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What Kind of a Thing Is Schizophrenia?

Specific Causation and General Failure Modes

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Abstract

The status of schizophrenia as a disorder has been controversial since its original description by Kraepelin and Bleuler. This chapter critiques a prominent theory of schizophrenia espoused by Meehl in 1962 that spurred a great deal of research into its genetic origins and subthreshold manifestations. In particular, a decade of findings on the meta-structure of mental disorders, the development and course of at-risk youth, and genetic epidemiology can be understood as direct challenges to the idea of a specific etiology for the disorder. Instead of a well-mannered diagnostic entity, schizophrenia and thought disorder more generally delineate a psychosis spectrum linked to a number of other psychiatric outcomes, including, but not limited to, bipolar affective disorder. In addition, studies of the cognitive impairments associated with the disorder show that a generalized deficit is a prominent behavioral feature of the disorder. This chapter concludes by noting that spectrum constructs do not preclude generating and testing falsifiable hypotheses. The use of a fault tree analysis, as employed in reliability engineering, may be helpful in delineating such hypotheses explicitly. This perspective gives rise to a new set of priority questions.

Introduction

Marilyn Monroe had just died under mysterious circumstances. John F. Kennedy announced that within ten years the United States would put a man on the moon. Back in the Kremlin, Nikita Khrushchev decided that within ten days the Soviet Union would position missiles in Cuba. In the midst of such tumult, the histories written about September 2, 1962, tend to overlook the

fact that a generation of genetic epidemiology, experimental psychopathology, and nosology was being inspired. A generally anodyne affair, the American Psychological Association's presidential address would be transformed this evening by Paul Meehl (1962). In his customary fashion, he managed to be both flamboyant and tightly argued. Neologisms—schizotaxia, schizotypy, and hypocrisia—were introduced. Rather than symptoms of thought disorder, they would enter the language with which we would think about schizophrenia and risk for schizophrenia. There is no hyperbole in claiming the speaker that night was one of the greatest thinkers about psychology and psychopathology of his generation, and even his century. He was also wrong.

Examining the way in which Meehl was wrong in his presidential address on schizotaxia, schizotypy, and schizophrenia allows us to approach a more intransigent question: What kind of a thing is schizophrenia? What kind of a thing is schizophrenia that it should afflict so many, across the world, irrespective of potential or position? What kind of a thing is schizophrenia that families are sundered and lives brought to a standstill or even ended? And, from a scientific perspective, what kind of a thing is schizophrenia that it might so deceive the insights of our clearest thinkers and scatter our efforts to understand it across all corners of the brain?

I begin by reviewing the theory espoused by Meehl to elucidate its dependence upon a specific etiological mechanism. Thereafter I draw together evidence from four domains, including work on the meta-structure of psychopathology, work on the development of the disorder, its course over time, and its genetic epidemiology. These data challenge Meehl's emphasis on a specific etiology by showing that schizophrenia may be best thought of as a syndrome that can be described as an open concept that is linked by correlational, rather than necessary or sufficient, relationships with various symptoms and with other forms of psychopathology. These findings are consistent with additional work on the cognitive neuroscience of schizophrenia which I will review. Finally, I suggest some ways to make progress when hypothesizing about syndromes.

A Legacy of Specificity and Falsifiability

A Falsifiable Hypothesis of Schizophrenia

From the podium that night, Meehl hypothesized that "the statistical relation between schizotaxia, schizotypy, and schizophrenia is class inclusion: All schizotaxics become, on all actually existing social learning regimes, schizotypic in personality organization; but most of these remain compensated" (Meehl 1962:832). Importantly, for this philosopher of psychology, the theory made predictions that were falsifiable. He hypothesized that few individuals with schizotaxia (carriers of a dominant schizogene) decompensated to such

a degree that they were diagnosed with schizophrenia. Schizophrenia, therefore, waited at the end of a probabilistic chain of events. The chain began with the inheritance of a dominant schizogene whose proximal effect was synaptic slippage, or hypokrisia. Synaptic slippage affected the organism in a number of different ways, including "soft" neurological and psychological signs, associative thought disorder, and an exaggerated experience of negative feedback. These dysfunctions were what then led to the schizotypal personality, as distinguished by loose associations, anhedonia, ambivalence, and interpersonal aversiveness.

While Meehl broadened the phenotypes that he saw as relevant to schizophrenia, he narrowed what he called the "etiological specificity" of schizophrenia. In this regard he followed closely on Bleuler's 1911 theory that schizophrenia was fundamentally a disorder of disconnectivity (Bleuler 1911/1950), which in its turn was informed by the Kraepelinian dichotomy between schizophrenia and affective psychosis (Kraepelin 1919/1971). Meehl stated that "what makes schizotaxia etiologically specific is its role as a necessary condition" (Meehl 1962:831). In the parlance of modern developmental psychopathology, Meehl's theory stressed the *equipotentiality* of the dominant schizogene, which is to say this single cause might be manifest in a number of different ways (Cicchetti and Cannon 1999). Anyone without schizotaxia who had the same experiences might develop some other disorder, but they would not be schizotypal and they could not go on to develop schizophrenia. Therefore, it was not mothering that caused schizophrenia (a popular theory among many in Meehl's audience). Some mothering styles (or other environmental factors) might more readily potentiate a psychotic episode, but these could not be considered the ultimate cause.

This theory came at a crucial time, when psychodynamic explanations were waning and learning theories were joining with a newer kind of psychology that emphasized cognition and affect. Meehl's became a theory of central importance to schizophrenia, and psychopathology more generally. The early work of Irving Gottesman and James Shields (1967, 1972) grew from the perspective of a latent biological risk factor that may be expressed in a manner other than manifest psychosis. This developed in time into our current conception of an endophenotype, or intermediate risk indicator (Gottesman and Gould 2003). In conjunction with a modern neuroscience of brain mechanisms, this concept is central to the U.S. National Institute of Mental Health's emphasis on Research Domain Criteria (Insel and Cuthbert 2011). Taxometrics (i.e., the search for statistically distinct groups within a continuous distribution of such indicators) was developed in large part to test Meehl's schizotaxia hypothesis (Faraone et al. 2001). Meehl's work also resonated in the Danish Adoption Study conducted by Seymour Kety, David Rosenthal and colleagues, where disease manifestation was found to trace through genes more than environments, and the first signs of the unexpressed genetic liability to schizophrenia would later be described and labeled schizotypy (Kety et al. 1971). Meehl's

ideas inspired the scales developed by Loren and Jeanne Chapman, who began a cottage industry of self-report scales for identifying people (generally undergraduate students) at risk for schizophrenia, and later psychosis more broadly (e.g., Chapman et al. 1994; Eckblad and Chapman 1983). In a related development, the emphasis on a specific biological etiology led them to emphasize that indicators of that biological etiology need also be specific, rather than a general risk factor (Chapman and Chapman 1973a). One consequence of this elegant idea has been a four-decade long obsession in the experimental psychopathology of schizophrenia with the psychometric properties of experimental tasks and how well or poorly they match the properties of control tasks (Chapman and Chapman 1973b, 1978; MacDonald 2009; Strauss 2001). In the ensuing 50 years, the impact of the ideas of Meehl's presidential address has been profound and far-reaching.

