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How the Diagnosis of Schizophrenia Impeded the Advance of Knowledge (and What to Do About It)

William T. Carpenter Jr.

Abstract

Schizophrenia is sometimes conceptualized as a disease entity where all patients share the same fundamental causal mechanism and core brain pathophysiology. Alternatively, it is viewed as a clinical syndrome comprising several different causal mechanisms and pathophysiologies. In the latter concept, differences between individuals may be substantial and this heterogeneity reduces the power of most study designs. Currently schizophrenia is viewed as a mental disorder with implications of a clinical syndrome and without compelling evidence of a homogeneous disease. Most investigations over the past century, however, have been designed without addressing heterogeneity. Acquisition of knowledge has thus been impeded.

Recent paradigm shifts in the schizophrenia construct are intended to provide more valid and more robust approaches to new knowledge. These include:

1. Identifying patient subgroups to enrich study cohort homogeneity on causal pathway and pathophysiology.
2. Deconstructing schizophrenia from the top down by identifying key domains of psychopathology using each domain as the pathology of interest.
3. Approaching the deconstruction from the level of the neural circuit or behavioral construct to investigate molecules, genes, and pathways related to known neural circuits and behavioral constructs which, in turn, are related to psychopathology domains.
4. Using stages of vulnerability development prior to fully manifest schizophrenia as study targets, to conceptualize causal pathways to early vulnerability that are not specific to schizophrenia as well as later stages associated with pathological variables which have greater disorder-outcome specificity.

The first paradigm shift can be informative for a form of schizophrenia that may not generalize to all forms of the disorder. The last three provide for more specific study targets but address pathologies that will cut across current disorder boundaries. The fourth paradigm, in particular, calls attention to preventive and resiliency factors as well as causal factors.

Introduction

Schizophrenia is a mental disorder with the status of a clinical syndrome rather than a specific disease entity. The central thesis presented here is that equating a heterogeneous clinical syndrome with a disease entity has impeded the acquisition of knowledge. For over 100 years, the paradigm of schizophrenia as a disease entity has been dominant, and the implications of this have been profound. Before discussing the limitations of the disease model and alternatives with greater heuristic value, a definition of key terms may be helpful.

- *Nosology* refers to the classification of medical diseases. A disease class has greatest clarity when based on known etiology/cause and/or specific pathophysiology. Diagnostic classes are also necessary in the absence of etiology/pathophysiology knowledge and may be better considered disorders or clinical syndromes.
- *Disease entity* is a disease based on etiology/pathophysiology, presumed or proven, that distinguishes it from other diseases. It is the knowledge of cause and mechanism that distinguishes a disease entity from a disorder, and uniformity of cause and mechanism that distinguishes it from a clinical syndrome.
- A *syndrome* is the association of several clinically recognizable features such as symptoms and signs that often occur together in patients.
- A *mental disorder* or *mental illness* is a psychological or behavioral pattern which deviates from normal and is generally associated with distress, dysfunction, and/or disability. Mental disorders are generally defined by a combination of how a person feels, acts, thinks, and/or perceives.
- A *domain of psychopathology* comprises signs and symptoms conceptualized as relating to a single construct. In schizophrenia, diagnosis is based on a combination of signs and symptoms. Domains attempt to reduce heterogeneity by defining unified symptom/sign constructs such as hallucination or avolition.
- *Dimensions of psychopathology* place domains of psychopathology on a severity continuum in terms of specific observable variables or hypothesized underlying processes.
- *Deconstruction* means identifying domains of psychopathology within a syndrome, recognizing that persons classified within the syndrome

will vary as to which domains are actually present. In schizophrenia, no domain is unique to the disorder.

