three independent samples (Kirkpatrick et al. 1998), although it was not replicated in a fourth sample from a different center (Dollfus et al. 1999). A qualitative comparison with months of birth in the general population in the first article suggested that the rate of summer birth in deficit SZ exceeded that of the general population, although there was no direct comparison of season of birth in SZ subgroups and population controls. Given the excess of summer birth in deficit SZ, it could be speculated that the excess of winter birth in SZ found in several studies may be specific to nondeficit SZ. Therefore, this association between summer birth and deficit SZ appears particularly promising and would be compatible, for example, with a pathogenic effect of the influenza virus in the deficit subgroup.

First and second degree relatives of Kraepelinian and non-Kraepelinian SZ cases have been compared on their risk for SZ, schizoaffective disorder, unspecified functional psychoses, and SZ spectrum personality disorders (affective disorders were not reported) (Keefe et al. 1987). Relatives of Kraepelinian SZ probands were found to have a higher morbidity risk for SZ and a higher frequency for a positive family history of SZ spectrum disorders in any first or second degree relative. However, the diagnoses in relatives were based exclusively on the FH method, making these results preliminary, for the reasons discussed above.
A reanalysis of the Maudsley twin sample (Corrigall and Murray 1994) found that co-twins of probands with congenital psychoses had a higher risk for congenital psychoses and that co-twins of probands with adult-onset psychoses had a higher risk for adult-onset psychoses and nonpsychotic depression. Although these results lent some support to a relationship between psychopathology in relatives and subtype of the probands, the evidence was weakened by the following limitations: (1) probably because of modest sample size, none of the comparisons reached statistical significance; (2) the study was not restricted to SZ probands, as some of the subjects suffered from psychotic affective or schizoaffective disorder (Farmer et al. 1987) and were probably classified in the adult-onset subgroup, which may have spuriously increased the evidence for a relationship between adult-onset psychoses and affective disorders; and (3) the absence of a control group prevented the assessment of whether the risk for psychopathology in relatives of either subgroup of probands exceeded those of the general population.

Discussion

In this section, we summarize (table 4) and discuss the results for each subtyping strategy in the light of three current models of heterogeneity (McGuffin et al. 1987; Tsuang et al. 1990; Andreasen and Carpenter 1993; Buchanan and Carpenter 1997).

Differences Between Deficit and Nondeficit SZ. The main findings were as follows. First, adequate reliability was achieved by several research groups, and one study found a high degree of concordance between the PDS and the SDS. Attempts at replicating the latter results are needed, although, as Kirkpatrick et al. (1998) argue, the similarities found between SDS- and PDS-defined deficit SZ suggest that these two instruments identify similar patients. Second, comparisons of the severity of the clinical symptoms outside the definition of the subtypes yielded equal or lesser severity of hallucinations and delusions in deficit than in nondeficit SZ and showed strong evidence for more severe depressive symptoms in nondeficit SZ. Third, natural history studies yielded poorer premorbid and current social functioning in deficit SZ, increasing frequency of the deficit syndrome during the first 5 years of illness, and stability of the deficit syndrome once established. Fourth, a meta-analysis yielded a statistically significant association between deficit SZ and male gender. Fifth, there was preliminary support for poorer response to social skills training in deficit SZ. Sixth, no replicated differences between deficit and nondeficit SZ were found on biological markers. However, deficit SZ showed more extreme abnormalities than nondeficit SZ on several biological markers in single, unreplicated studies. These aspects spanned structural and functional brain imaging, postmortem brain studies, neuropsychological and eye tracking performance, abnormalities in monoamine metabolites level (although some findings were conflicting), neurological soft signs, and spontaneous dyskinesias. Conversely, compared to deficit SZ, nondeficit SZ showed a greater decrease in prefrontal volume and abnormal lateral asymmetry of visual information processing. Seventh, an excess of summer birth in deficit SZ was found in three independent samples, and more frequent Borna virus antibodies in deficit SZ were found in a single study. However, there were no published family studies of these subtypes. (See addendum.)

