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Which Aspects of Heterogeneity Are Useful to Translational Success?

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Abstract

Schizophrenia brings challenges of heterogeneity at multiple levels related to symptomatology, behavior, outcome, genetics, and pathophysiology. The clinical disorder may capture more than one disease mechanism, which has certainly been an impediment to research progress. This chapter summarizes discussions on the utility and problems of the current, syndromal diagnosis. Three potential conceptual paradigms for addressing the heterogeneity problem in schizophrenia are identified and discussed, as are the potential opportunities and challenges for future research using these conceptual frameworks.

What Do We Mean by the Schizophrenia Construct?

Schizophrenia is a common disorder with significant personal, medical, and societal implications. Diagnosis is based on observed behavior, the duration of symptoms, and impaired functional outcomes. Many clinical symptoms are described in schizophrenia but the core clinical symptom domains are delusions, hallucinations, disorganized speech, disorganized psychomotor behavior, and negative symptoms (e.g., avolition). This categorical diagnosis is operationalized in current classification systems by the World Health Organization (ICD-10) and the American Psychiatric Association (DSM-5).

The schizophrenia construct, originally termed dementia praecox, emerged from the work of Kraepelin in the late nineteenth century (see Carpenter, this

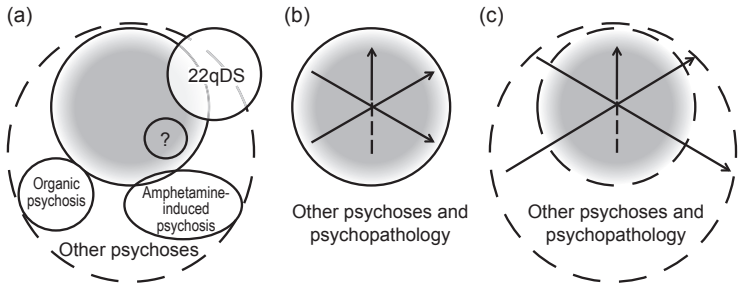

Figure 5.1 Three models of the schizophrenia construct, delimited in gray: (a) categorical heterogeneity, (b) internal dimensional heterogeneity, and (c) broadly dimensional heterogeneity. Each model suggests a different research agenda to make progress in understanding the disorder.

volume). Kraepelin proposed a unifying pathological process for a putative disease state that involved avolitional and dissociative psychopathology and poor clinical outcome. Modern classification was influenced by the subsequent work of Bleuler, Schneider, and others with some shifting from the original concept. A reliable approach to the definition of schizophrenia has emerged. However, the boundaries of this construct are not the same as those of the original construct, where there is a shift in emphasis away from the combination of negative symptoms and thought disorder toward reality distortion symptoms (i.e., hallucinations and delusions).

A diagnosis based on specific etiology and pathophysiology defines a disease entity and is a closed construct (Figure 5.1). In a closed construct, membership is defined by necessary and sufficient conditions. In contrast, a diagnosis in the absence of this knowledge is more appropriately described as a disorder or syndrome and, as such, constitutes an open construct that may comprise a number of diseases not yet specified by etiopathophysiology, with potential overlap between signs and symptoms of these and other diseases. In either case, clinical diagnosis can be based on specific criteria predicated on symptoms, onset, and course through which clinicians understand disorder prototypes. Matching an individual patient to the most likely prototype provides a differential diagnosis. Within the open, syndromal construct of schizophrenia, there are at least some identifiable closed constructs or specific disease entities, such as a small subgroup of patients defined by the presence of genetic etiology based on 22q11.2 deletions (Murphy 2002).

What Have We Learned from the Schizophrenia Construct?