The bone of contention for this chapter is not that schizophrenia does not have important biological antecedents, or that Meehl had those wrong. Indeed, much of Meehl's theory, including much of his self-deprecating physiologizing, seems remarkably prescient: description of the nature of failures of synapses would be recognizable as an early formulation of a glutamate or even a GABA hypothesis. The concept of a schizophrenogenic mother is dead and this chapter will not resurrect her. Nor will this chapter fault Meehl's contention, even as late as 1990, that a single major locus underlies schizophrenia (Meehl 1990). This is known to be patently wrong. What is most interesting about the way in which the theory is wrong is that schizophrenia is not caused by schizophrenia genes per se. This assertion lies at the heart of Meehl's hypothesized specific etiology. What is interesting about it is that schizophrenia is caused by genes that encode many proteins, across many brain and nonbrain systems. These genes appear to raise the risk for many kinds of psychiatric and perhaps other kinds of disorders. Therefore, what is most striking about how incorrect Meehl was is how *nonspecific* the biological etiology of schizophrenia now appears to be.

Conceptualizing Concepts

What makes schizophrenia troublesome is that it inhabits two worlds at once. It is, on the one hand, a *diagnosis*, and thus, as a diagnosis, we can determine who has it and who does not have it. From there one can go on to ask how common it is, which treatments do and do not ameliorate its symptoms, and what pathophysiological features people with the diagnosis share. As a diagnosis, schizophrenia is a closed concept. Closed concepts are constructs to which one can provide a definition stating what is necessary and sufficient for membership. For example, one can state the necessary and sufficient conditions for a fuel-efficient vehicle or a positive urine drug screen. Just so, diagnoses according to the modern Diagnostic Statistical Manual (DSM) or the International Classification of Diseases (ICD) are closed concepts about symptoms, the

impact of which will be covered at greater length in the next section. Meehl's theory also very consciously closes the concept of schizophrenia. The diagnosis of schizophrenia applies only to people with a dominant schizogene who decompensate. Anyone else who appears to be psychotic (of whom there should be very few) does not have schizophrenia but rather a "phenocopy." Unfortunately, this does not comport well with the way the world works.

The other world schizophrenia occupies is the one in which we live, wherein the disorder is part of a *syndrome*. Syndromes are different from diagnoses in that they reflect symptoms and other measurable signs that often occur together. Such descriptions are helpful in that the presence of one or more features of a syndrome alerts the caregiver to probe for the presence of its other aspects. As a syndrome, schizophrenia is an open concept. The definition of an open concept cannot be precisely specified; there may be no necessary or sufficient conditions for membership. Instances of an open concept have a "family resemblance" to one another, and we recognize members of the class by their similarity to exemplars of the concept. Most concepts are open concepts, acquired through experience rather than definitions. One could hazard a closed concept for a chair, perhaps defined as "a piece of furniture designed for a single individual to sit upon." Such definitions are beset by boundary conditions where reasonable people will disagree. Is a beanbag chair a chair? How about a comfortable rock? Of course schizophrenia is not a chair, but like a chair, a rigid definition can have unintended consequences. It can limit thinking and progress by suggesting an artificial homogeneity among the members of the class and an artificial boundary between members of the class and other informative conditions.

Schizophrenia is a kind of failure of mental functioning, but it is not a particular kind of failure. A laundry list of the symptoms people with schizophrenia or psychosis share with other diagnoses is wide and varied. As with bipolar disorder, dementia, or delusional infestations, schizophrenia can give people mistaken ideas about the motivations of others. As with Parkinson's disease, schizophrenia can cause people to perceive things that are not present. As with overmodulated posttraumatic stress disorder, schizophrenia can blunt peoples' emotional reactions to those perceptions, or like undermodulated posttraumatic stress disorder, schizophrenia can enhance those reactions. Like Alzheimer's, schizophrenia can result in problems in encoding and recalling information. Phenomenological similarities occur all across medicine and are in this sense nothing special. However, they are far from trivial insofar as they are often used to guide treatment. People with delusions are often prescribed antipsychotic medications irrespective of whether their diagnosis is bipolar disorder, dementia, delusional infestations, or schizophrenia. People with cognitive deficits have been found to benefit from computer-guided cognitive remediation regardless of whether their diagnosis is stroke, Alzheimer's disease, or schizophrenia.

The syndrome of schizophrenia is, therefore, not a particular kind of failure of mental functioning, it is a constellation of failures that tend to co-occur, and this co-occurrence can begin to take on a coherent shape when examined across a sufficiently large group of people. Although much of the remainder of this chapter will examine studies that have delineated schizophrenia as a closed concept, one with necessary and sufficient conditions designed for the purpose of reliable diagnosis, our purpose is to examine the broader features of the syndrome as an open concept. That is, although much of the data available treats schizophrenia the way we wished it would exist in the world for scientific purposes, with a specific manifestation derived from a specific etiology, we will avoid this temptation. Instead, we will try to discern schizophrenia as an open concept to see if we have the means to examine the spectrum in the world that we are given.

Finding Schizophrenia in the World We Are Given

Finding Schizophrenia in the Meta-Structure of Psychopathology

A number of analytic techniques have been devised over the years to allow researchers to ask questions about open concepts, including exploratory and confirmatory factor analysis. One advantage to such methods is that, using the data from the world we are given rather than the world we desire, they can help determine what an open concept refers to and does *not* refer to within a single framework. Such models thereby specify, within the limits of the granularity of the data, what kinds of symptoms group together and, just as importantly, what symptoms do not. Although there is a very large factor analytic literature, only recently have these tools been aimed at understanding how psychosis fits within the meta-structure of other symptoms.

Using a combination of exploratory and confirmatory factor analysis, Markon (2010) examined the structure of psychopathology using a British psychiatric epidemiological survey of over 7,000 adults. Here, psychosis symptoms were quantified using items from the Psychosis Screening Questionnaire and the SCID-II personality disorders screening questionnaire, and analyses were performed on the covariation between all the various DSM-IV criteria. In this analysis, a single factor labeled "thought disorder" was the label used for the latent symptom factor most closely associated with the syndrome of schizophrenia, or the schizophrenia spectrum. Thought disorder was identified as a higher-order factor defined by loadings from paranoia (.95), disorganized attachment (.70), inflexibility (.63), schizoid characteristics (.61), and eccentricity (.57) (see Figure 2.1a). In addition to their loadings on thought disorder, hostility (.60) also loaded on externalizing (.30), and hallucinations and delusions (.54) also loaded on internalizing (.30). Unfortunately, mania was poorly represented among the items included. In addition, the higher-order

