Systematic Reviews of Categorical Versus Continuum Models in Psychosis: Evidence for Discontinuous Subpopulations Underlying a Psychometric Continuum. Implications for DSM-V, DSM-VI, and DSM-VII

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classification, epidemiology, latent, nosology, schizophrenia, schizotypy

Abstract
Diagnostic systems, phenotype models, and theories of etiology incorporate propositions on the underlying nature of psychosis and schizophrenia phenotypes. These propositions, whether implicit or explicit, are that the distributions of the phenotypes, or the phenotype experiences themselves, are dimensional or categorical. On one hand, evidence on the epidemiology of schizophrenia phenotypes suggests symptom phenotypes may not be bound by conventional diagnostic thresholds but instead may blend imperceptibly with subclinical, statistically frequent experience, supporting continuum viewpoints. On the other hand, evidence on the population structure suggests a latent categorical structure; the population may be composed of two types of people. However, both sets of evidence are beset by methodological limitations that point unequivocally to the need to move beyond current diagnostic conceptualizations, observation, and anamnesis of psychosis, and toward responsive and scientifically refutable formulations of schizophrenia.
INTRODUCTION

Madness, frenzy, and melancholy are confounded by Celsus, and many writers; others leave out frenzy, and make madness and melancholy but one disease, which Jason Pratenis especially labours, and that they differ only secundum majus or minus, in quantity alone, the one being a degree to the other, and both proceeding from one cause. They differ

intensio et remissio gradui, saith Gordonius, as the humor is intended or remitted. (Burton 1628, vol. 1, p. 140)

During the past decade, numerous reports on the epidemiology of schizophrenia have been published such that there are now significant numbers of reviews of the subject, systematic and otherwise (Bromet & Fennig 1999, Häfner 2000, Jablensky 2000, McGrath et al. 2008, Messias et al. 2007, Murray et al. 2003, Saha et al. 2005, Tandon et al. 2008). On one hand, these reviews appear to paint a consistent picture. The annual incidence of schizophrenia is in the order of 0.2 per 1000, the lifetime prevalence of schizophrenia is around 0.4% to 0.7%, and there is significant variability in incidence and prevalence rates. Variables that predict incidence or prevalence rates include family history, age, sex, season of birth, prenatal factors, substance abuse, urbanicity, minority or migrant status, autoimmune disease, and socioeconomic development. For some of these predictors the available evidence is not unequivocal.

There also appears to be general agreement that research into the epidemiology of schizophrenia is affected by methodologically challenging issues and methodological problems. These include the absence of a pathognomonic marker of the disorder, unavoidable reliance on the clinical interview, meeting the demand for clinical utility, the level of interrater agreement or reliability, variability across the lifespan, and the demand for conceptually compatible analysis methods both in primary research and systematic review (Jablensky 2000; McGrath et al. 2008; Murray et al. 2003; Saha et al. 2005, 2008; Tandon et al. 2008). Importantly, evidence suggests that study quality is correlated with some epidemiological findings (Saha et al. 2005). Less frequently, doubts about the construct validity of the schizophrenia diagnosis are expressed (McGrath et al. 2008, van Os & Verdoux 2003).

On the other hand, there is a striking range of views on the overall status of the epidemiology of schizophrenia. Jablensky (2000)
suggested that the main features of the epidemiology of schizophrenia were well established by the late 1930s, saying, “the contours of the epidemiological map of schizophrenia were by and large complete before World War II” (p. 274). Messias et al. (2007) hold a quite different opinion, saying, “even as late as 25 years ago, the epidemiology of schizophrenia was nearly a blank page” (p. 333). In the middle, McGrath et al. (2008) borrow the contours metaphor to emphasize the need to reappraise the established dogma surrounding the epidemiology of schizophrenia: “The contours of this landscape can no longer be considered flat and featureless” (p. 74).

There are several recent high-quality reviews of the epidemiology of schizophrenia (e.g., McGrath et al. 2008, Messias et al. 2007, Saha et al. 2005, Tandon et al. 2008). It is not our aim to attempt to match these here. Instead, our objective is to examine the question: Does schizophrenia have a categorical or continuous latent structure? We begin by clarifying the meaning of this question and identifying expectations based on diagnostic classifications, theoretical models of causality, and phenotypic models. We go on to consider evidence of continuity in phenotypic expression, focusing predominantly on the clinical and subclinical phenotypes. We then address what we regard are obstacles to a scientific epidemiology of schizophrenia and ideas on the future of research and practice in this area.