An experiment is a question which science poses to Nature, and a measurement is the recording of Nature's answer.—Max Planck (1949)

For a century, there has been an ongoing debate about the utility of the schizophrenia construct. It is well to bear in mind the assessment of this long-running debate made by Karl Jaspers (1946/1997:567): "For many years the border between manic-depressive insanity and dementia praecox has vacillated considerably in a kind of pendulum movement without anything new emerging." Jaspers recognized the difficulty of precisely defining the border between these conditions, and he acknowledged the near-impossibility of deciding on a diagnosis in certain cases. He did not, however, doubt that there is something valid about this distinction to which we seem always to return, writing that "there must be some kernel of lasting truth not present with previous groupings" (Jaspers 1946/1997:568).

Diagnostic approaches for schizophrenia in DSM and ICD provide a basis for reliable classification of cases. The current, open construct, syndromal definition of the disorder has been validated by evidence at the genetic, physiological, brain imaging, psychological, social, and epidemiological levels (Keshavan et al. 2008; Tandon et al. 2008). Using these classification systems, groups of cases can be distinguished from comparison groups (usually non-ill controls) on variables such as:

- a family history of schizophrenia and other mental disorders,
- genetic risk factors,
- paternal age,
- a history of prenatal insult,
- perinatal complications,
- neurodevelopmental deficits,
- childhood abuse,
- cognitive deficits,
- structural or functional brain differences, and
- physical health issues (e.g., reduced insulin sensitivity).

Despite robust group differences, diagnostic biomarkers with sensitivity and specificity for classification of individual patients have not yet been developed.

The schizophrenia construct also defines a patient group which has particular needs. This has been important in the development of treatments, in particular in the development of antipsychotic medication for the treatment of positive symptoms (Leucht et al. 2011) as well as in the development of a number of psychological (Wykes et al. 2008, 2011) and psychosocial interventions (see Mueser, this volume) that have focused on improving functionality and the promotion of recovery. In addition, the significant personal, family, public health, and societal consequences of schizophrenia are enormous and have implications from the level of individual patient care to health policy. People with schizophrenia have reduced life expectancy (17–25 years across available international studies; Hennekens et al. 2005; Tiihonen et al. 2009; Kilbourne et al. 2009; Chang et al. 2011), substantial comorbidities (Carrà et al. 2012), increased rates of homelessness and incarceration (Foster et al. 2012), and high

levels of unemployment and impoverishment of social roles (Salkever et al. 2007). Further clarification of the disabilities produced by schizophrenia is necessary, as, to date, this information has had only a minimal impact on advocacy, peer support, and healthcare planning and provision.

Despite more than a century of research, our understanding of the biological basis for schizophrenia is limited. If there is a core disease entity, this is unlikely to map neatly to clinical boundaries based on behavior, symptom duration, and impaired functioning. Furthermore, there is marked variability in clinical presentation within the schizophrenia syndrome. Any two given patients may share no symptoms at all, at least as defined according to standards, and thus have very different courses of illness. Therefore, it is reasonable to ask whether the construct of schizophrenia has been useful or an impediment to research and treatment. Next we raise challenges to the use of the schizophrenia construct and propose ways in which the construct continues to be useful.

Is the Construct Useful or an Impediment to Translation?

Schizophrenia poses challenges of heterogeneity at multiple levels (Figure 5.2). No two patients with this diagnosis present similarly to the clinician: symptom constellations and behavioral abnormalities vary between individuals, and often even within individuals across time points (clinical and behavioral heterogeneity). The pathophysiological substrate of the illness varies between individuals: although the various biomarkers differ between patients with schizophrenia and healthy subjects, considerable overlap exists and none of them is present in the vast majority (pathophysiological heterogeneity). Finally, etiological factors have been proposed (most notably genetic factors), but none is necessary and sufficient for disease causation. The limited progress in developing pathophysiological and etiological understanding of schizophrenia is often attributed to such heterogeneity.