- For present purposes, let us consider a *behavioral construct* to be a behavior that can be specified as a phenotype whose physiology involves a known neuroanatomic framework or neural circuit (e.g., fear, working memory).
- *DSM* and *ICD* are diagnostic manuals published by the American Psychiatric Association (APA) and the World Health Organization to provide a nosology with information and criteria for diagnosis of each class. In DSM, "A criteria" define the symptoms required for diagnosis of a case.
- A *schizophrenia construct* is an organized view of the concept of schizophrenia including principle defining features. Diagnostic prototypes and criteria relate to the construct and may change as the construct is revised over time.
- *Heterogeneity of schizophrenia* poses the central problem for a clinical syndrome where individual cases vary substantially on key features. One case may have disorganized thought and behavior and negative symptoms, another may have hallucinations and delusions without negative symptoms or disorganized behavior, while still another may have disorganization with psychomotor abnormalities but without negative symptoms. A study design that includes such diverse cases while testing for a neural circuit for hallucinations or a gene associated with negative symptoms or a treatment for disorganization is weakened to the extent that some or many subjects do not actually have the phenomena of interest.
- *Medical model*: schizophrenia has traditionally been considered a medical disorder. A medical model implies disease pathophysiology, but an understanding of pathways to the pathophysiology as well as an understanding of the consequences of this pathology require integrating information across levels of human functioning. A broad medical model encompassing social, psychological, and biological data and concepts is essential to achieve an integrated view that relates to individual cases as well as to an overarching construct. Use of a medical model, however, does not imply biological reductionism, since causes of psychopathology can come from any number of levels, including interpersonal and environmental ones. Experimental designs are reductionistic by necessity (at any level of a functioning organism). Biomedical reductionism is adequate for certain study designs, but not for a construct of schizophrenia.

Schizophrenia has traditionally been conceptualized, via the medical model, as a disease and until recently, this concept has driven research efforts and understanding of what appears instead to be a clinical syndrome or a class of

disorders. Much has been accomplished, but most study designs treat schizophrenia as a disease entity, in part because methods to reduce heterogeneity decisively have only recently emerged. The proposition addressed here is that schizophrenia, when treated as a disease rather than a clinical syndrome, has *limited the acquisition* of knowledge.

The history of the dominant construct can be briefly summarized as follows. In the late nineteenth century, the disease entity approach was validated through the identification of various infectious diseases, including tertiary syphilis—a disease entity associated with psychosis. Mental disorders had putative disease entities such as hebephrenia, catatonia, and paranoia, each associated with psychotic symptoms. In the late nineteenth century, Kraepelin (1919/1971) postulated a unifying pathological process involving the unique combination of avolition (e.g., weakening of the will such that initiation of action and thought are impaired) and dissociative psychopathology. He also proposed dementia praecox as a disease separate from manic depressive disease. Bleuler (1911/1950) provided strong support for the disease entity concept by viewing dissociative pathology as primary and fundamental in all cases. However, he also raised the issue of syndrome, referring to the group of schizophrenias. The behavioral manifestations of dissociative pathology were broad and often subtle (e.g., separation within thought, loss of intimate connection between thought and action and thought and feeling, fragmented or vague speech). When schizophrenia was diagnosed with subtle abnormalities of thought, the boundary of the disorder became inflated and the link with avolition was weakened.

The concept of schizophrenia changed again in the middle third of the twentieth century. Schneider (1959) attempted to clarify and narrow the concept by emphasizing understandability of special experiences as being the symptom pathology of first importance in identifying cases. Experiences such as hearing a voice with a running commentary, referring to the patient in third person, or bizarre forms of delusions such as thoughts being inserted by alien forces shifted the concept toward reality distortion pathology and away from avolition and disorganized thought and experience. Langfeldt (1939) explicitly addressed the perceived problem of diagnosing schizophrenia in cases that did not have the same affliction as found in true schizophrenia. Using Schneiderian first-rank symptoms and other reality distortion phenomena (e.g., massive derealization) he separated true schizophrenia from pseudo-schizophrenia in an attempt to define the core or nuclear aspects of the construct.