DEFINITIONS

Latent

Schizophrenia is a latent construct insofar as it is unobservable. In contrast, the observable manifestations of schizophrenia are evident across social, functional, behavioral, motor, cognitive, affective, physiological, anatomical, and other biological domains. Given sufficient manifestations in an individual, an inference is made that schizophrenia is present. Thus, “latent” in this sense has a very narrow meaning, something intangible, which cannot be seen despite even florid manifestations, and “schizophrenia” is a concept that extends well beyond criteria for its diagnosis.

A second referent of “latent” that also receives some use here is an underlying statistical variable. Latent variables are those that are inferred on the basis of statistical evidence. Common examples include continuous latent variables identified through factor analysis, often called factors, and categorical latent variables identified through latent class analysis.

Continuous

Quite how questions on the latent structure of schizophrenia are posed or addressed in research varies substantially because there are several different meanings to which “continuous” and its synonyms and antonyms are applied. Measuring cross-sectional behavior, cognition, and affect, one can identify manifestations of schizophrenia that resemble experiences reported by individuals who do not meet diagnostic criteria for schizophrenia. Promoting this notion, Strauss (1969) argued against the practice of rating manifestations of schizophrenia dichotomously, and Kretschmer (1936) and Crow (1998) argued against the notion of a schizophrenia entity. Thus, in this sense, questions about continuity are concerned with whether the processes giving rise to schizophrenia are the same as those that give rise to phenomena that bear some resemblance to the signs or symptoms of schizophrenia.

Observing the intrapersonal course of schizophrenia, one can identify signs or symptoms that appear to be exacerbations of subclinical function or subjective experience that predate the onset of schizophrenia by months or years (an der Heiden & Häfner 2000, Schultze-Lutter 2009). Fluctuations in manifestations may arise through moderation or mediation by intrinsic (e.g., sensitization) or extrinsic processes (e.g., environmental stressors). Thus, in this second sense, the principal focus is continuity of phenomenology across time.

Third, examining the composition of populations, general population sample variability...
in manifestations of schizophrenia may arise solely from graduated interpersonal differences within members of a single population, the mixing of two or more discontinuous homogeneous subpopulations, or some combination of these situations. Thus, Meehl’s (1990; see also Lenznerweger 2006) view on the liability for schizophrenia suggests the commingling of two subpopulations, whereas Crow’s (1990, 1995) and Claridge’s (1997) views are aligned with the notion of continuous interpersonal differences across representative general population samples. A special case of the population composition question is encountered in contrasts of differences between schizophrenia and other serious mental disorders. Here, Crow (1990) could be said to belong to a continuum camp, across from the Kraepelinian dichotomy, the deficit-nondeficit distinction, Meehl’s (1990) schizotaxia-schizotypy-schizophrenia model, and in the extreme, those who attribute conceptual significance to the formulation provided by the American Psychiatric Association (Am. Psychiatr. Assoc., e.g., 1994). These appear to be the three chief referents of “continuous.” The focus in this review is on continuity in experience and population structure.

EXPECTATIONS

From Classification Systems

Clearly, superficial discontinuity is explicit in the notion of classification. Whether superficial discontinuity implies latent discontinuity or otherwise is less clear. On one hand, the acceptance of the classification systems in research settings, the lack of any significant body of work on the construct validity of schizophrenia classifications (Jansson & Parnas 2007), and the proliferation of classification systems in the 1970s and 1980s are observations that may be called in defense of the inference that classification implies discontinuity of experience and population structure. This is the practice of the field and follows from the pragmatic demands of administration, provision of care, communication, statistical analysis, and so on. Certainly, discontinuity is a reasonable hypothesis to test.