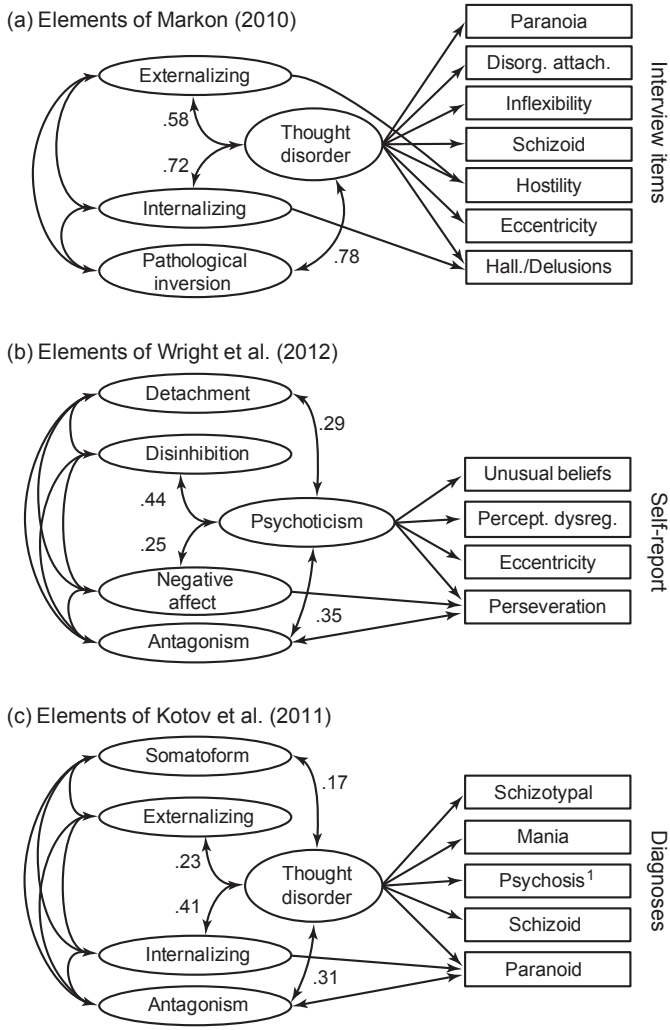

Figure 2.1 Three models of the meta-structure of psychopathology derived from (a) Markon (2010), (b) Wright et al. (2012), and (c) Kotov et al. (2011). Latent symptom dimensions are labeled within ovals. Only correlations with thought disorder/psychoticism are reported. Rectangles show indicators of thought disorder/psychoticism and are listed in descending order of loading strength. Indicators for other latent symptom dimensions are not reported. [1]Because Axis I psychotic diagnosis imposes a series of hierarchies, psychotic disorders in Kotov et al. (2011) were grouped into a single category and were not further distinguished.

thought disorder factor was closely associated with the three other factors in the model: pathological inversion, internalizing, and externalizing. A second study that used interview data from a smaller sample of schizophrenia patients, their first-degree relatives, and controls also discerned closely overlapping

factors (Tackett et al. 2008). The term "thought disorder" comes from this labeling convention and is not meant to convey the more specific meanings and distinctions associated with thought disorder that occur in the schizophrenia literature.

Apparently this structure is also evident in self-report questionnaires, assuming those measures include adequate pathology across the factors. In this case, Wright et al. (2012) examined responses from 2,900 undergraduates who had completed the 220-item Personality Inventory for DSM-5. This measure was designed to be a self-report measure of the 25 facets underlying the proposed personality disorders for DSM-5. As illustrated in Figure 2.1b, the five-factor solution reported was similar to that found in previous work. There were two factors of internalizing disorders (detachment and negative affect) and two factors of externalizing (antagonism and disinhibition). Finally, there was a factor labeled psychoticism, which was somewhat related to all of the other factors (correlations from .25–.44). Psychoticism was most closely related to the facets of perseveration, eccentricity, unusual perceptual experiences, and unusual beliefs.

In both Markon's (2010) and Wright et al.'s (2012) models, there is a high to very high rate of covariation between the latent factors. One possibility is that the relationships among these higher-order factors reflect common mechanisms that fail across the two disorders that covary. For example, keeping distance from one neighbor is rated as an instance of eccentricity and as an example of an indicator variable for antagonism. However, it is useful to note that this covariation may also have been modeled by a general factor. (For a formal model of a general psychopathology factor in a study that did not evaluate thought disorder, see Lahey et al. 2012.) If such a model is appropriate, what might this general factor represent? One possibility is that it represents a general psychopathology vulnerability factor. A second possibility is that it reflects the *result* of psychopathology; that is, the impact of a dysfunction in the world that has broad implications for mood and cognition. A third possibility it that it is spurious, simply representing a response bias. This third possibility could perhaps be addressed to some degree by evaluating this covariation at a diagnostic level rather than at an interview or self-report level.

Another study to have looked at the meta-structure of diagnoses was Kotov et al. (2011) who examined co-occurrence patterns from diagnostic interviews among 2,900 adults seeking outpatient treatment. Because only diagnosis and the number of mood episodes were available for analysis, and because Axis I psychotic diagnosis imposes a series of hierarchies, psychotic disorders were grouped into a single category and could not be distinguished with finer grain resolution. Even so the best-fitting model demonstrated five higher-order factors quite similar to those of Markon (2010): internalizing, externalizing, somatoform, antagonism, and thought disorder (see Figure 2.1c). In this case, thought disorder also showed the highest loadings for schizotypal personality disorder (.91), mania (.72), psychosis (including schizophrenia and a number

of other hierarchical categories of psychoses, .70) and schizoid (.51) personality disorder. Paranoid personality disorder was significantly related to thought disorder (.21), but was also related to internalizing (.36) and antagonism (.41), thereby demonstrating one of the most ill-mannered patterns of covariation of any of the 28 disorders measures. Therefore, this approach found nothing like a Kraepelinian dichotomy between schizophrenia and bipolar affective disorder.

In addition to relationships between diagnoses and higher-order factors, the Kotov model (Figure 2.1c) demonstrated relationships between the higher-order factors themselves. In this case, thought disorder showed strong relationships with internalizing and antagonism and somewhat lower, but significant, relationships with externalizing and even somatoform symptoms. These relationships, though, were notably lower than when using item-level data. This may reflect the desirable result of removing response biases which could have moderately inflated reports of symptoms across disorders. Alternatively, this covariance may mean that information about psychopathology and distress which did not meet the cut-off for diagnoses was thrown away and not further modeled. Despite using diagnosis-level data, there continues to be evidence for a general psychopathology factor. Nested within that general psychopathology factor is a thought disorder factor that does not conveniently split schizophrenia from any of these other forms of psychosis.

This growing literature approaches psychosis as an open concept, guided by the covariance structure of symptoms or items as they coalesce into facets and syndrome and then into factors. It is reminiscent of the discussion *within* the schizophrenia literature that has percolated since the 1980s, focusing on the appropriate factor structure for schizophrenia (for review, see Peralta and Cuesta 2001). Note that in contrast to the meta-structural approach highlighted herein, the within-schizophrenia factor structure work has been predicated on a diagnostic boundary around the schizophrenia construct (see Corvin et al., this volume; Figure 2.1b vs. 2.1c). It does, however, provide a level of granularity for resolving heterogeneity that the meta-structural approach has not yet addressed. The extent to which these two approaches can mutually inform each other requires further exploration.