It is important to note that with dementia praecox, Kraepelin established a putative disease entity based on avolition/dissociative pathology. Bleuler accepted this view but considered dissociative pathology the fundamental and primary pathology. Bleuler made clear that reality distortion symptoms were secondary phenomena and not fundamental to the construct. However, applying the Bleulerian concept also involved inward withdrawal (autism), affect pathology (e.g., restricted experience and expression of emotion), ambivalence

in thought and action, as well as associative pathology—often referred to as Bleuler's four As. These manifestations may be subtle in many cases, and the movement from the Kraepelinian emphasis on observable signs and course criteria to less observable psychological constructs had the unintended consequence of broadening the concept and raising doubts as to the validity of the diagnosis. The construct based on work by Schneider and Langfeldt was viewed as addressing this problem by separating true or nuclear schizophrenia from pseudo-schizophrenia. This was accomplished, however, through a major shift in the construct away from avolition and dissociative pathology and toward reality distortion without validating the true versus pseudo distinction. Nonetheless, this latter approach was very influential as DSM-III was prepared and published in 1980.

A final note before proceeding to DSM-III: Jaspers (1963) viewed impaired empathy as fundamental to schizophrenia. Empathy here refers to the sense that one appreciates the mind and feelings of another through automatic processing not dependent on complex language communication. Impaired empathy was considered to be in the same class of special schizophrenia experiences described by Schneider. Schneider (1959) identified a set of "first-rank" symptoms and made a clear distinction between understandable delusions (e.g., delusions of poverty in a depressed person) and bizarre delusions (e.g., believing an unknown external source is responsible for one's thoughts). First-rank symptoms represented a pathology of ego boundary or reality distortion quite distant from the avolition/dissociative pathology described by Kraepelin (1919/1971). Jaspers's concept was, perhaps, misconstrued and poor rapport may better represent impaired empathy. Note that the most discriminating features in differential diagnosis are omitted from the A criteria in DSM-III and are only partly in place in DSM-IV. These are: poor rapport, lack of insight, and restricted affect (Carpenter et al. 1973).

With its publication in 1980, DSM-III put a new paradigm for diagnosis in place. Previously developed for research, explicit criteria on which to make a diagnosis were formulated for each disorder. Clinical, research, and epidemiologic diagnoses were to be based on ascertainment of the specific criteria. Previously, clinicians would rely on training and experience, an understanding of prototypes for various disorders, and a general description of each disorder. The approach now included the explicit determination of criteria that needed to be met in each case. With the broad international acceptance of DSM-III, the schizophrenia concept at the symptomatic level was explicitly related to delusions, hallucinations, disorganized thought, and psychomotor abnormalities and required the presence of at least two of these four psychopathology domains. With DSM-III the field had operationalized criteria with documented reliability. Little noticed was the remarkable shift in concept in the direction of reality distortion and away from avolition. Negative symptoms, characterized by experience and expression of emotion and avolition/anhedonia/asociality, were not included in the DSM-III criteria. Cases of schizophrenia could now

be defined by the presence of just hallucinations and delusions. This is remarkable considering two empirical findings in the 1970s. First, symptoms of first rank had been documented in other mental disorders. Separating broadly defined schizophrenia into true and pseudo-schizophrenia with Schneider's or Langfeldt's criteria failed to support validity based on disorder development, course, outcome, or functional status. Second, the most discriminating features between different psychotic disorders were restricted affect, poor rapport, and poor insight, none of which were included in the A criteria. Parenthetically, negative symptoms were added to the A criteria in DSM-IV, but so was the criterion that a single bizarre delusion or hallucination could fulfill A criteria.

DSM-IV, published in 1994, contained two significant changes related to the avolition/reality distortion dialectic. First, negative symptoms were added to the A criteria and now two of the five were required: delusion, hallucination, disorganization, psychomotor, and negative symptoms. Second, an exception was made to allow A criteria to be met by a single hallucination or delusion if considered bizarre. Bizarre, for practical purposes, can be considered a first-rank symptom of Schneider. Parenthetically, schizoaffective disorder was introduced in an attempt to address cases where schizophrenia criteria are met in the context of extensively overlapping major mood episodes.