On the other hand, there is also recognition that pragmatic demands do not necessarily equate to conceptual or theoretical significance. The authors of the most widely used classification system, the International Classification of Diseases (ICD-10; World Health Org. 2004), note the instrument emerged from practical demands, not theory. The authors of the most frequently used system, the Diagnostic and Statistical Manual of Mental Disorders (DSM; Am. Psychiatr. Assoc. 1980, 1987, 1994, 2000), are somewhat more thorough in their disclaimer. From 1980 onward, the American Psychiatric Association (APA) explicitly rejected any conceptual or theoretical implications arising from the DSM-III structure for the latent structure of psychopathology in general, including questions on the relationship between normality and abnormality (Am. Psychiatr. Assoc. 1980, p. 6). That is, the authors did not intend that the modular categorial model inherent in the DSM-III structure be interpreted as implying that psychopathology has a latent categorial structure.

This qualification reflects the APA’s objective to minimize theoretical bias in classification, particularly where etiology is unknown. This objective was first most evident through the removal of “reaction” from the diagnostic labels that were used in the first edition (Am. Psychiatr. Assoc. 1952). However, in providing this more robust disclaimer, the authors effectively paint schizophrenia and other diagnoses as without epistemic or conceptual merit; although there may be pragmatic value or clinical utility in drafting patients’ problems into various groupings or subgroupings, such groupings are arbitrary, make-believe constructions. At the very least, if one takes the qualification seriously, DSM is silent on the latent structure of schizophrenia.

From Theories of Phenotypes

Several theorists have proposed clear boundaries between or among phenotypes.
Historically, the most recognized phenotype boundary is that which Emil Kraepelin proposed between dementia praecox and manic-depressive insanity, now referred to as the Kraepelinian dichotomy (Angst 2002). This dichotomy has received extensive criticism (e.g., Crow 1990, 1991; Curtis et al. 2000; Greene 2007; Ovsiew 2000). Finding fault with the broadening of the schizophrenia notion, Murray & O’Callaghan (1991) suggest the Kraepelinian dichotomy may still hold for a more narrowly defined dementia praecox, or “congenital psychosis.” They characterize congenital psychosis as having an insidious onset with prominent negative symptoms and neurocognitive impairment and without significant affective symptoms. A similar construct was identified by Carpenter et al. (1988, Kirkpatrick et al. 2001), who describe a qualitatively distinct class they referred to as the deficit syndrome or deficit schizophrenia. The key feature of this classification is the presence of primary enduring negative symptoms in the context of DSM schizophrenia.

Tsuang et al. (2000a,b) argued for a qualitatively distinct phase in the course of schizophrenia, predating the onset of schizophrenia proper, that they referred to as schizotaxia or preschizophrenia. They describe the condition as equivalent to schizophrenia in the absence of psychosis, although the criteria are a little narrower than this would imply. Schizotaxia is diagnosed in individuals who exhibit prominent negative symptoms and neuropsychological impairments and who are first-degree biological relatives of individuals with schizophrenia. If such an individual subsequently develops psychosis, schizophrenia is diagnosed.

A notable irony with the deficit schizophrenia and schizotaxia constructions is that these require the assumption that schizophrenia is a natural category. Kirkpatrick et al. (2001) refer to deficit schizophrenia as being a discrete disease within the schizophrenia syndrome. Thus, if deficit schizophrenia is a latent disease entity, its boundaries do not cross those of schizophrenia. Yet there is no clear reason why deficit schizophrenia could not occur in the absence of DSM schizophrenia. The same illogic applies to Tsuang et al.’s (2000a) schizotaxia because of the criterion that this is only diagnosed in first-degree relatives of individuals with schizophrenia.

There are also prominent theories of phenotype onset and course in which discrete classes are identified (an der Heiden & Häfner 2000, Bromet & Fennig 1999, Schürhoff et al. 2004, Welham et al. 2000). A recent example is provided by McGorry’s (2007, McGorry et al. 2006) clinical staging theory in which five key stages in the course of schizophrenia are identified. However, as stated above, continuity versus discontinuity in the course of schizophrenia is not within the scope of this review.

From Theories of Etiology

Theories of etiology may incorporate, explicitly or implicitly, hypotheses on the nature of schizophrenia. Table 1 contains a summary of contemporary theories of the etiology of schizophrenia, or, at least, important signs and symptoms of the disorder, identified through a selective review of recent literature. In this literature, biological explanations preponderate, although this may simply be a function of the literature we considered. In outlining their theories, few authors identify explicit propositions on continuity or otherwise of experience or population structure (Crow 1990, 2008; Lenzenweger 2006; Meehl 2004; van Os et al. 2000). On the whole, this issue is rarely addressed in a direct manner.