From this approach, thought disorder emerges as a dimension of psychiatric symptoms regardless of whether it is measured using traditional psychiatric interviews or self-report scales. The thought disorder factor is most easily observed in samples with high rates of psychopathology, but it can also be observed in healthy samples if the samples are both large enough and the number of items with psychotic content is sufficiently large. In previous work, such as in the model of Eysenck (Eysenck et al. 1985), thought disorder was likely invisible because as Eysenck's scales developed, psychoticism items took on more of the content of antagonism or psychopathy, perhaps due to the relative prevalence in the population of individual differences in antagonism relative to thought disorder. Importantly from the perspective of thinking about schizophrenia as a specific, taxonic entity as Meehl would suggest, thought disorder

here is distinct from, but correlated with, other psychiatric symptom dimensions, such as internalizing and externalizing, even when looking at diagnoses rather than self-report as a means to control for response bias. Still, this is only a partial control. Perhaps specificity for the diagnosis would be more evident when examining children at risk for developing the disorder.

Finding Schizophrenia in the Development of Psychopathology

Studies of children at risk for developing schizophrenia have a long tradition dating back to the early 1970s (Erlenmeyer-Kimling and Cornblatt 1987; Erlenmeyer-Kimling et al. 1984). Initially, these projects targeted only the offspring of schizophrenia patients as a means to enrich the sample that would eventually convert to psychosis. As the number of risk indicators increased, family history of schizophrenia became only one of several criteria for being considered at high risk for converting to psychosis. A number of studies have now used multivariate combinations of signs and symptoms to predict onset of a psychotic syndrome, defined as a more-or-less open concept with various criteria depending on the needs and data available to the investigators (for a review, see Goldstein et al. 2010). In one study, genetic risk for schizophrenia with recent functional deterioration, unusual thought content, suspiciousness, social impairment, and a history of drug abuse were the strongest predictors of decompensation to psychosis within 2 1/2 years (Cannon et al. 2008). A number of such schemes now exist that allow us to speak with varying levels of precision about *ultra high-risk status* and *at-risk mental states* (Goldstein et al. 2010; Yung et al. 2007, 2008).

While much of this work has focused on prediction of psychosis, there is a growing sense that such states do not *specifically* predict schizophrenia, or even a broader vulnerability to the schizophrenia spectrum. Reports focusing on the offspring of patients as a single risk factor report significant increases in any kind of psychosis with and without concurrent affective disorders and some cases show nonsignificant increases in affective disorders without psychosis (Goldstein et al. 2010). This is consistent with more recent work, mostly discussed at conferences but not yet published, where there is growing evidence that at-risk mental state criteria capture a population of youth who are vulnerable to a much wider variety of psychiatric conditions. One report on nonconverters selected for being at clinical high risk for schizophrenia reported high levels of anxiety and depression at both baseline and follow-up (Addington et al. 2011). It was noted that these levels declined from baseline but remained elevated.

Longitudinal studies of this nature are critically important if we are to realize the goal of preventing schizophrenia. Interestingly they provide some insight into the broader swathe of mental disorders for which these young people are at risk and which, in the face of effective prevention programs, might be ameliorated. However, given samples that number in the hundreds, they

may be of limited power to reflect the equipotential of genes that represent the schizophrenia spectrum. In addition, the direction of inference is upside down if our effort is to challenge the specificity of schizophrenia as defined by Meehl. An ardent defender of a schizogene taxon might say that the cases which did not go on to develop schizophrenia still had schizotypy or were only mistakenly believed to be at risk for schizophrenia initially, due to imperfect inclusion criteria of the at-risk mental state. It may therefore be particularly useful to examine even larger, epidemiological cohorts to determine how the presentation of the disorder changes over time.

Finding Schizophrenia in the Course of the Disorder

Another way of asking the developmental question is to determine what, if any, changes in diagnosis occur over the course of the disorder. This question has frequently been asked in the context of whether subtypes of schizophrenia, such as catatonic or paranoid, are consistent over time. This approach is useful for the purpose of determining whether these subtypes are natural kinds. In fact, the subtypes have proved to be of such little use that they will not continue to be used in DSM-5 (Tandon and Carpenter 2012). Similar strategies can determine how the diagnosis of one disorder affects risk for other disorders later in life. One study examined more than 16,000 Danes born between 1955 and 1991 and admitted to the nation's psychiatric clinics or hospitals with a diagnosis of schizophrenia, schizoaffective, or bipolar affective disorder (Laursen et al. 2009). In relying on chart diagnoses, one must assume subsequent diagnosticians would rely to a great degree on previous psychiatric diagnoses, thereby lending an artificial high consistency to diagnoses that truly independent raters would not experience. Indeed, in smaller studies a much higher rate of diagnostic hopping has been reported using independent research diagnoses (Bromet et al. 2011). Still, given the rarity of these disorders it does not take a large number of shifts to new diagnoses to discern significant levels of comorbidity, based on the likelihood of switching from one diagnosis to another irrespective of which diagnosis was made first. Here, risk for bipolar affective disorder among patients diagnosed with schizophrenia and vice versa was twenty times higher by age 45 than the risk for either disorder in the general population. Risk of schizoaffective disorder converting to schizophrenia or vice versa was sixty times higher, whereas risk for schizoaffective disorder converting to bipolar affective disorder was over one hundred times higher. These findings are largely consistent with analyses of the meta-structure of psychopathology, insofar as the manifestation of one of these disorders markedly increases the likelihood of manifesting another subsequently. These data are somewhat difficult to interpret, however, as they may be influenced by help-seeking behaviors or reflect comorbidity only in those most liable for psychiatric conditions. One way to improve on this perspective might be to examine comorbidity within families to examine the etiologic specificity of liability genes.

Finding Schizophrenia in the Genes of Families

To test whether the relationships among latent symptom dimensions are spurious is to examine whether genetic risk is transmitted in a manner consistent with a general thought disorder factor that is also significantly related to other symptoms factors. Two early studies that asked whether genetic risk for schizophrenia was specific or shared with other psychiatric disorders suggested some level of specificity (Kety et al. 1971; Onstad et al. 1991). However, genetic epidemiology for rare disorders requires large sample sizes, and these studies were of a more modest scale. Two other recent studies have found that, in the same populations from which the earlier samples were drawn, genetic risk does indeed appear to be shared with other psychiatric disorders. One study, which looked at the families of 35,000 people with schizophrenia and another 40,000 with bipolar disorder, reported that risk for bipolar disorder among the parents and offspring of schizophrenia patients (relative risk 5.2%; 95% CI 4.4–6.2) was similar to risk for bipolar disorder among the parents and offspring of bipolar patients (relative risk 6.4%; 95% CI 5.9–7.1) (Lichtenstein et al. 2009). The relatives of bipolar patients were also at a significantly increased risk of schizophrenia, although this was somewhat lower than the risk among the relatives of schizophrenia patients. A second study went beyond bipolar disorder to examine the genetic epidemiology of psychiatric disorders more generally, including developmental disorders, in the entire population of Denmark (Mortensen et al. 2010). In addition to schizophrenia, the relatives of schizophrenia patients were at increased risk for eight other types of psychiatric disorders, including bipolar and other affective disorders, substance use, as well as personality and "other" mental disorders. The exceptions were nonsignificant increases in risk for Alzheimer's disease only in the offspring of schizophrenia patients, and for bipolar affective disorder only in the siblings, but not the parents, of schizophrenia patients. Though beyond the scope of this review, there is a growing catalog of the specific genetic polymorphisms and mutations that show up as risk factors for multiple psychiatric disorders (e.g., Fanous et al. 2012).