This issue squarely raises the question as to whether, or to what extent, the construct of schizophrenia is useful or constrains further progress in understanding the diagnosis, etiology, treatment, or even prevention of the syndrome. The fact that schizophrenia does not have a set of necessary and sufficient criteria leads to considerable differences of opinion as to its origins, and disagreement regarding proper treatment. To some degree this may lead to confusion and misperceptions by others outside the field. However, this must be viewed in the context of treatment gains that have been made based on pharmacological, psychological, and social interventions. An argument has been made that the schizophrenia construct is stigmatizing. In some countries, such as Japan, an attempt has even been made to change the name of the disorder (Sato 2006). Society rather than biology determines how we respond to people with mental illness. Based on experience from other areas (e.g., mental retardation or learning disabilities), where the establishment of a new nomenclature

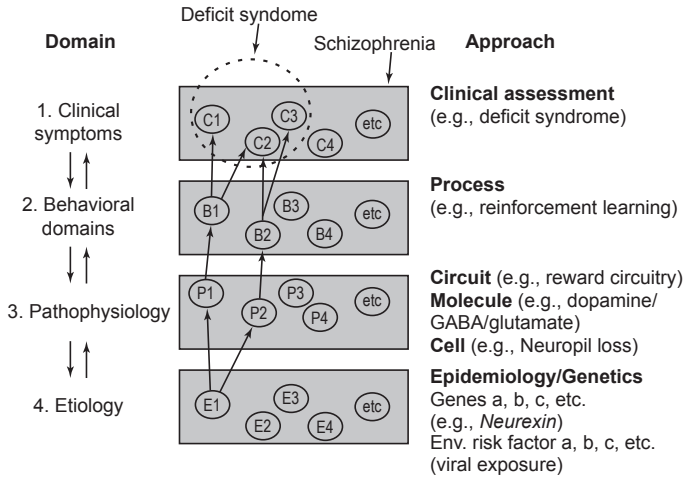

Figure 5.2 Modeling schizophrenia at the level of clinical symptoms (C), behavior (B), pathophysiology (P), and etiology (E). The figure indicates how future research could be integrated across different levels of analysis.

did not result in treatment improvements or outcome, we feel that changing the name is unlikely to resolve the problem.

The current definition, which is based on Kraepelin's proposition for a unifying pathological process, assumes that schizophrenia is a single brain disease. However, there is much evidence to suggest that schizophrenia is not a single disease entity. What is far from clear is the extent to which the current definition of the syndrome captures all relevant disease entities, how many diseases there might be, and, if there are many, whether these represent one or more distinct pathological processes.

Diagnosis has been useful, as it allowed specific treatments to be applied to groups of people who share (at least some) similar features and permitted these interventions to be evaluated. However, it is increasingly recognized that diagnosis has limited utility, that new ways of conceptualizing the disorder(s) are needed, not least to aid the development of more effective treatments. For example, there is substantial variability between patients with schizophrenia for measures of cognitive impairment, positive symptoms, negative symptoms, disorganization, and insight into the nature of their condition. In addition, many people with schizophrenia have comorbid conditions, such as mood disorders, anxiety disorders, and substance abuse, that are often not assessed in clinical practice but can significantly affect outcome. The overemphasis on the development of dopamine antagonists/antipsychotics for the treatment of positive symptoms has resulted in important unmet therapeutic needs (i.e., cognitive impairments, negative and anxiety symptoms) for which these agents have limited, if any, benefits. The use of dimensional measures of psychopathology has been helpful, for example, in fostering the development of psychological

interventions that target specific symptoms (e.g., cognitive behavioral therapy for persistent positive and negative symptoms, cognitive remediation for cognitive impairments). Given the evidence for certain subgroups within the disorder of schizophrenia (e.g., deficit syndrome), there are likely to be better ways to engage with and address treatment heterogeneity; however, the etiological bases for this remain to be determined.