When considering each theory, we asked two questions that derive from the narrow assumption that a latent categorical etiological model would require a singular dichotomous causal agent: Does the key mechanism of causation operate in an all-or-none fashion? Is the key mechanism singular or characterized as a final common pathway or bottleneck in the causal chain? We reasoned that if either of these conditions were not met, there would be little reason for anticipating the schizophrenia phenotype would be a unitary latent category.
Table 1  Recently expressed accounts of the etiology of schizophrenia

<table>
<thead>
<tr>
<th>Theory</th>
<th>Description or quote of core pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Accelerate aging</td>
<td>Schizophrenia is a syndrome of accelerated or compressed aging prior to the onset of the disorder. Schizophrenia may reflect an outcome of a singular cause of accelerated aging (Kirkpatrick et al. 2008).</td>
</tr>
<tr>
<td>Byproduct of language</td>
<td>The proximal etiology is “a deviation in the process of conversion of thoughts into phonological output [and] of the decoding of the input into its possible meanings” (Crow 2008, p. 38).</td>
</tr>
<tr>
<td>Common disease, common alleles</td>
<td>Numerous single nucleotide polymorphisms, no one of which contributes significant variance to risk for schizophrenia, in combination constitute the genetic basis for schizophrenia (Intl. Schizophr. Consort. 2009).</td>
</tr>
<tr>
<td>Common disease, rare alleles</td>
<td>“Many mutations predisposing to schizophrenia are highly penetrant and individually rare, even specific to single patients or families… different families harbor different mutations… any one family carries only one or two mutations” (McClellan et al. 2007, p. 194).</td>
</tr>
<tr>
<td>COMT val/met susceptibility</td>
<td>COMT mediates low dopamine activity in the prefrontal cortex, giving rise to increased dopamine activity in the mesolimbic cortex (Williams et al. 2007).</td>
</tr>
<tr>
<td>De novo mutation</td>
<td>De novo germline or somatic mutations, arising through replication errors in the paternal germ line or through maternal folate deficiency, affect neural development or function, causing schizophrenia (Cheng et al. 2008, Malaspina et al. 2001, McClellan et al. 2006).</td>
</tr>
<tr>
<td>Desynchronized neural activity</td>
<td>“Schizophrenia involves abnormal oscillations and synchrony [of neural activity] that are related to cognitive dysfunctions and some of the symptoms of the disorder” (Uhlhaas et al. 2008, p. 927).</td>
</tr>
<tr>
<td>Developmental psychopathologic</td>
<td>Environmental stressors and maladaptive parenting characteristics impact on biological vulnerability to cause schizophrenia. This impact is moderated by child, maternal disorder, and caregiver support characteristics (Wan et al. 2008).</td>
</tr>
<tr>
<td>Dopamine hypothesis</td>
<td>Elevated presynaptic striatal dopamine is a final common effect of multiple specific etiologies and causes psychosis through disruption of incentive salience. In contrast to psychosis, multiple neurophysiological systems underlie negative symptoms of schizophrenia (Howes &amp; Kapur 2009).</td>
</tr>
<tr>
<td>Disconnection</td>
<td>“Impaired control of synaptic plasticity that manifests as abnormal functional integration of neural systems” (Stephan et al. 2006, p. 929), stemming from multiple etiologies causing anatomical disconnection, functional disconnection, or both.</td>
</tr>
<tr>
<td>Endocrine disruption</td>
<td>Synthetic and natural compounds cause “an abnormal endocrine environment, predominantly in fetal life, that leads to schizophrenia” (Brown 2009, p. 256).</td>
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<tr>
<td>Genetic susceptibility</td>
<td>Multiple genes confer susceptibility to schizophrenia; however, the effects of specific genes are confined such that they affect the expression of narrower clinical phenotypes (Owen et al. 2007).</td>