Taking a long view, schizophrenia, or dementia praecox, was originally conceived of as an open concept in terms of its signs and symptoms. Over time, the openness of the original diagnostic concept became reified or treated as an object for study and treatment. The fact that this may have occurred for good reasons (e.g., to generate falsifiable hypotheses or reliable diagnostic categories) may not justify clinging to the nosology of a closed concept if it detracts from scientific and clinical progress, for example by artificially polytomizing psychopathology into bins to be studied in isolation. The desire for having a closed concept of schizophrenia serves as the proverbial lamppost under which we are looking for keys we dropped; despite all the evidence to suggest that we dropped our keys somewhere in the shadows where concepts are not so clear

cut, we keep hunting within this little pool of light because that is where we are comfortable looking.

I have argued here that the statistical and methodological tools developed to address open concepts show that schizophrenia shares features and risk factors with a number of other diagnoses characterized by thought disorder. Thought disorder is, in turn, related in some way to other disorders on the internalizing and externalizing spectra. Meehl and other theorists would have predicted that there would be evidence for a specific etiology of schizophrenia. Instead, not only is genetic risk for schizophrenia shared with related forms of thought disorder, there is also evidence that some aspects of genetic risk are quite general. That is, risk is conferred across psychiatric symptom factors broadly. Given that we have failed to find specificity at the level of signs and symptoms, let us now examine whether cognitive or affective mechanisms have been useful in characterizing specific aspects of thought disorder.

Pinpointing the Cognitive Mechanisms That Underlie Schizophrenia

In arguing above for schizophrenia as an open concept, I made the points that schizophrenia shares symptoms, a developmental course, and etiological factors with a number of schizophrenia spectrum disorders. It also shares etiological factors and symptoms with other serious and persistent mental disorders, such as bipolar affective disorder and, to a lesser degree, unipolar depression and the internalizing spectrum, and perhaps also attention deficit disorder and the externalizing spectrum more broadly. In addition, it certainly shares symptoms, and may share some etiological factors, with disorders of aging such as Alzheimer's disease. Still, this may not be considered particularly strong evidence against a closed concept of schizophrenia. Could there not still be a core cognitive dysfunction from which thought disorder cascades? Such a cognitive process might reflect Meehl's hypothesized development of schizotypy, such as a loosening of associations, a lack of pleasurable responses, indecisiveness, or negative responses to interpersonal interactions. Alternatively, failure might be more evident as the direct effect of schizotaxia reflected in "soft" neurological and psychological signs, associative thought disorder, or abnormalities in processing negative feedback. A failure of working memory functioning has also been suggested as an alternative failure from which other psychotic symptoms follow (Goldman-Rakic 1991). Therefore, one thing that would be useful to find would be a cognitive process—and by this I mean to include affective and interpersonal processes—that was awry in schizophrenia.

There has been evidence at one point or another for failures in all of these processes in schizophrenia patients. The problem is an abundance of cognitive impairments, because the literature is rife with such cognitive impairments. This widespread reduction in patient performance has been spoken of as a

generalized deficit. To date, the largest and most consistent signal associated with patient performance is the generalized deficit. Across a broad variety of tasks, the generalized deficit is about 1.0 standard deviation (Dickinson et al. 2007). In comparison to effect sizes in other domains, such as pathophysiology, this generalized performance deficit remains the most reliable way to distinguish patients from controls (Heinrichs 2005). Performance deficits of this magnitude might reflect medication side effects or some other impact of the condition, such as demoralization. Medications generally do little to ameliorate this deficit in performance (Green et al. 2004a), but there is little evidence to suggest that medication or other treatment factors are primarily to blame. Prospective studies show that in many cases these deficits appear to be present well before the disorder is diagnosed (Brewer et al. 2006). The deficit may also reflect part of the genetic liability of schizophrenia. A deficit with an average magnitude of about .34 standard deviations is also found across many neuropsychological tasks in unaffected first-degree relatives of patients with schizophrenia (Snitz et al. 2006).

This evidence of a generalized deficit among patients with schizophrenia, somehow related to an unexpressed genetic liability, has been largely unsatisfactory. Some scholars have responded by arguing that the appearance of a generalized deficit, like thought disorder itself, could result from a failure of a specific process that just happens to be required for all tasks. For example, the observations of Kraepelin, Bleuler, and others inspired the notion that attentional processes may be particularly disturbed in schizophrenia patients. Intelligence and neuropsychological tests require attention to the test administrator and the stimuli to perform accurately. Therefore, a specific deficit in attention might impair performance on tests of many different abilities. Numerous studies support this notion; patients are impaired on tasks thought to tap attention, generally studied as selective attention (Luck and Gold 2008). One supportive piece of evidence is that an impairment on a putative attentional task, the AX continuous performance task (CPT), was more predictive of conversion to psychosis than any other test in the classic New York High-Risk Project (Cornblatt and Erlenmeyer-Kimling 1985). However, the case based on this evidence is problematic for the following reason: in the context of a disorder with a large *generalized* deficit, one needs to demonstrate a *differential* deficit; that is, a deficit over and above the impaired performance on other tasks (Chapman and Chapman 1973b). This is often accomplished in terms of a group by task interaction. However, this approach is only valid if the tasks being compared are psychometrically matched. This means that the tasks must be at least equally sensitive to a generalized deficit, a criterion that rarely occurs by chance. (Additional approaches to this problem have been discussed by Knight and Silverstein 2001.) Due to this tangle we do not know, for example, whether the children who went on to become schizophrenia patients performed worse on the AX-CPT because they had a specific deficit in selective attention or whether the AX-CPT was simply more sensitive to their generalized deficit.

Cornblatt and Erlenmeyer's finding is in no way unique in this regard; another large-scale prospective study found verbal memory performance discriminated prodromal individuals from controls, and among prodromes it predicted a faster conversion to psychosis (Seidman et al. 2010). Since this was not a differential deficit, it is unclear whether there was anything special about this cognitive domain, or simply something special about the test; that is, it was the most sensitive instrument to variation in a generalized deficit that was what really predicted the outcome.