A further criticism of the syndromal diagnosis is that it is potentially too simplistic in operationalizing complex phenomenology. The experience of psychosis needs to be seen in the context of the person and his/her environment, as this may define the experience of symptoms. The converse is also true in that at a symptom level, a delusion involving perceived harm by others may have quite a different quality and treatment implications than a delusion involving the control of movement by an external entity. For example, the biases in attribution and jumping to conclusion style that is characteristic of paranoia (Lyon et al. 1994; Moritz et al. 2012) have proven amenable to cognitive behavioral therapy (Chadwick et al. 1996), with its emphasis on behavioral experiments and examination of evidence for and against different ideas. On the other hand, it has been proposed that delusions involving control of movement and self-representation in space, including passivity phenomena, may result from visual processing disturbances (Landgraf et al. 2012), suggesting that an improvement in visual functioning might prove beneficial in addressing these delusions. Dimensional measurement may help in this regard and has been recognized in the diagnostic revisions for schizophrenia made in DSM-5.

The dimensional approach also comes with the potential challenge of pseudospecificity. For example, a number of studies have demonstrated that negative symptoms significantly improve when antipsychotic medications are administered to people in the midst of an acute episode of the illness. However, these beneficial negative symptom effects have been shown to be secondary to the primary effect of antipsychotic medications on positive symptoms. In follow-up studies, when the same agents have been used to treat clinically stable people with schizophrenia with persistent negative symptoms, only limited benefits for this aspect of the illness have been observed.

For the clinician, the syndrome is useful in identifying the wider treatment challenges, where a simpler psychosis construct would not. The emphasis on functional impairment and duration of symptoms, although arbitrary and even if they are perhaps the most relevant dimensions from a clinical perspective, brings into focus a group of patients who are likely to have enduring mental health problems and require planning for future care delivery.

Despite some progress, and as noted by Carpenter (this volume), progress in finding the causes of schizophrenia has been slowed by including what appear to be several heterogeneous syndromes in the same group in most of schizophrenia research. The problem is becoming more apparent as the armamentarium of investigative methods expands. Schizophrenia is a “black box” with a fuzzy boundary definition. We do not have sufficient evidence to replace

the definition with constructs incorporating newer neuroscience or cognitive-based theories, such as "failure of neuroconnectivity syndrome"or "social and cognitive deficit disorder." We can certainly alter the dimensions of the "box," but in the absence of empirical evidence, we cannot know whether it is more useful to widen or narrow the diagnostic criteria. Findings from schizophrenia genetics illustrate this point.

From genetic epidemiology, we can define a family of schizophrenia spectrum disorders which share many of the group features of schizophrenia previously described (Kendler et al. 1993). It is well established that many of these group features (e.g., imaging, electrophysiological, and cognitive variables) extend to family members with no psychiatric diagnosis. More recently, large register-based population cohorts indicate clustering of other psychiatric disorders, including bipolar disorder, depression, and autism in the families of schizophrenia patients (Lichtenstein et al. 2009; Mortensen et al. 2010; Sullivan et al. 2012b). These data suggest significant fusion or overlap of the boundaries across a number of psychiatric diagnostic categories. This sharing could relate to a shared core pathology, a shared noncore pathology (e.g., anxiety), and/or a pre-disorder vulnerability platform shared by both disorders or nonpathological confounds (e.g., lifestyle factors more common to these groups). Evidence from molecular studies (e.g., genome-wide association studies) provides empirical support, at least for the overlap of common, small (odds ratio <1.3) genetic risk factors between schizophrenia and bipolar disorder (International Schizophrenia Consortium 2009). Molecular studies have also revealed a series of rare structural genomic variants (copy number variants, CNVs) of larger effect on risk (odds ratio 3–20) in a subgroup of patients (for a review, see Malhotra and Sebat 2011). As was the case with 22q11.2 deletion syndrome, the newer risk CNVs (e.g., deletions at 1q21.1, 3q29, 15q11.2, and duplications at 16p11.2 and 16p13) all show evidence of pleiotropy. This means that each CNV has variable influences on multiple phenotypic outcomes (e.g., schizophrenia, autism, intellectual disability, epilepsy, and obesity).