Heterogeneity Models and the Deficit Versus Nondeficit Subtypes. In this section, we describe three current models of heterogeneity (i.e., the distinct disorders, the continuum of severity, and the distinct domains models) and we examine the extent to which they were supported in published studies on deficit and nondeficit SZ. Distinguishing between these three models of heterogeneity is essential for interpreting the differences between SZ subtypes because these three models have very different implications for the design of studies on the pathophysiology of SZ.

The pattern of differences between deficit and nondeficit subtypes may suggest that they represent distinct disorders (we termed this first pattern the "distinct disorders" model of heterogeneity). Indeed, deficit SZ appeared more severe than nondeficit SZ for several validators, and conversely, nondeficit SZ yielded more extreme findings for three validators (i.e., depressive symptoms, prefrontal atrophy, asymmetry of visual information processing). In addition, the association of a summer birth with the deficit syndrome would also fit with the distinct disorders model, as summer birth is not an indicator of severity. The distinct disorders model would suggest that deficit and nondeficit SZ represent mutually exclusive disorders with distinct pathophysiology and that investigations on the pathophysiology of SZ should study these subtypes independently.

However, the three differences for which nondeficit SZ yielded more extreme findings should be considered as nondefinitive for three reasons. First, the greater severity of depressive symptoms in nondeficit SZ may be partially tautological. Indeed, in patients showing both depressive symptoms and negative symptoms, the latter are likely to be judged secondary to depressive symptoms. Consequently, these patients would be excluded from the deficit subgroup, which would
and the disorganized ones, which can have their own
neuropsychological domains could be the positive
erogeneity) rather than distinct disorders. Other orthog-
onal characteristics, we termed this third pattern the "con-
continuum of severity" model of heterogeneity (McGuffin
et al. 1987). In such a continuum of severity model,
more severe abnormalities and nondeficit SZ would have a similar etiology,
the deficit subtype having a more severe loading for
these etiologic factors. With this model, combining
deficit and nondeficit patients in a case-control study
would not diminish the power to identify the etiologic
factors of SZ. In addition to the pattern of more extreme
findings in deficit SZ, the systematic ordering of per-
formance observed on neuropsychological and eye
tracking tasks is also typical of a continuum of severity
model. Indeed, with very few exceptions, deficit cases
showed the worst performance, normal controls showed
the best performance, and nondeficit cases displayed a
performance between that of the other two groups.

Finally, the deficit/nondeficit categories may iden-
tify a distinct psychopathological domain (we termed
this third pattern the "distinct domains" model of het-
erogeneity) rather than distinct disorders. Other orthog-
onal psychopathological domains could be the positive
and the disorganized ones, which can have their own
pathophysiology, different from that of the deficit
domain. As a consequence, deficit SZ would be
expected to yield more extreme findings on the patho-
physiology indicators of the deficit domain, but deficit
and nondeficit SZ patients would not differ on the indi-
cators of the other two domains. Taken in isolation, this
pattern of findings is very similar to a continuum of
severity model. Consequently, the distinction between
the continuum of severity and the distinct domains
models requires the simultaneous study of more than
one putative domain. For example, if a neurobiological
abnormality was found to be associated with the deficit
syndrome and another neurobiological abnormality with
persistent positive symptoms in the same cohort of
patients, a strong point could be made for the distinct
domains model. Unfortunately, studies on deficit versus
nondeficit SZ have so far focused exclusively on the
deficit syndrome, which does not allow a more defini-
tive test of the distinct domains model for deficit SZ.
(See addendum.) However, previous evidence
(Andreasen et al. 1995) that positive, negative, and dis-
organized symptom dimensions have distinct correlates
strongly suggests that the distinct domains model is a
very plausible explanation for the differences found
between deficit and nondeficit SZ. If the distinct
domains model were right, the etiology of SZ would be
easier to elucidate through the study of these distinct
dimensions. However, contrary to the distinct disorders
model, which posits distinct pathophysiologies in mutu-
ally exclusive subgroups of patients, the distinct
domains model suggests that domains are not exclusive
and can co-occur in a given patient. Therefore, a given
group of patients could provide information on the
pathophysiology of each of these domains.

We are thus left with three plausible models of het-
erogeneity that could account for the differences
observed between deficit and nondeficit SZ. The
methodological recommendations made below may help
to discriminate between these various models.