The desire to understand schizophrenia by determining what specific and differential cognitive deficit underlies patients' generalized deficit has motivated some investigators to adapt experimental cognitive tasks for studying individual differences in clinical traits such as psychosis (Carter and Barch 2007; MacDonald and Carter 2002). These efforts have still to yield a definitive account of how any specific deficit may underlie the generalized deficit, much less how any specific deficit may lead to the symptoms of schizophrenia. An example of the problem comes from two research programs, which have been mindful of the interpretive snarls in patients' performance, that have examined two very different functions of the brain: visual integration and context processing. First, visual integration is the capacity to extract larger percepts from a field of stimuli. Because this is generally quite easy, Silverstein and colleagues (Silverstein et al. 2000, 2012b; Uhlhaas et al. 2004) developed a task which places a larger circle among a field of irrelevant stimuli to make it more difficult to integrate the pieces of the circle. By manipulating the strength of the signal that unifies the edges of the circle, it can be made to disappear into the background in the manner that traces each participant's psychometric function suggestive of a specific deficit. The psychometric functions of patients with schizophrenia show much lower levels of visual integration than controls. At the other end of the brain, namely the prefrontal cortex, investigators have been studying context processing. Context processing refers to the aspect of cognitive control that represents and actively maintains task-relevant information despite subsequent noise, and is in this way related to both selective attention and some aspects of working memory. Using a variant of the AX-CPT, Cohen and colleagues have demonstrated a differential deficit in one condition of the task sensitive to context processing relative to another condition that does not measure context processing but is of similar difficulty and therefore, perhaps, as sensitive to a generalized deficit (Cohen et al. 1999; Jones et al. 2010a; MacDonald et al. 2005b). While it would be simplest if patients had only one specific deficit, evidence for two or more specific deficits might be useful if they reflected different aspects of the condition. Indeed, the two tasks draw upon two very different networks: visual integration relies largely on visual cortices (Silverstein et al. 2009a) whereas context processing relies primarily on prefrontal-parietal networks (e.g., MacDonald et al. 2005a). Unfortunately, the two tasks appear to reflect on the same aspect of psychotic heterogeneity.

Performance on both tasks was related to disorganization symptoms to about the same degree: $r = .47$ for visual integration (Silverstein et al. 2000) and $r = .41$ for context processing (Cohen et al. 1999; see also Gold et al. 2012). One could be forgiven for seeing these efforts as again identifying factors related to general disease severity rather than lighting upon a special key for understanding schizophrenia.

The prominence of the generalized deficit in schizophrenia gives rise to another line of thinking. There has long been a notion of "g," known also as generalized intelligence or positive manifold (Spearman 1904). The broad nature of the generalized cognitive deficit in schizophrenia raises the question as to whether thought disorder in broader population studies and disorganization in patient studies reflects a "deficit g" or a negative manifold. Recent work addressing this question in an epidemiological sample examined the siblings and twins of people who went on to develop schizophrenia (Fowler et al. 2012). This study found that the genetic correlation between schizophrenia liability and intelligence was modest but significant: –0.26. The fact that this relationship is not stronger may reflect limitations of the assessment battery. Standardized tests for military service from which these data were drawn may not be optimized for probing the relevant portion of the distribution. Alternatively, they may reflect the fact that psychosis, while significantly related to cognitive ability, also stands apart from this additional generator of individual differences.

In this section we sought to determine whether specific cognitive processes, to include both affective and interpersonal processes, could help us determine whether there was a key cognitive mechanism whose failure led to schizophrenia. This is an ill-posed question because a definitive answer requires a thorough search of all possible cognitive mechanisms. Even so, to date the literature shows that the most prominent aspect of schizophrenia-related cognition is the generalized deficit. Many have argued for a number of specific deficits (Cohen and Servan-Schreiber 1992; Grace 2000; Hall et al. 2009; Howes and Kapur 2009; Phillips and Silverstein 2003), and it still may be the case that a single deficit, or a canonical cortical dysfunction (Carandini and Heeger 2012), rooted in a basic and widespread aspect of cortical circuitry, accounts for a wide range of observed cognitive impairments in schizophrenia. For our current purpose, suffice it to say that a cognitive perspective has not yet provided a key for unlocking the nature of schizophrenia and, given the effort and intellect thus far expended, we must consider the possibility that it cannot. It appears to have struck upon some of the same, poorly bounded psychopathological severity that we observed when considering symptoms, development, course, and genetics. Thus, let us move on to the question of how to make scientific progress with this ill-defined construct as we find it in the world. To do this, I will suggest that we turn for inspiration from experimental psychology to the engineering sciences.

Falsification and Failure Modes

For the purposes of record keeping and billing, there is nothing as reassuring as a nicely delineated category. This intuition has infused our science with the ideal of rigorous definitions and of necessary and sufficient conditions. We are seduced into thinking that we need closed concepts to formulate strong, falsifiable hypotheses. In this final section, let us consider whether science and treatment are hindered by open concepts and, if so, whether this cost can be reduced in any way.

Clinically, psychiatrists and other clinicians treat disorders one individual, even one story, at a time. In much of practice, diagnostic criteria are used to generate questions about symptoms that may not be proffered. The treatment itself, however, is more often focused on symptoms, or even anecdotes. Thus, whether you come to a psychiatrist with schizophrenia or Alzheimer's disease, if the presenting symptom is persecutory ideation you are likely to be prescribed an antipsychotic medication and it will be a D_2 dopamine antagonist. Unfortunately, if you present with prominent negative symptoms, whether from schizophrenia or posttraumatic stress disorder, the psychiatrist will not have a particularly rich armamentarium. So, a more open conception of psychosis may not imply major changes in clinical practice. In science, though, one of the reasons we are reluctant to move toward a more open conceptualization of thought disorder and the psychosis spectrum is a concern that we lack the tools for thinking about how insufficient and unnecessary factors can influence each other in a manner that results in disordered thought. Even where we are comfortable *thinking* about such things, it is a challenge to build falsifiable hypotheses about causes that are difficult to characterize. This reluctance may give way to enthusiasm, or even obviousness, should the proper tools be made available for understanding what kind of a thing schizophrenia is.

We have already alluded to some of the statistical tools that can be used to gain an understanding of the type of a thing that comprises schizophrenia. Confirmatory and exploratory factor analyses and model fitting cope with open concepts through covariance structures. Also in the domain of modeling, but of a different sort, artificial neural networks work from exemplars of a concept rather than explicit definitions. This provides neural networks with flexibility to integrate more information as a means to, for example, discriminate between two groups or predict symptoms from brain data. A branch of the engineering sciences known as reliability engineering may provide another complementary tool to allow us to integrate studies and make explicit hypotheses about open concepts.