The critical question in genetics is how to translate these findings into an etiological understanding of schizophrenia. The heterogeneous population identified by the DSM-IV and ICD-10 criteria represents potentially many different pathophysiological or etiological processes. With no clear strategy to reduce heterogeneity, disambiguating the statistical association with small effects in large numbers of subjects or large effects in very small groups is challenging. Investigating genetic findings requires an ability to validate these findings using other paradigms (e.g., animal models). To do this requires some understanding of which heuristic framework to use to account for heterogeneity optimally (for further discussion, see Williams and Gott, this volume). The current genetic data is insufficient to support widening the schizophrenia construct into a broader "neurodevelopmental disorder" construct. However, CNV findings challenge us to ask if having a pathogenic mutation of, for example, a

gene like *Neurexin-1* (Rujescu et al. 2008; Kirov et al. 2008) or *VIPR2* (Vacic et al. 2011) independently affects risk of autism and schizophrenia, or whether the mutation impacts a neurodevelopmental mechanism which can have as its consequence either autism or schizophrenia, or some features of both. These rare forms may represent discrete disease entities within the syndrome or diseases that overlap with the syndrome. Under the current criteria, schizophrenia is diagnosed by exclusion of cases with known medical etiology. How will these new genomic disorders shape diagnostic practice? In our view, to restrict the syndrome of schizophrenia by excluding novel genomic disorders, which may be etiologically informative, appears unhelpful.

Paradigms for Addressing the Heterogeneity Problem in Schizophrenia

> Measure what is measurable and make measurable what is not. —attributed to Galileo (1564–1642)

The challenge facing our field is to develop paradigms in addition to a diagnosis that address the significant heterogeneity and provide more robust approaches to etiology, pathophysiology, prevention, and therapeutic research. Heterogeneity is not a problem unique to schizophrenia. Cancer serves as a useful analogy. In the case of breast cancer, diagnosis was initially made according to phenotypic features (e.g., tumor node, metastases); later classifications included histological grading (based on tumor cell differentiation) and even more recently include underlying causes and mechanisms (e.g., those with known genetic causation, those with altered estrogen receptor sensitivity). Throughout all of this, the concept of cancer still remained and the field happily accepted diagnostic pluralism, with all three approaches to classifying the disease being used as needed for the appropriate purposes. At the molecular level, it is interesting to note that some cancer centers conduct DNA sequencing on the tumor tissue of every individual patient and use this to inform treatment; this suggests a unique disease entity for each person. Here, heterogeneity alone was not a barrier to improving nosology and treatment.

Investigating disorders of the brain naturally presents additional challenges. However, progress has been made for brain disorder syndromes, including epilepsy and intellectual disability. In the case of schizophrenia, we are hampered by the lack of an objective measure or biomarker for defining individual cases of the disorder. In the absence of specific markers or pathology, what may be most relevant at this stage are paradigms with a strong evidence base that optimize discovery, treatment, and patient care by reducing heterogeneity. Meeting the standard principles of scientific measurement and addressing differences in study design, research measures, and research settings are general challenges to any new paradigm. We recognize that discovery is an iterative process and that useful paradigms must be sufficiently flexible to allow new hypotheses

to be challenged and incorporated or rejected as we try to understand the syndrome. This will require integration across levels of analysis and disciplines. In a wider sense, to bring about advances in neuroscience and other disciplines to bear on the study of schizophrenia, we need to have greater interaction across research disciplines to improve discovery.