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<tr>
<td>Glutamate and dopamine dysregulation</td>
<td>Reduced activation of NMDA receptors and increased activation of striatal dopamine receptors give rise to the negative and positive symptoms of schizophrenia, respectively (Stone et al. 2007).</td>
</tr>
<tr>
<td>Hippocampal or PFC lesions</td>
<td>The schizophrenia phenotypes arise from primary insults to the hippocampus or prefrontal cortex mediated by abnormal synaptic pruning or myelination affecting limbic system activity (White et al. 2008).</td>
</tr>
<tr>
<td>Meta-theoretical gene-environment interaction</td>
<td>Synergistic interaction of genes and environment yields psychosis through a final common pathway (van Os et al. 2008).</td>
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<tr>
<td>Microbial infection</td>
<td>Early exposure of genetically susceptible individuals to microbial agents (e.g., Toxoplasma gondii, Cytomegalovirus) can result in a schizophrenia syndrome later in development. The key mechanisms are unknown but may be direct or indirect and may involve dopamine synthesis, limbic system structures, or autoimmune responses (Yolken &amp; Torrey 2008).</td>
</tr>
<tr>
<td>Muscarinic hypothesis</td>
<td>Low muscarinic receptor density disturbs cholinergic neurotransmission, engendering psychosis and disruptions of cognitive, motor, and affective functions observed in schizophrenia (Raedler et al. 2007).</td>
</tr>
<tr>
<td>Neural diathesis-stress</td>
<td>A neurobiological diathesis involving the hypothalamic-pituitary-adrenal axis and a cortisol-dopamine link is vulnerable to stressors, particularly those involving social evaluation and uncontrollability (Jones &amp; Fernyhough 2007, Walker et al. 2008).</td>
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<table>
<thead>
<tr>
<th>Theory</th>
<th>Description or quote of core pathology</th>
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<tbody>
<tr>
<td>Neurodevelopment-neurogenesis</td>
<td>Disruption of neurogenesis mediated by genetic (e.g., DISC1) and environmental (e.g., viral infection) factors contributes to risk for schizophrenia and related severe mental disorders (Hennah et al. 2006, Mao et al. 2009).</td>
</tr>
<tr>
<td>Neurodynamic</td>
<td>A reduced prevalence of rapidly conducting cortico-cortical axons gives rise to reduced functional and anatomic asymmetry and, critically, disrupts time-sensitive neurointegration, particularly in the right hemisphere (Miller 2008).</td>
</tr>
<tr>
<td>Nutritional deficiency</td>
<td>Nutritional deficiency (e.g., folic acid deficiency) during critical developmental periods disturbs fetal development, creating congenital abnormalities and risk for schizophrenia (Zammit et al. 2007).</td>
</tr>
<tr>
<td>Schizotaxia-schizotypy</td>
<td>Schizotaxia is a dichotomously inherited brain state, affecting neurointegration through aberrant synaptic transmission, producing through interaction with the environment a personality phenotype that is the liability for schizophrenia (Lenzenweger 2006, Meehl 2004).</td>
</tr>
<tr>
<td>Sensitization</td>
<td>Psychosis is a sensitized response to recurring psychosocial stressors that engender social defeat. The response is mediated by dopamine sensitization disrupting the hypothalamic-pituitary-adrenal axis (van Winkel et al. 2008).</td>
</tr>
<tr>
<td>Traumatogenic</td>
<td>Psychotic experience arises from the interaction of external stressors with information-processing proclivities or impairments: hallucinations, when trauma gives rise to intrusive cognition that is misattributed to external agents because of poor source monitoring; delusions, when attachment and trauma interact with processing biases and negative self-esteem, engendering perceived threat and paranoia (Bentall &amp; Fernyhough 2008).</td>
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</tbody>
</table>