Reliability engineering, a subdiscipline of systems engineering, addresses the capacity for a system (in this case the brain) to perform its required functions within specified parameters over the course of its lifetime. The psychiatric equivalent of nosology and pathophysiology is a failure modes and effects analysis. In reliability engineering, a failure is defined as "the termination of the

ability of an item to perform a required function" (International Electrotechnical Commission 1990). It may be odd to think of the brain as an item, but it is quite common to think of it as a system "designed" as it were by evolution, with many components that work in concert. It is certainly not a stretch to imagine those components having a range of operations, and for any one of them to fail to perform its required function within that system. A failure mode is the effect, or the symptoms, by which such a failure is observed for that item.

I submit for consideration that what we call thought disorder broadly presents several failure modes of the brain. This is perhaps most easily thought of as one failure mode for the moment. This failure may represent a small and limited failure event, which simply reflects a failure in that particular state. A failure may also be more extensive, called a fault, which implies the failure is a trait and that in most cases the system will not be able to perform a required function. Such a trait could be thought of as what we call "schizophrenia." The idea of failures and faults would certainly be recognizable to Meehl, as they are reflected in the theory of schizotaxia as subthreshold signs of vulnerability or schizotypy, and only in some cases would this lead to a fault: fully decompensated schizophrenia. However, the perspective of failure modes and effects analysis would seem to open up a number of additional ways of thinking about the problem of schizophrenia, thereby providing access to formal thinking and tools for examining the brain system and its schizophrenic failure modes.

Consider Figure 2.2a, which illustrates a conceptual framework introduced by Cannon and Keller (2006) for thinking about the cascading and cumulative effects of different genes on the manifestation of the disorder. This framework was introduced to provide a unifying model for the many diverse gene systems implicated in the schizophrenia diatheses and to illustrate a systematic set of hypotheses about how endophenotypes up and down the watershed might be more or less related to their sources (genes and perhaps environmental or stochastic factors) and more or less related to their outcome (schizophrenia, or system failure). For example, Cannon and Keller use a working memory deficit as an example of an endophenotype that may be the result of many genes (not) working together. This, in turn, may work with other endophenotypes to increase risk for symptoms, which are then very likely to be manifest as a disorder. Along the way, none of the contributors to working memory deficits are necessary or sufficient. Similarly, no endophenotype is necessary or sufficient for the expression of symptoms. The particular mix of tributaries, however, will contribute to the heterogeneity of symptoms observed in the symptoms and the disease presentation, as suggested by the width of the watershed at the terminus. By providing a framework for conceptualizing how diverse factors might summate, the watershed model approaches the failure mode idea of reliability engineering. It may have a number of additional virtues, but one thing it does not do is make explicit predictions. To the contrary (correctly, I believe), it tells the scientist what kind of prediction *not* to make about schizophrenia (one gene or neurotransmitter system → one mechanism → one disorder). It

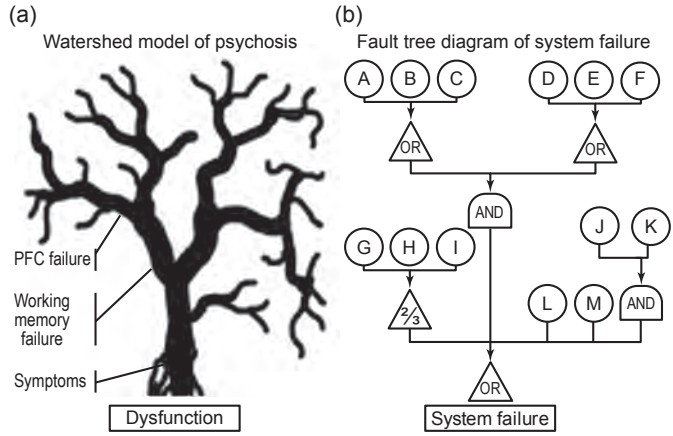

Figure 2.2 Two frameworks for understanding complex etiology: (a) Watershed model after Cannon and Keller (2006). PFC = prefrontal cortex. (b) Fanciful fault tree diagram illustrating the Boolean logic gates that connect contributory factors or events (A–M). For an AND gate, all factors must be present; for an OR gate, any factor must be present; for a "Voting OR" gate (e.g., 2/3), a minimum number of factors must be present (after Cannon and Keller 2006).

would be more useful to have a framework that allowed us to combine these tributary factors within a more explicit framework.

Figure 2.2b illustrates a way in which the watershed framework might be reconceptualized as a fault tree analysis. Fault tree analysis is an approach developed by Bell Laboratories in the 1960s for the U.S. Defense Department using a reliability engineering approach. The tree is a top-down structural model that shows the logical paths connecting various contributing causes and specifying the manner in which these can lead to a system failure (ReliaSoft 2012; Ericson 2011). Among other virtues, for example, it allows one to calculate the likelihood of a system failure if the likelihoods of the constituent events are known. For example, the reliability of the first OR gate (the likelihood of it *not* contributing to a system failure) is equal to the product of the reliabilities of all its constituent events (e.g., $R_A \times R_B \times R_C$). In turn, the reliability of the top AND gate is equal to the sum of the reliabilities of its constituent events minus the likelihood of both failures occurring (e.g., $R_A \times R_B \times R_C + R_D \times R_E \times R_F - [R_A \times R_B \times R_C \times R_D \times R_E \times R_F]$). Such calculations could therefore cascade through the diagram. Conversely, the likelihood of a system failure can be taken into account to push the algebra backward to identify failure rates of constituent events needed.

The scheme may provide a number of advantages for psychopathologists, and the study of schizophrenia in particular, insofar as it suggests ways in which we might pull apart and systematize the complexity of these disorders. The diagram and these operators just scratch the surface of the kinds of causal relationships available for consideration in such an analysis. To whet the

appetite, other such gates include exclusive OR (XOR), priority AND, load sharing, standby, sequence enforcing, inhibiting, and transfer gates—each with its own computational characteristics. An additional role for a formal fault tree analysis is that it allows one to make more objective calculations about where an intervention is likely to be most effective in improving the overall reliability of the system.

From Equipotentiality to Multipotentiality

To anyone who already recoils at how people are treated like machines in modern medicine, the reliability engineering approach will only confirm their worst suspicions. However, for those of us who believe the choice between open concepts and falsifiable hypotheses is a false choice, reliability engineering, generally, and fault tree analysis, more specifically, may be particularly appealing. This is because it provides a means to model explicitly how multiple miniscule factors, none of which are necessary or sufficient, can summate into a disorder like schizophrenia with its personal tragedies, family crises, and large societal costs. In the parlance of development psychopathology, this is *equipotentiality* (Cicchetti and Cannon 1999), and it suggests that there are multiple pathway models of disease development.

Whereas one of the shortcomings of the watershed analogy is that the upstream factors might be thought to contribute inevitably to downstream manifestation, like water flowing downhill, the fault tree is better able to capture basic facts about the etiology of schizophrenia. For example, a fault tree could be used to explain why heritability of liability to schizophrenia might be 80%, but MZ twin concordance could be only 50%. That is, most of the ultimate factors are genetic, but those genes must combine with nongenetic (stochastic or environmental) factors that now serve as rate-limiting factors and reduce the genes' penetrance. It may also be relevant to heterogeneity in treatment response, and could be applied to understanding how premorbid functioning affects clinical presentation and outcomes. Most importantly, such explicit models allow for testable, albeit more complicated, hypotheses.