We have identified three potential conceptual paradigms for considering schizophrenia (see Figure 5.1). The first model (Figure 5.1a) represents categorical heterogeneity. In this case the open construct of the syndrome can be parcellated into different, identified closed constructs. These can stay within the syndrome for further research (e.g., novel 1q21 deletions or future disease entities) or can be "carved out" from the construct once a medical cause is elucidated (e.g., syphilis as a cause of psychosis). Currently, closed constructs would be removed from the syndrome in this model if they have the symptom criteria but fail the etiological rule-out or symptom duration specifier for schizophrenia (e.g., amphetamine-induced psychosis). Whether this approach is helpful for studying etiology or pathophysiology may require further consideration, although it is a clinically useful distinction. To take another example, many neurodevelopmental syndromes (e.g., verbal and nonverbal learning disabilities) can include features found in schizophrenia such as negative symptoms, disorganization, poor social cognition, and visual processing impairments (see the discussion on comparative studies in Silverstein et al., this volume), features that are not generally considered in the diagnostic criteria for these syndromes. This has led to a relative lack of potentially useful studies comparing, for example, schizophrenia and neurodevelopmental syndromes on their similarities and differences in etiology, course, and phenomenologies. Here, clinical but not research utility has been served. As more is understood about the genetic etiology of intellectual disability syndromes (many are associated with well-characterized genetic mechanisms), these could be conceptualized as potentially useful schizophrenia models. The defining characteristic of this model is that heterogeneity is reduced by identifying and separating different categories within the schizophrenia construct.

In the second model (Figure 5.1b), we conceptualize dimensions within the schizophrenia construct. The internal dimensional heterogeneity model could include the dimensional constructs in, for example, hallucinations, delusions, depression, mania, disorganization of thought, restricted affect, psychomotor abnormalities, avolition, and cognition impairment. However, it could also accommodate other dimensions related to how the disorder presents (e.g., temperament or other personality dimensions). In contrast to the first model, heterogeneity within the construct derives from continuous factors, and identifying the heterogeneity is addressed by understanding these factors and accounting for them in treatment.

The third model (Figure 5.1c) is similar to the second, but allows for extension of the dimensions beyond the core syndrome and could include traits (e.g., in related psychotic disorders) that vary on a continuum in the general

population (e.g., anhedonia, paranoia, psychosis) (van Os et al. 2009). This model emphasizes broadly dimensional heterogeneity and is similar to the Research Domain Criteria (RDoC) approach, which includes dimensional measures of behavioral and neural circuit response (e.g., negative valence systems or arousal/regulatory systems). An extension would be to see this model within a broader platform of risk states (e.g., high-risk studies for schizophrenia or the concept of a pluripotent risk state). Again this could include aspects of normal variation (e.g., lability, introversion, alienation). In contrast to the second model, heterogeneity within the construct of schizophrenia is thought to be related to continuous factors that are also operative in other conditions. From this perspective, heterogeneity within schizophrenia informs and is informed by symptoms and individual differences found in other psychiatric disorders and in the general population.

Working with These Paradigms

A key purpose of developing new paradigms is to facilitate analysis across disciplines and at multiple levels to maximize discovery. There are examples from the literature where including this second dimensional level of measurement has proved helpful for analysis across disciplines (e.g., with the deficit syndrome concept). We propose a framework that involves four levels of analysis: clinical symptoms, behavior/cognitive domains, pathophysiology, and etiology (see Figure 5.2).

This is a multidirectional framework, in which there is integration across analyses. We suggest that this framework could be helpful in allowing more collaboration between clinical research in patient populations and basic scientists working with model systems. This framework is similar conceptually to the RDoC but is less constrained.

Such an approach generally emphasizes the building of associations between two levels of analyses (e.g., a pathophysiological process and a behavioral measure). There are additional examples where research reaches across three levels of analysis; for example, transgenic mouse models which examine both the pathophysiological consequence of a mutation and alterations in behavior, or human neuroimaging studies which link activation abnormalities to impaired cognitive processes and symptoms. These links are generally tested using as few variables as possible to avoid multiple comparisons.