Kraepelian Versus Non-Kraepelian SZ. The main
findings were as follows. First, adequate reliability was
achieved by the developers of this strategy and by one
other group. Second, comparisons of the severity of clini-
cal symptoms yielded equal severity of hallucinations
and delusions in Kraepelian versus non-Kraepelian SZ
during psychotic relapse, and more severe negative symp-
toms and more severe thought disorder in Kraepelian
SZ. Third, there was limited evidence for differences
between Kraepelian and non-Kraepelian SZ on natural
history validators. Fourth, we found no comparison on
gender ratio. Fifth, there was replicated evidence for bet-
ter response to neuroleptic treatment in non-Kraepelian
SZ. Sixth, there was unreplicated preliminary evidence
for abnormal asymmetry of lateral ventricles and for more
severe progressive ventricular enlargement in Kraepelinian SZ. Seventh, there was preliminary evidence for a higher risk for SZ in relatives of Kraepelinian versus non-Kraepelinian SZ. This pattern of differences between subtypes supports a continuum of severity model, because Kraepelinian subjects yielded more extreme findings across several validators, while non-Kraepelinian SZ subjects were not found more severe on any of the validators. However, because few of these findings were replicated, and because there are several other validators on which Kraepelinian SZ and non-Kraepelinian SZ have yet to be compared, this conclusion cannot be definitive.

It should be stressed that if a continuum of severity model were appropriate to account for the differences between Kraepelinian and non-Kraepelinian SZ, these subtypes could still have important implications for studies on the etiology and pathophysiology of SZ. Indeed, because Kraepelinian cases would have a more important loading on etiologic factors (Greenberg 1992), comparing Kraepelinian cases to controls could increase statistical power. In addition, the continuum of severity model would suggest that comparing Kraepelinian and non-Kraepelinian subtypes could yield important information on the determinants of outcome.

Congenital Versus Adult-Onset SZ. The main findings were as follows. First, adequate reliability was achieved by the developers of this strategy but was not tested by other groups. Second, there were no comparisons on the severity of the clinical symptoms outside the definition of the subtypes, natural history validators, gender ratio, treatment response, and biological markers. Third, there was preliminary evidence for differential patterns of familial psychopathology in congenital versus adult-onset SZ. These differences between these subtypes fit a distinct disorders model because different types of psychopathology are found in relatives according to proband subtype. However, given the methodological limitations discussed above, these results are preliminary and warrant further studies of these subtypes.

Overall Conclusions on the Three Subtyping Strategies

None of the three subtyping strategies yielded replicated differences between subtypes across all validators. This shortage of replicated differences may be due only to the novelty of these subtypes; for most validators, available information stems from single, unreplicated studies. The amount of available information appears more or less sufficient depending on the perspective from which the subtypes are judged. For example, the clinical relevance of the deficit and nondeficit subtypes has been unequivocally established by strong evidence for differences in outcome between these subgroups, even if the information is not sufficient to definitively establish the validity of these subtypes from an etiologic perspective. At this stage, these subtyping strategies can be regarded as promising strategies to identify homogeneous SZ subtypes, although additional studies are needed to further test their validity. The accumulated evidence for the validity of these subtyping strategies, particularly the deficit/nondeficit one, is certainly sufficient to warrant their use in future case-control or genetic studies of SZ, because the subtyping of patients is relatively inexpensive when compared to some of the high-tech procedures (e.g., functional brain imaging). The use of such subtypes in molecular genetic studies of SZ is particularly appealing, because such studies are likely to provide the most definitive evidence on the validity of any subtyping strategy.

Priorities for Future Studies

The following recommendations can be made for future studies.

First, family studies of these subtypes are direly needed. Not a single published family study of these subtypes used blind best estimate diagnoses in relatives (see addendum), although there was preliminary evidence that non-VPO (i.e., adult-onset) SZ may represent a severe expression of genetic liability to affective disorders. Such familial co-aggregation of affective disorders and non-VPO SZ could reflect genetic anticipation (Mérette et al., 2000). However, an association between outcome and the type of psychopathology in relatives may reflect diagnostic misclassifications. Indeed, some non-VPO SZ cases may represent severe affective disorders misdiagnosed as SZ because such cases are often more difficult to diagnose than prototypical VPO SZ and nonpsychotic affective disorders (Roy et al. 1997). Hence, an increased risk for affective disorders in relatives of non-VPO SZ probands could be an artifact of the misclassification of psychotic affective disorders within that subgroup. Future studies should make every possible effort to exclude such psychotic affective disorder patients from the proband groups.