By viewing schizophrenia as a disease entity based on Kraepelin's dementia praecox, reinforced through Bleuler's view of the primary and fundamental pathology being found in all cases, the disease entity concept was expanded to a construct of "schizophrenia as a brain disease"—a construct which was used to endorse a medical model and, in theory, to reduce stigma. The concept has been further reinforced as the neurodevelopmental hypotheses gained traction. Most research data is generated in study designs which compare people diagnosed with schizophrenia to psychiatrically healthy subjects or schizophrenia as a disorder compared to other disorders. Only a fraction of reported studies attempt to reduce heterogeneity and relate study findings to a specific pathology. The impediment to acquisition of knowledge can be seen in genetic studies where the design accepts a diagnosis of schizophrenia as the phenotype despite the broadly held view that multiple phenotypes exist and vary from case to case. Another telling example is the equating of schizophrenia with psychosis and sixty years of developing dopamine antagonists for psychosis and viewing them as anti-schizophrenia drugs. This resulted in sixty years of "me-too" drug development for one aspect of the construct while the therapeutic needs in other critical pathologies (e.g., impaired cognition and negative symptoms) remained unmet (Buchanan et al. 2005; Kirkpatrick et al. 2006).

The remaining discussion assumes that the proper construct at this point in time for schizophrenia is that of a clinical syndrome with heterogeneity of manifestation across individual cases (widely documented) and presumed heterogeneity at the level of etiology and pathophysiology. This heterogeneity, if not addressed in study designs, weakens the opportunity for discovery. To illustrate the problem, imagine an imaging, genetic, postmortem study of

dementia where a relatively small number of cases are compared to controls without a brain disorder. If subjects are selected based on impaired short-term memory, the study cohort may include cases of Alzheimer's disease, multi-infarct dementia, Pick's disease, normal aging, and pernicious anemia. This mixture will reduce the chances of discovering pathology associated with each specific form of dementia. Fortunately, for many forms of dementia there is sufficient knowledge to reduce the heterogeneity with diagnosis. As a clinical syndrome, schizophrenia presents, however, some of the problems associated with dementia before separate disease entities could be defined.

Why Classification Failed

Classification is, of course, essential for many valid purposes. To advance knowledge of disease etiology, pathophysiology, treatment, prevention, and cure, the dominant paradigm is quite limited and represents a flaw, often fatal, in many research designs. Failure to address heterogeneity in schizophrenia has resulted in the following:

- Biomarkers or endophenotypes are not established to validate the diagnosis in the individual case.
- Drug discovery cannot be rationally based on known molecular pathophysiology.
- Risk factors have not led to effective prevention.
- Psychopharmacology has made very limited progress since chlorpromazine was introduced sixty years ago. Scores of "me-too" antipsychotic drugs have been approved but only clozapine is recognized for its superior effectiveness.
- Many genes with small effects have not yet been linked effectively to meaningful phenotypes (as suggested by genome-wide APA studies).
- Group findings with many variables that distinguish a schizophrenia cohort from a non-ill cohort may have little discriminating power between schizophrenia and "near-by" psychotic disorders.
- Power in any research design is presently reduced by the incorrect expectation that all subjects with schizophrenia actually have the pathology related to the variable of interest.
- When a variable hypothesized to be related to schizophrenia is observed in all subjects with the diagnosis, likely explanations include antipsychotic drug effect, shared lifestyles, or that the variable is related to psychosis in general and is thus not specific for schizophrenia.

Genome-wide APA studies generally treat a clinical syndrome as though it were a disease entity. Classification, however, has failed because of heterogeneity across diagnosed individuals on variables such as risk factors, etiology pathways, developmental pathways, endophenotypes, onset, manifest symptoms,

course, treatment response, and associated features, such as neurological soft signs and cognition. Currently, there are no pathognomonic manifestations of schizophrenia and no biomarker with the sensitivity and specificity required for diagnosis in the individual case.