In many instances, an inference of continuity is drawn because the theory is inconsistent with a latent categorical model, because the authors propose a mechanism alongside other etiologies without distinguishing a phenotype, or because the authors implicate the combined action of numerous binary components. Several implicated mechanisms appear to have a dichotomous nature, such as de novo mutations (Cheng et al. 2008) and rare highly penetrant genes (McClellan et al. 2007), or a singular pathway, such as specific etiologies for accelerated aging (Kirkpatrick et al. 2008) and estrogen disruption (Brown 2009). However, these attributes in isolation do not lead to the supposition that schizophrenia is a latent class experience or structure.

The majority of these theoretical notions or hypotheses are not readily converted into conjectures on the latent structure of schizophrenia. Understandably, the models are couched in low- or no-risk speculative terms. Authors qualify their accounts as relating to one of many paths to schizophrenia, as providing a general disposition to the disorder, as accounting for a subset of cases of schizophrenia, or as relating to the symptoms but not the disorder.
However, two exceptions are those put forward by Crow (1990, 2000, 2008) and Meehl (1962, 1990, 2004).

In Crow’s (1995, 2008) theory of psychosis, dimensionality is a proposition alongside universality and absence of an environmental determinant, which together form the basis of his theory that psychoses—affective and nonaffective—emerge from a breakdown in the mechanisms that translate thought to utterance and speech perception to thought. Crow argues that schizophrenia and affective psychoses differ in a quantitative manner only, that both derive from a single genetic mechanism.

Meehl (1962, 1990, 2001, 2004) proposed that schizophrenia is the product of gene–environment interaction. The key inherited attribute is schizotaxia,1 which was defined as a brain state characterized by reduced differentiation of synaptic response probabilities to temporospatial input patterns, the proximal outcome of which is impaired neurointegration. In all cases in which schizotaxia is present, a personality phenotype, schizotypy, develops, although the expressivity of schizotypy is variable and heterogeneous. The relationship between schizotypy and schizophrenia is continuous; there is a discontinuity between schizotypes and the complement nonschizotypes; and affective psychoses fall within the complement group.

Summary
Throughout the history of schizophrenia theorizing and research, few have proposed explanatory models that imply or specify that schizophrenia exists as a discrete latent entity clearly demarcated from other states of psychopathology as well as from normality. Indeed, a commonality of accounts dating back to Hippocrates is the inference of continuous fundamental processes underpinning normality, eccentricity, and mental disease (Maher & Maher 1994), just as is portrayed in the opening quotation from Burton (1628). In contrast, epidemiologists aim to elucidate cause by counting things. Understandably, then, the study of the epidemiology of schizophrenia has been very well served by categorical definitions of the disorder and its subtypes (e.g., Am. Psychiatr. Assoc. 1994). Much of the research on schizophrenia falls into this conceptual hodgepodge: The essence of the disorder is thought to be or is treated as dimensional, but diagnosis is categorical.

EVIDENCE AND ITS DEARTH
There are clear theoretical bases for a broad set of hypotheses on the nature of the experience and population structures of schizophrenia. By far the most commonly implied or expressed view is that schizophrenia is a dimensional construct, although authors seldom verbalize whether they are referring to continuity of experience or population structure. There is also notable support for discontinuities: discontinuities between normalcy and risk states as well as among disorders. Drawing these expectations together, we consider evidence focused on three core expectations.

On Continuity of Experience and Clinical Phenotypes: A Systematic Review
We reasoned that, if the symptom phenotypes are continuous, the rates at which these occur in the general population should be greater than the rate of schizophrenia. To examine this expectation, we undertook a systematic review as follows.

We obtained the intersection of three sets of MEDLINE entries for research published from 1950 to (17 July) 2008: (a) entries containing one or more of the (truncated) keyword phrases “delus,” “hallucinat,” “paranoi,” “thought disorder,” “disorgani speak,” “loose association,” “incoherence,” “derailment,” “tangential,” “negative symptom,” “flat affect,”

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1Meehl’s schizotaxia is fundamentally different from the schizotaxia notion proposed by Tsuang et al. (2000a); these two conceptions occupy different levels of analysis.
“blunt” affect,” “affective flattening,” “alogia,” “poverty of speech,” “avolition,” “disorganized behavior,” “catatonia,” “social isolation,” “social withdrawal,” “psychosis,” “psychotic,” “schizophrenic,” or “schizotyp”; (b) entries containing one or more of “incidence,” “prevalence,” “sensitivity,” or “specificity”; and (c) entries containing “general population,” “normal population,” “normal individuals,” “normal sample,” “healthy population,” “healthy individuals,” “healthy sample,” “community individuals,” “community sample,” “nonpsychotic,” “survival,” “screening,” or “subclinical.” The resulting intersection set contained 2652 entries. We read the title of each paper and, as necessary, the abstract and the paper itself to find reports on the incidence or prevalence of symptoms of schizophrenia in general population samples. Papers were retained in the review if they met all of the following criteria and there was sufficient information to determine that this was the case:

1. The paper describes one or more studies of schizophrenia symptom phenotypes, or experiences resembling such phenotypes, in general population samples.
2. The sample size available for analysis was at least 100.
3. The results included precise incidence or prevalence rates of dichotomous phenotype outcomes, or count data or scores from which such rates could be derived.
4. Participants were not recruited through secondary or tertiary health services (e.g., ophthalmology services), prisons, or aged-care facilities.
5. At least 80% of the sample was less than 65 years of age.
6. Outcome indices do not conflate schizophrenia with nonschizophrenia phenotypes, such as affective or dissociative phenotypes.
7. Schizophrenia symptom phenotypes were not sleep-related (e.g., hypnopompic and hypnagogic hallucinations).

We also searched for other relevant research among citations in papers meeting these criteria. Where possible, we extracted the following variables from each report: A cohort name and attributes, including: sampling population; method of recruitment; response rate; age (range, mean, and standard deviation); the proportions of males and participants older than 64 years; and important sample inclusion and exclusion criteria. Where the proportion of participants older than 64 was not reported, and descriptive statistics for age were available, the standard normal distribution was used to estimate the likely proportion older than 64 years.

We also noted the symptom phenotype and the methods for its assessment, including: instrument names; mode of assessment (self-report, lay interview, professional interview, or observer ratings); number of items in the instrument; the reference timeframe; the threshold number of items with affirmative responses by which phenotype outcome was determined; exclusion criteria applied to affirmative responses (such as stemming from misunderstanding, relating to plausible experience, due to drug use or medical conditions, or relating to inconsequential experience); and in the case of graded ratings, severity, frequency, or other threshold for phenotype presence. If the outcome score conflated two or more schizophrenia symptom phenotypes (e.g., hallucinations and delusions), we recorded the ratio of phenotype items.

We recorded the rate data and data-handling attributes, including weighting to correct for sampling design, reporting of mean rate versus any endorsement, and the denominator. Where more than one rate was available from a cohort or an article, each nonredundant rate was recorded along with the above variables that characterized its derivation.

The analysis objective was to examine the distribution of observed rates in these samples. Following Saha et al. (2008), we did not reduce rates from included studies to meta-analytic or weighted means. This has the considerable disadvantage of obscuring variability in rates. Instead, as Saha et al. (2008) propose, we focus on variability of rates primarily by presenting the collated data graphically. A second advantage of this approach is that it can permit inclusion of multiple rates from cohorts. However, if a
methodological characteristic is correlated with phenotype rates as well as the number of rates or publications per cohort, inclusion of multiple rates from a single cohort could alter the overall observed variability in rates. Therefore, in the case of hallucinations, delusions, and psychosis, for which there were large numbers of prevalence rates, we also used Monte Carlo permutation sampling to model the variability that would have been observed had only one prevalence rate per cohort been reported. Specifically, each of 10,000 permutations involved randomly selecting one prevalence rate from each multirate cohort and the sole rate for single-rate cohorts. The median rate × cumulative relative frequency curve was then obtained, as were the observed 95% margins. Observed margins were smoothed using the loess local polynomial regression smoothing function in R (R Development Core Team 2004). Monte Carlo permutation sampling was not used for incidence rates, of which there were not large numbers.

We identified 56 papers that met criteria for inclusion in the review. These 56 reports contained 285 rates for the prevalence (254 rates) or incidence (31 rates) of hallucinations (81 rates), delusions (68 rates), disorganized speech (6 rates), negative symptoms (7 rates), disorganized behavior (2 rates), or catatonic behavior (2 rates). Some rates related to the presence of any feature of psychosis (here, defined as hallucinations, delusions, or both; 82 rates), any criterion A symptom of schizophrenia (9 rates), social isolation (18 rates), or the combination of psychosis with disorganized speech (10 rates). The 285 rates were derived from analyses of 42 study cohorts. Among the 56 papers, 16 provided a single rate whereas the median number of rates obtained was 3 per paper; one paper provided 48 rates (Rössler et al. 2007).