Second, because the three subtyping strategies reviewed defined subtypes a priori, it is not known which of the criteria used in these various definitions are the most crucial. Instead, it may be advantageous to empirically derive definitions of VPO and non-VPO SZ, based on criteria that are recognized as essential for the validity of psychiatric syndromes (Robins and Guze 1970). For example, variables predicting VPO in probands and those predicting SZ in relatives could be used to define a VPO subtype, while variables predicting better outcome in probands and those predicting affective disorders in relatives could be used to define a non-VPO subtype. In addi-
tion, multivariate statistical classification techniques (i.e., latent class and cluster analyses) can be used to define subtypes based on patterns of similarities and differences (Goldstein et al. 1990; Castle et al. 1994; Sham et al. 1996). However, several complex issues are raised by the use of these techniques (Everitt and Mérette 1990): (1) the definition of the classes or clusters may depend on the statistical technique used; (2) the definition of subgroups may depend on the choice of variables; and (3) it may be difficult to decide on the number of classes or clusters to retain, because several statistical criteria exist to guide this decision and these various criteria may lead to different conclusions.

Third, future studies have to take into account dimensional models of heterogeneity by studying simultaneously the determinants of several dimensions of psychopathology or physiopathology (Andreasen et al. 1995). Indeed, as was discussed above, such models are an essential alternative to categorical models of heterogeneity (Andreasen and Carpenter 1993). In addition, recent studies (Van Os et al. 1996, 1999) have suggested that psychopathological dimensions yield better predictive power than diagnoses for several aspects of outcome in psychotic patients. Such dimensional models of heterogeneity can be used to test for possible continuities across current diagnostic categories (e.g., bipolar disorder and SZ) (Maziade et al. 1995; Toomey et al. 1997).

Fourth, it is of interest to study the degree of overlap between the various strategies to subtype SZ according to outcome, in order to determine the extent to which results obtained with one approach to subtyping generalize to other approaches. Some degree of overlap may be suggested by the finding that poor outcome and greater severity of negative symptoms are common to Kraepelinian and deficit SZ. In addition, the overlap between VPO and treatment-resistant SZ needs to be studied because treatment response may also be pertinent to identify etiologically homogeneous subtypes (Brown and Herz 1989).

Fifth, attention must be paid to sample size and power, because studies of heterogeneity are expected to require large samples to achieve satisfactory power. Some sampling procedure could be used to increase power. For example, it may be advantageous to sample SZ with outcome toward the ends of the severity spectrum. Such a sampling procedure would increase the proportion of subjects with extreme values on variables such as premorbid adjustment or response to treatment, thereby increasing the power to identify meaningful relationships. In addition, while age of onset did not appear to differentiate any of these subtypes, most studies of these subtypes probably did not include a sizable proportion of cases with very early onset (VPO; i.e., before 15 years of age) SZ, as is usual in samples of adult SZ cases. Available evidence that VEO SZ yields a particularly poor outcome (Maziade et al. 1996a, 1996b) would suggest that such cases are more likely to be from the deficit, the Kraepelinian, or the congenital subtype, providing an impetus for studying these subtypes in samples of VEO SZ. Another precaution that could increase the power to find differences between subtypes would be to exclude patients with an ambiguous classification from either subtype. This misclassification problem, which affects other subtyping strategies as well (Roy and Crowe 1994; Roy et al. 1995), could explain the systematic ordering of neuropsychological performance found in deficit SZ subjects, nondeficit SZ subjects, and normal controls. An example of an ambiguous classification that may reduce the homogeneity of the nondeficit subgroup is the difficulty in distinguishing between primary and secondary negative symptoms in the presence of severe and persistent disorganization symptoms. In case of doubt, the SDS recommends considering the negative symptoms as being secondary. As a consequence, some of these cases classified as nondeficit may in fact suffer from deficit SZ.