Overcoming Classification: How to Accelerate the Acquisition of Knowledge

The field of research has generally accepted schizophrenia as a disease entity paradigm for the past hundred years or so. To shift from a dominant paradigm is usually difficult, although alternative paradigms, new and old, are available:

1. Reduce syndrome heterogeneity by identifying subgroups, each representing a putative disease entity. Examples: traditional subtypes such as hebephrenia or paranoid, good versus poor premorbid development, and deficit versus nondeficit based on presence or absence of primary negative symptoms.
2. Deconstruct the syndrome construct into psychopathology domains. Examples: Strauss et al. (1974) stipulates six domains, Cuesta and Peralta (1995) eight domains, and eight domains have been placed in Section 3 of DSM-5 (American Psychiatric Association 2013).
3. Establish separate developmental pathways, each being an independent variable in the study design. Example: the interactive developmental model represented in Figure 3.1.
4. Establish stages of psychopathology development with each stage being an independent variable. Examples: stages in the neurodevelopmental model (Weinberger 1987; Murray and Lewis 1987) or clinical staging (Hogarty et al. 1995; McGorry et al. 2010).
5. Address psychopathology from a behavioral construct representing a phenotype closely related to clinical manifestations on the one hand and to brain anatomy on the other. Example: the NIMH Research Domain Criteria initiative (RDoC 2011).
6. Hypothesize a biomarker as the point of entry and select subject according to the presence of the biomarker at a level thought to represent pathophysiology (e.g., predictive pursuit in eye movements). Example: select subjects according to deviation from norm on a biochemical, imaging, or psychophysiological phenotype (Braff et al. 2007; Turetsky et al. 2007; Schork et al. 2007; Gur et al. 2007; Thaker 2008).

Earlier efforts to reduce heterogeneity involved identifying subgroups within the schizophrenia syndrome. Traditional subtypes of schizophrenia reflect some important subgroup differences (e.g., genetics of hebephrenia vs. paranoid subtypes), but have not proven to be strong heuristics for investigative purposes. This, in part, is because subtypes are not stable within the individual

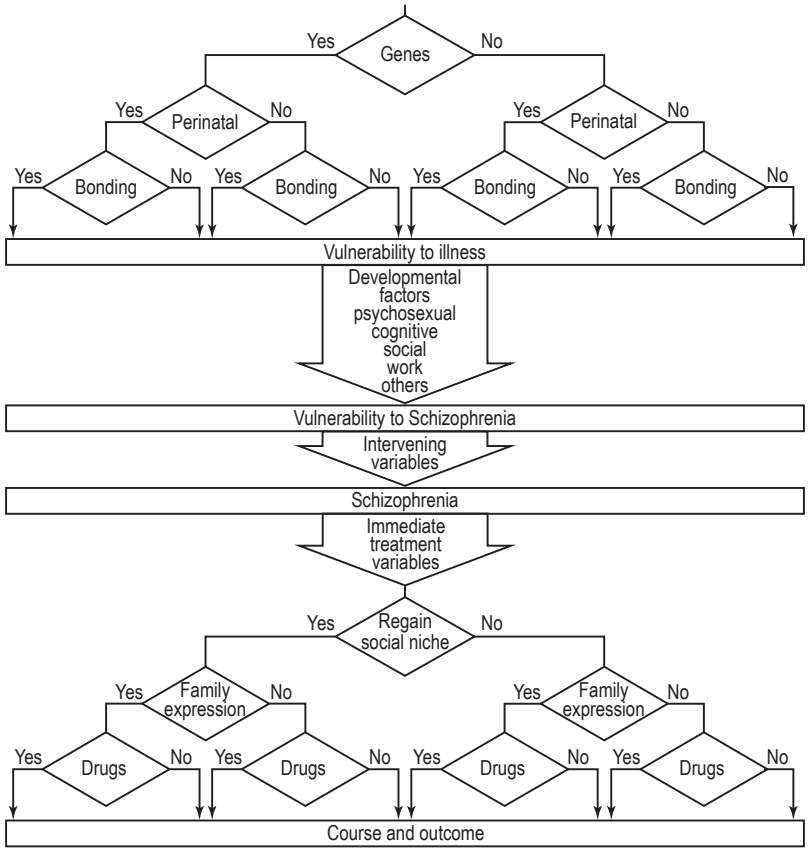

Figure 3.1 Schema for an interactive developmental systems model of schizophrenia; reprinted from Strauss and Carpenter (1981) with permission from Springer Science+Business Media B.V.