The careful reader may not yet be convinced of the usefulness of a fault tree analysis for understanding schizophrenia as a failure mode of the brain. The central pillars of this chapter have been the lack of a specific etiology for schizophrenia and the lack of a consistent presentation of the disorder, across people and within the same person over time. If there is one thing the fault tree analysis clearly does, it is that it uses a diverse set of risk factors to predict a *specific* failure. Figure 2.3 illustrates another fanciful diagram, insofar as the causes and relationships refer to no particular factors or disorders in particular. It does, however, suggest two ways in which fault tree diagrams may be superimposed or combined to generate comorbidity. The comorbidity between Disorder 1 and Disorder 2 is driven by the factors A–F that can lead people, depending on the status of conditions G–M, to have just Disorder 1 or both

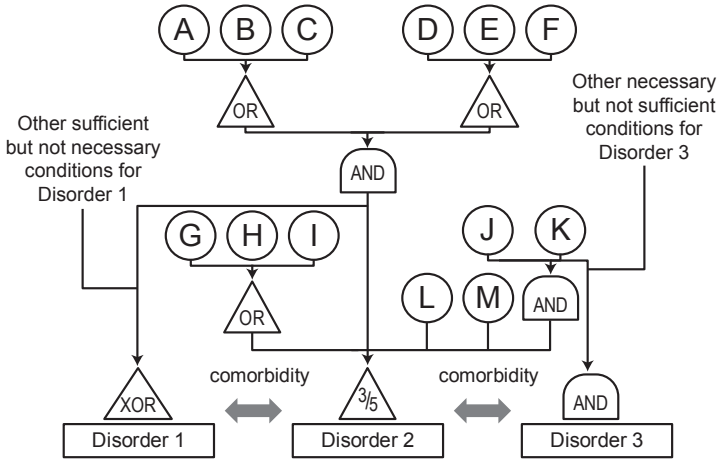

Figure 2.3 Fanciful layered fault tree diagram allowing for hypotheses about sources of comorbidity. XOR = exclusive OR; 3/5 = "3 out of 5 Voting OR" gate (see Figure 2.2). Note that here disorder represents any particular failure mode of the brain, including a failed mechanism, decreased ability, or psychiatric symptom.

Disorder 1 and Disorder 2. Disorder 1 can also be caused by other, completely unrelated, factors. Comorbidity between Disorder 2 and Disorder 3 is driven by J and K. Together, J and K are one of several potential risk nodes needed for Disorder 2. Together with another set of distinct risk factors, J and K contribute to Disorder 3. In this manner, the kinds of patterns of comorbidity observed in Figure 2.1 can be hypothesized and evaluated.

A reliability engineering research program may proceed from several angles. Currently, we examine whether people with schizophrenia are more likely to have a particular etiological factor. Fault tree diagrams could allow one to test specific predictions about rates of psychiatric morbidity in people with a particular etiological factor, or better yet across multiple etiological factors. Alternatively, one could test predictions about rates of various etiological factors in people with a particular condition. Such hypotheses could be bootstrapped using data mining techniques to identify the key etiological factors and their interactions to quantify their impact on schizophrenia or related conditions; analyses could then be extended to examine the impact of those etiological factors on "near-by" disorders.

Working With the Heterogeneity of Thought Disorder

Conceptualizing schizophrenia as being the final manifestation of a single cause propagated through a series of further probabilistic conditions and events, as proposed by Meehl (1962, 1990), was a productive spur for innovative research about the etiology of schizophrenia. Many other theories have followed that likewise propose a specific etiology. Unfortunately, theories predicated

on specific etiologies have also led us astray. For example, we were overly optimistic about the probability of finding schizophrenia genes and the specificity inherent in such theories fails to predict the blurring of diagnostic lines. This blurring of lines is reflected in the comorbidity of psychotic symptoms with other affective and interpersonal symptoms, the nonspecific risk associated with prodromal states, and patients' movement across mutually exclusive diagnostic boundaries over the course of a lifetime.

In this chapter I have grappled with the question of what kind of a thing is schizophrenia, given a broader view of symptom co-occurrence, development, and genetic epidemiology. The perspective that I have adopted here still pushes us toward the conclusion that schizophrenia is part of a broader, open concept of a thought disorder syndrome. In the space available, I have not unpacked and addressed all of the data that defenders of a specific etiology and pathophysiology might bring to bear. Thus, an important discussion to have is whether there is remaining evidence of such specificity that provides an intellectual redoubt of specificity for the disorder. Such a foundation may be built of pharmacological, neuroanatomical, or cognitive evidence; in its current state, molecular genetic evidence would appear to be an unlikely source of such findings.

Thought disorder syndrome may represent a failure mode of the brain, of the kind that can be quantified and illustrated using a fault tree diagram. Such a perspective may be useful for reconciling and organizing diverse findings across the study of schizophrenia. This possibility opens a number of questions, some of which focus on the idea of a fault tree analysis itself:

1. If the brain is a graded system, its performance is more akin to small differences contributing to *variability* rather than *failures*. Is the brain really even amenable to fault tree analysis, which focuses on a dichotomous outcome?
2. If so and the brain is amenable, what are the main branches of a fault tree analysis? What are the contributory components to those branches?
3. Are our measurement tools and hypotheses of a sufficiently precise nature to test specific branches of a fault tree for psychosis?
4. Many deficits associated with thought disorder appear to propagate into diverse domains of cognition and behavior. Is a fault "web" of causality a more appropriate representation of events rather than a top-down "tree"?

Another set of questions relates to nosology. For example, how does a failure mode perspective of psychopathology reflect on new nosological systems, such as DSM-5 put out by the American Psychiatric Association or the Research Domain Criteria (RDoC) defined by the U.S. National Institute of Mental Health? DSM-5 is built around a system of categories that largely ignores these sources of comorbidity. RDoC is built around cognitive neuroscience mechanisms. As RDoC is conceptualized, mental disorders manifest as a failure of one or several of these mechanisms. Can the tools of reliability

engineering be integrated within these frameworks to account for this evidence of nonspecificity of thought disorder, and its relationships with other forms of psychopathology?

Finally, is there a category of risk factor that is general across the thought disorder spectrum, or across psychopathology even more generally? For example, the established risk factors for schizophrenia include a number of general stressors such as age, season of birth, prenatal factors, substance abuse, urbanicity, minority or migrant status, autoimmune disease, and socioeconomic development. Are these also risk factors for other psychiatric and neurological disorders?

Our understanding of schizophrenia, psychosis, and thought disorder has been guided by the work of many great thinkers. Findings from the last fifty years have pushed us toward an ever more inclusive view of the causes and effects of the constellation risk factors and symptoms related to schizophrenia. If we are to systematize and build upon this literature, the next fifty years will require better use of our tools to cope with open concepts.