Sixth, longitudinal studies suggest that functional outcome and deficit symptoms stabilize after the first 5 years of illness (Westermeyer and Harrow 1988; Fenton and McGlashan 1994; Kirkpatrick et al. 1994). Consequently, to ensure that poor outcome is not transient, to allow for symptoms such as the deficit ones to emerge, and because the risk for diagnostic unreliability decreases with longer followup (Roy et al. 1997), it appears preferable to use a sample of cases who are at least 5 years past onset. Alternatively, prospective followup studies of incident cases for at least 5 years are needed, because the prospective followup studies could allow more accurate measurements of several clinical variables.

Seventh, attention should be paid to the effect of neuroleptic treatment on course of illness because insufficient treatment is clearly a factor that could result in a poor outcome. Therefore, it could be useful to require, for example, that people with VPO SZ have had at least two adequate trials with neuroleptics, to make sure they are not simply insufficiently treated patients. Moreover, to assess the deficit syndrome, investigators would ideally control the treatment, which could make easier the distinction between primary and secondary negative symptoms. Controlling the treatment could allow the use of the so-called atypical neuroleptics, which recent studies have shown to be superior to classical ones in terms of decreasing the severity of negative symptoms and in being less likely to cause parkinsonian syndromes (Marder et al. 1997; Tollefsen and Sanger 1997).

Eighth, sampling strategies with a well-defined sampling frame, such as the Suffolk study (Kirkpatrick et al. 1996), would help to assess the generalizability of findings and
might prevent sampling biases that may occur in convenience samples such as those used in most of the studies reviewed.

Ninth, the developers of these three subtyping strategies and other researchers (Brockington et al. 1992; Maziade et al. 1995) agree on the need to use longitudinal data to derive meaningful subtypes. Because the goal of these subtyping strategies is to find subtypes differing on crucial etiologic aspects, it is important to emphasize lifetime measurements that are less likely than cross-sectional measurements to be overly influenced by short-term fluctuations. Therefore, this emphasis on longitudinally based clinical assessment is warranted.

Tenth, replications of previous findings should obviously be sought to establish the validity of those findings. Providing detailed information on methodological aspects and on the clinical characteristics of the subjects under investigation is of utmost importance to assess the potential sources of discrepancies among studies. The replication of the studies that found nondeficit SZ more severe on some validators would be particularly important, because such replications would significantly strengthen the case for deficit and nondeficit SZ being distinct disorders.

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Addendum

Since the completion of this manuscript, additional articles comparing deficit and nondeficit SZ have been published. Their most important among findings include the following.

First, data from the Camberwell Register Psychosis Series (Kirkpatrick et al. 2000a), using the PDS, found (1) an association between summer birth deficit SZ, further replicating the association already observed in three previous data sets; and (2) an association between deficit SZ and the presence of SZ in relatives, and between nondeficit SZ and the presence of other psychiatric disorders in relatives. However, the reliance on information from probands’ charts to diagnose relatives precludes considering these findings definitive.

Second, data from the Irish High-Density Study of Schizophrenia (Ross et al. 2000) found evidence that deficit vs. nondeficit subtypes “breed true” by observing a significant rate of concordance for deficit vs. nondeficit subtypes among sibling pairs affected by SZ.

Third, data from the Roscommon Family Study of Schizophrenia (Kirkpatrick et al. 2000b) found a trend for an association between deficit subtype of SZ probands and SZ in relatives, and a significant association between deficit subtype of the proband and “deficit-like” symptoms in unaffected relatives.

Fourth, we found a first paper simultaneously seeking the correlates (e.g., various types of neurological soft signs) of psychotic and disorganized as well as deficit symptoms (Arango et al. 2000), as proposed in the present review. This paper reported distinct patterns of correlations for each of these three symptom dimensions, thereby lending support to the distinct dimension models.

Fifth, two functional imaging studies have recently reported (Heckers et al. 1999; Delamillieure et al. 2000) an association between hypofrontality and deficit SZ.

Altogether, these studies significantly add to the evidence for the validity of the distinction between deficit vs. nondeficit subtypes and clearly warrant a more widespread use of these subtypes.

Bibliography


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