and many features are shared across the subtypes. A more robust approach has been to subdivide schizophrenia according to dichotomies, for example, reactive versus process schizophrenia, acute versus insidious onset schizophrenia, and good versus poor prognostic schizophrenia. These subdivisions were robust from a premorbid and course of illness perspective. Shortcomings, however, include (a) the failure to validate the etiological implications of the process and reactive dichotomy, (b) presuming that insidious and acute referred to the nature of onset of the same disease rather than distinguishing separate etiopathological pathways, and (c) conceptualizing a poor developmental pattern as prognostic rather than as an early manifestation of a syndrome subgroup.

These earlier attempts failed to establish a strong candidate disease entity within the schizophrenia syndrome. More recently, investigators at the Maryland Psychiatric Research Center segregated schizophrenia into a subgroup with

and a subgroup without primary negative symptoms. Hypothesized as a disease entity, several lines of evidence support this proposition (Messias et al. 2004; Kirkpatrick et al. 2001).

Deficit schizophrenia systematically differed from schizophrenia without primary negative symptoms on a range of variables, including epidemiological risk factors and aspects of neuroimaging and postmortem tissue analysis. However, while using a single domain of pathology to reduce heterogeneity in the deficit subgroup, it fails to address heterogeneity in the larger nondeficit subgroup. The hypothesis that deficit schizophrenia has a distinct etiopathophysiology that leads to psychosis (i.e., different from the pathway to psychosis in nondeficit cases) is interesting, but it may not be as robust as a construct that views negative symptoms as, or along a continuum of, a domain of psychopathology. This alternative interpretation—that primary negative symptoms are a domain of pathophysiology rather than necessarily marking a different pathway to psychosis—may offer a stronger heuristic approach. In this context, negative symptoms represent an independent variable in study designs. Domains of psychopathology form the primary target for etiological, pathophysiological, and therapeutic discovery (Carpenter et al. 1988; Carpenter and Buchanan 1989).

This explanation was advocated in 1974 with negative symptoms, positive symptoms, and pathology observed in the interpersonal sphere as three candidate domains (Strauss et al. 1974). This framework was prompted by Strauss, who considered dimensions as alternatives to categorical classification (Strauss and Carpenter 1975; Strauss 1969).

In recent years, this approach has gained traction with domains of cognition and negative symptoms being identified as critical unmet therapeutic needs. The DSM-5 Psychosis Work Group has pursued the deconstruction paradigm in parallel with categorical classification. Based on prior evidence for the utility of a dimensional approach to schizophrenia (Strauss et al. 1974; Peralta and Cuesta 2001; Cuesta and Peralta 1995), DSM-5 describes eight dimensions in Section 3, each conceptualized as a domain of psychopathology important to psychotic illnesses, but varying in manifestation in subjects within each of the relevant syndromes. The psychopathology domains, rated from 0–4 for severity, are: delusions, hallucinations, disorganized thought, psychomotor abnormalities, restricted affect, avolition, depression, mania, and cognition impairment. This paradigm raises the possibility of identifying a range of pathologies as the target of investigation with a diagnostic class being involved for general relevance; however, the domain of pathology has specific relevance. Here one seeks genes for, say, depression across diagnostic classes rather than genes for major depression disorder, or for reality distortion across syndromes rather than for schizophrenia as defined by reality distortion. There is potential here for a dramatic reorganization of scientific enquiry.

Four Paradigm Shifts to Consider

Heterogeneity characterization is involved in the first three paradigms that will be discussed whereas the fourth involves staging.