In addition to collecting data across multiple levels of analyses, a newer generation of statistical and data-mining algorithms have opened up new ways to examine these data. There are, for instance, increasingly viable methods to examine relationships across multiple levels of analysis using many variables at once. Procedures such as *independent components analysis* can be used to sort large matrices of data into simpler covariance structures. Such correlational links can provide important targets for understanding causality,

particularly in cases where multiple pathways can be examined and compared. In addition, a new approach to data-mining algorithms, known as *frequent pattern mining* (Ceglar and Roddick 2006; Han et al. 2007; Tan et al. 2005), has been developed for just these kinds of problems across a number of areas in industry and science. Frequent pattern mining has a solid theoretical foundation derived in part from formal concept analysis (Ganter et al. 1999), and it now has a number of efficient algorithms which seamlessly incorporate inferential statistics, intelligent algorithms, data reduction, and pattern-pruning strategies to maintain statistical power and increase computational efficiency, even when the number of variables and patterns considered is large (Fang et al. 2010, 2012). Such data-mining approaches provide another viable means for drawing together data across heterogenous data sets and extracting method-related variance to observe more clearly the relationships associated with potentially causal pathways.

Measured parameters may be defined, but these need to be validated and reliably measured using available technology. This will change, in some cases rapidly. For example, there are opportunities to develop level 1 assessment tools for symptoms, psychological or phenomenological states through the Internet or mobile phone interfaces. These could provide unprecedented access to "real-world" subjective phenomena in large patient samples.

At level 1 in the model, the investigator would define symptom domains of interest such as obsessive symptoms, avolition, or thought disorder. This would enable more specific and robust investigation of the phenomena at levels B (behavioral), P (pathophysiological), and E (etiological). A symptom domain may identify a subgroup of interest as illustrated by using primary negative symptoms to separate deficit schizophrenia from nondeficit schizophrenia with substantial differences between the two groups at levels B, P, and E. Based on phenomenological exploration, there is also the potential for discovery of more subtle but perhaps more decisive dimensions or matrices of subjective experience. For example, this could be based on disturbance of the "minimal self" or "basic self" sometimes termed "ipseity" (the basic sense, usually implicit, of existing as a subject of experience or as an agent). It might also target the closely related issue of fundamental temporal structuring of experiences. In turn, this could generate hypotheses for testing at level 2 or 3, by examining psychological processes or normal circuits subserving self-experience temporality or interconnected processes of motivation and emotion.

At level 2, there is the possibility of investigating how process relates to clinical symptoms (level 1) as well as to circuitry (level 3). Level 2 is an important intermediate level which might also be understood as a relay between pathophysiological processes and clinical symptoms. Taking reinforcement learning as one example, a level 2 behavioral process might translate into different clinical symptoms, such as depressive mood, perseveration, or risk-taking behavior. On the neural level, disturbances in an orbitofrontal-limbic-striatal circuit are supposed to mediate reinforcement learning (Cools et al.

2002; Remijnse et al. 2005). However, differential activation (hypo- or hyperactivation) has been associated with the anticipation of and response to reward or punishment, or the switch of one's own behavior according to the feedback (e.g., Linke et al. 2012; O'Doherty et al. 2001). Therefore, a neural systems perspective which spares the currently ongoing behavioral/cognitive process would not solve heterogeneity in observed neural activation patterns in, for example, schizophrenic patients and related psychopathologies. We would hence argue that experimental investigations should not focus on one single level of analysis but acquire data on clinical symptoms (C) as well as on psychological (B) and pathophysiological (P) processes. The accurate measurement of the different domains, which implies thorough operationalization according to principles of test theory (i.e., validity and reliability), is indispensable for such an approach. With fast developing utilities of, for example, machine learning algorithms and clustering methods, we should be able to challenge an integrative analysis of these different levels in the future. With common correlational approaches, multimodal data can be related even to date.

An example at Level 3 is the recent implication of alterations in gamma oscillations, which reflect aberrant synchronization of neural activity in parvalbumin-positive cortical GABA neurons as underlying executive function and working memory impairments in schizophrenia (Gonzalez-Burgos et al. 2011).