The first paradigm views disease entities within the syndrome as independent variables rather than schizophrenia at the syndrome level. In a sense, this is an old and frequently tried paradigm that has not been very productive. The traditional subtypes have not provided a strong heuristic approach. Patients often have features of several subtypes, and symptoms and subtype presentation can vary significantly across psychotic episodes in the same person. Other approaches have been more closely associated with course and prognostic variables (e.g., good vs. poor prognosis, process vs. reactive). These dichotomies have lost traction as subgroups for two related reasons. First, the tautology between predictor and predicted became evident: asociality prior to psychosis predicts asociality after psychosis, prior occupational function predicts future function, etc. Second, many factors associated with prognosis are now conceptualized as early morbid manifestations of the disorder, not independent moderator factors. Prominent in more recent work within this paradigm is the development of deficit schizophrenia as a putative disease entity. This subgroup appears validated by factors associated with etiopathophysiology. However, separating deficit schizophrenia from other schizophrenia leaves the larger cohort without precise defining features, and the number of disease entities that remain is not known. Despite modest progress to date, future research within this paradigm is expected to be more robust when the syndrome can be subdivided based on biomarkers. The term "biomarker" refers to variables robustly associated with a pathology that results in a more valid grouping of cases. Increased homogeneity at the biological level is assumed, but biomarkers may be derived from any level of functioning (e.g., genetics, physiology, cognition, behavior).

Consider now a second paradigm based on deconstructing the syndrome into psychopathology domains. The fundamental assumption here is that symptom/sign complexes can be defined with greater homogeneity, and dependent variables may relate to a domain rather than to all subjects in a syndrome cohort. From a clinical perspective, psychopathology domains represent the evaluation and treatment targets that clinicians address. This paradigm calls for ascertaining the domain of interest in each subject and shifts the discovery process in the direction of psychopathology across diagnostic boundaries. From a drug discovery perspective, each domain can now be viewed as a potential indication for regulatory approval. In this framework, investigators will seek gene associations for depression, reality distortion, or psychomotor abnormalities either within the syndrome, by identifying specific cases, or across disorder boundaries. DSM-5 introduces in Section III a series of psychopathology domains to be used as dimensions across psychotic disorders.

The third paradigm calls for a more aggressive integration of neuroscience and behavioral science to identify behavioral constructs that have specific relationships to neural substrates; as such, they constitute the independent variables needed to address fundamental mechanisms as they relate to pathophysiology at the neural circuit level. Here it is assumed that several behavioral constructs are related to psychopathology (e.g., impaired positive valence in anhedonia related to depression). NIMH has prioritized moving research in this direction, cutting across diagnostic boundaries and levels of severity.

The fourth paradigm, which relates to staging, assumes that several pathways are involved in the formation of a general vulnerability toward mental disorders (see Cadenhead and de la Fuente-Sandoval as well as C. Morgan et al., this volume). During development, other factors may determine the direction taken in progression toward a diagnosable disorder. At the first stage, there may be very broad sharing of risk factors. Moving toward a particular disorder in the second stage may involve a more discrete set of variables. A third stage relates to the onset of a disorder or of psychopathology domains. Finally, still other factors may be involved in altering the course once a disorder is present. In this paradigm, investigators need to determine the stage of the independent variable and create evidence that bears on the development of features at that stage. The first two stages are particularly relevant to primary and secondary prevention as well as to the study of resiliency.

Two projects are nearing completion and will be influential in shifting research focus to domains of pathology or behavioral constructs:

1. DSM-5 and dimensional ratings of symptom domains across psychotic disorders. Hallucinations, delusions, disorganization of thought, restricted affect, avolition, psychomotor abnormalities, cognition, mania, and depression are specified in Section 3. These domains require clinical evaluation and treatment, but can also impact on discovery by orienting science away from syndrome and toward individual domains of pathology (e.g., cognition, mood, arousal, motor functioning). For instance, we think that the Food and Drug Administration in the United States and other regulatory bodies will recognize the domains as a consensus in the field and consider them as indications for drug approval. In time this may extend to include several disorders in clinical trials based on sharing the domain of interest. Already in place are methods for addressing cognition and negative symptoms in the context of schizophrenia (Buchanan et al. 2005; Kirkpatrick et al. 2006).
2. RDoC, with its elaboration of five behavioral constructs and related neural circuit substrates, represents NIMH's tactical approach, consistent with their strategic plan to develop information on pathophysiology at the neural circuit level for mental disorders. It is a direct repudiation of discovery based on clinical syndrome classification. Nonetheless, it will be essential to relate the behavioral constructs to specific clinical

manifestations of disorders. Guidelines for this translation are currently being developed.

For purpose of illustration, five behavioral constructs with demonstrated links to psychopathology are shown in Table 3.1. Methods are currently being developed to integrate the two approaches discussed above.

The deconstruction of schizophrenia according to the DSM-5 domains of pathology framework and RDoC behavioral construct/neural circuit framework and integration into clinical and preclinical study designs will change the acquisition of knowledge in the near future. The first paradigm shift, which identifies putative disease entities within the schizophrenia syndrome, will be available as biomarkers gain traction in separating a subgroup from the whole. Recent illustrations involve latent class analysis in gene association studies, where candidate genes appear to separate a deficit form of schizophrenia from other subgroups (Fanous et al. 2008; Holliday et al. 2009).

The fourth paradigm shift has been introduced for clinical therapeutics, where the nature of interventions are different for various stages, for example, prodromal, first psychosis, impaired cognition addressed during clinical stability, rehabilitation of functioning in chronic stages, etc. (Hogarty et al. 1995; McGorry et al. 2010). Moving this paradigm for discovery involves reconceptualizing the schizophrenia psychopathology. Rather than a clinical syndrome that evolves over time, the paradigm suggests that early risk factors may produce a general vulnerability for mental dysfunction. Later risk factors may shape the development of disorders where schizophrenia is only one of perhaps many disorder outcomes. Once a particular disorder is present, the focus of study may evolve from primary etiological and preventive factors to secondary

Table 3.1 Examples of behavioral constructs with demonstrated links to psychopathology (courtesy of Bruce Cuthbert, NIMH).

1. Negative Valence Systems • Acute threat (“fear”) • Potential threat (“anxiety”) • Sustained threat • Loss • Frustrative nonreward	3. Cognitive Systems • Attention • Perception • Working memory • Declarative memory • Language behavior • Cognitive (effortful) control
2. Positive Valence Systems • Approach motivation • Initial responsiveness to reward • Sustained responsiveness to reward • Reward learning • Habit	4. Systems for Social Processes • Imitation, theory of mind • Social dominance • Facial expression identification • Attachment/separation fear • Self-representation areas
5. Arousal/Regulatory Systems • Arousal and regulation, multiple • Resting state activity	

prevention. At each stage of disorder development, resiliency factors as well as causative/promotional factors are relevant (see Figure 3.1 for a representation of staging; Strauss and Carpenter 1981). Current studies that report, for example, overlap in candidate genes between schizophrenia and bipolar disorder would be reconceptualized in this staging paradigm as genes contributing to vulnerability to mental disorders, whereas candidate genes unique to each disorder would be conceptualized at the stage of a vulnerable individual developing a specific disorder.

The above paradigms relate to methods for obtaining knowledge on etiology, pathophysiology, prevention, treatment, and cure. Another shift in concept, perhaps paradigm, may be additive or synergistic with the above. This relates to concepts of resiliency and compensatory processes. As the disorder develops in any individual, a series of adaptive challenges unfolds. Attempts to prevent or repair dysfunctional mechanisms are central to prevention and therapeutics. An alternative view relates to determining how individuals successfully cope with impairment and reinforce natural strengths and/or determine how compensatory mechanisms can be enhanced.

Conclusion

Conceptualizing schizophrenia as a disease has impeded the acquisition of knowledge because of the heterogeneity of individuals with the diagnosis and the clinical syndrome status of the disorder. Four paradigms are currently available and may accelerate discovery in the near future by addressing heterogeneity. These paradigms identify subgroups as putative disease entities using psychopathology or biomarkers, deconstruct the syndrome into psychopathology domains, use behavioral or neural circuits as independent variables, and reconceptualize the development of mental disorders in stages, progressing from general vulnerability to more specific psychopathology outcomes. An additional consideration addresses personal characteristics and compensatory mechanisms that enable an individual to minimize illness effects and progression. It is expected that advancing knowledge on etiology and pathophysiology will provide a basis in the future for substantial reconsideration of the classification of mental disorders and the schizophrenia construct.