At level 4, we could identify a novel genetic risk factor and use this to identify molecular subgroups within the schizophrenia syndrome to be examined multifactorially at levels 1–3. At a physiological level, we could investigate at a molecular or circuit level using neuroimaging approaches, but also at a cellular level using animal systems or human-induced pluripotent stem cells from patients who carry a particular risk factor. The same types of human and animal experimental work can be applied to investigate at a behavioral domain and clinical symptom level.

To be effective, this approach relies on information sharing across groups and the development of large patient cohorts with information available on many parameters. This would allow for hypothesis generation using correlation analysis across levels of analysis in human subjects, which could then be validated in model systems. The reverse approach could also be applied, with wider availability of information on models from levels 2 and 3. The development of data sharing could be open source or through summaries of available measures by interested researchers. This could be provided at an "exchange" for potential collaborators.

Into the Future

The framework that we have suggested may be helpful in reducing heterogeneity in studies of schizophrenia. In this we call for multidimensional analysis. We wish to emphasize that this is not a standard call for large databases and

even larger international consortia. The potential application of this approach for standard statistical approaches, data mining, machine learning, or crowd sourcing may be apparent. We believe that this framework has the flexibility to allow individuals with creative ideas to examine novel hypotheses by bringing together unusual clusters of symptoms, risk factors, or other measures. These, in turn, can be tested across levels and validated to confirm or be discarded by a researcher so as to prioritize a more heuristically informative hypothesis.

The neurodevelopmental etiology of schizophrenia needs to be seen in the context of limited (current) understanding of the normal trajectory for neurodevelopment. Schizophrenia needs to be conceptualized in a developmental or staging context (Hickie et al. 2013; Wood et al. 2011). There is evidence for people at perceived high risk of schizophrenia, based on risk factors such as family history and being within the age of greatest risk. A subset of people will develop subsyndromal symptoms (e.g., anxiety or prodromal symptoms) while another will develop schizophrenia. These stages of the evolving illness may be determined in a temporal framework. For example, genetic and early environmental factors, such as viral exposure and periadolescent psychosocial stress, can serve as subsequent etiological "hits"; these etiological events may interact to produce the sequential evolution of pathophysiology and clinical features of the premorbid, prodromal, and psychotic phases of the schizophrenic illness (Figure 5.3). Epidemiological evidence suggests that a pluripotent risk state can be identified with a range of potential outcomes from a return to normal function to the development of the schizophrenia syndrome. However, better understanding of risk and resilience factors is needed to develop effective primary and secondary prevention strategies. Also required are prospective studies that examine interaction of risk and protective factors over time (for a discussion, see C. Morgan et al., this volume).

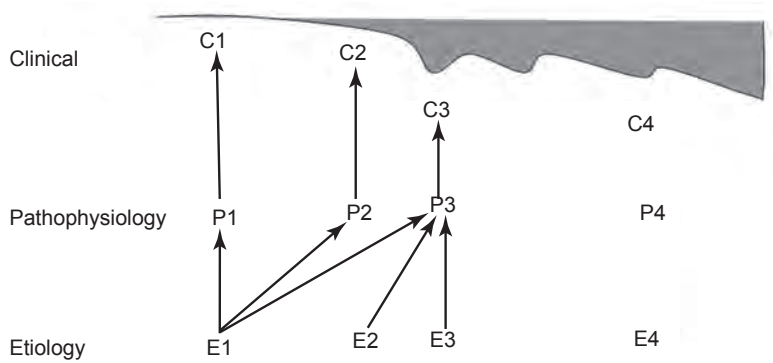

Figure 5.3 Representation of how different etiologies (E1, E2, etc.) could potentially contribute to different pathophysiology processes (P1, P2, etc.) with different clinical presentations across life span. This shows how etiological mechanisms may interact with each other and with brain development to influence a disease process.