Table 2 contains descriptive statistics for the observed prevalence and incidence rates, given as percentages. Figure 1 shows cumulative relative frequencies for the prevalence rates. If the prevalence rate of schizophrenia is approximately 0.4% to 0.7% (McGrath et al. 2008) and the annual incidence of schizophrenia is approximately 0.02%, it is clear that specific

Table 2 Percentiles and quartiles for recorded phenotype rates

<table>
<thead>
<tr>
<th>Percentile</th>
<th>n</th>
<th>10th</th>
<th>25th Lower quartile</th>
<th>50th Median</th>
<th>75th Upper quartile</th>
<th>90th</th>
</tr>
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<tbody>
<tr>
<td><strong>Prevalence rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>All</td>
<td>75</td>
<td>0.6</td>
<td>1.5</td>
<td>4.1</td>
<td>10.0</td>
</tr>
<tr>
<td></td>
<td>Permuted</td>
<td>31</td>
<td>1.2</td>
<td>3.1</td>
<td>7.1</td>
<td>14.6</td>
</tr>
<tr>
<td>Delusions</td>
<td>All</td>
<td>63</td>
<td>0.5</td>
<td>1.7</td>
<td>5.9</td>
<td>17.6</td>
</tr>
<tr>
<td></td>
<td>Permuted</td>
<td>29</td>
<td>0.9</td>
<td>2.2</td>
<td>7.2</td>
<td>17.7</td>
</tr>
<tr>
<td>Psychosis</td>
<td>All</td>
<td>69</td>
<td>1.5</td>
<td>4.2</td>
<td>7.4</td>
<td>16.3</td>
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<tr>
<td></td>
<td>Permuted</td>
<td>42</td>
<td>1.3</td>
<td>3.9</td>
<td>11.1</td>
<td>20.9</td>
</tr>
<tr>
<td>Disorganized speech</td>
<td>All</td>
<td>5</td>
<td>1.1</td>
<td>2.2</td>
<td>4.8</td>
<td>18.0</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>All</td>
<td>6</td>
<td>0.6</td>
<td>1.1</td>
<td>2.3</td>
<td>16.9</td>
</tr>
<tr>
<td>Social isolation</td>
<td>All</td>
<td>17</td>
<td>5.6</td>
<td>7.2</td>
<td>10.0</td>
<td>22.0</td>
</tr>
<tr>
<td><strong>Incidence rates</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hallucinations</td>
<td>All</td>
<td>6</td>
<td>0.8</td>
<td>1.4</td>
<td>1.7</td>
<td>3.9</td>
</tr>
<tr>
<td>Delusions</td>
<td>All</td>
<td>5</td>
<td>1.2</td>
<td>1.6</td>
<td>5.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Psychosis</td>
<td>All</td>
<td>13</td>
<td>1.0</td>
<td>1.0</td>
<td>2.0</td>
<td>11.4</td>
</tr>
<tr>
<td>Disorganized speech</td>
<td>All</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>6.7</td>
<td>—</td>
</tr>
<tr>
<td>Negative symptoms</td>
<td>All</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>0.9</td>
<td>—</td>
</tr>
<tr>
<td>Social isolation</td>
<td>All</td>
<td>1</td>
<td>—</td>
<td>—</td>
<td>9.0</td>
<td>—</td>
</tr>
</tbody>
</table>

Note: Phenotype rates are given as percentages.
Cumulative relative frequencies of schizophrenia phenotype prevalence rates. For disorganized speech, negative symptoms, and social isolation, the plot (lower right) shows all available rates. For hallucinations, delusion, and psychosis, the curve is the median cumulative relative frequency obtained using Monte Carlo permutation sampling, with 95% confidence intervals (dashed lines) and loess smoothed 95% confidence intervals (shading).

Figure 1

Specific symptoms are 3 to 28 times more prevalent and up to 2.6 orders of magnitude more incident than the disorder. A second key observation from these data is that there is significant variability of the rates across studies. In an earlier but narrower review (van Os et al. 2009), we found that higher prevalence rates of the psychosis phenotype were associated with less education, unemployment, immigrant status, ethnic minority status (except Asian ethnic status), lower income, being unmarried, being male, history of substance misuse (alcohol, marijuana, and other drugs), exposure to trauma or significant stressors, and greater urban density. Similarly, higher
incidence was associated with fewer years of education, ethnic minority status, substance misuse (alcohol, marijuana, and other drugs), and exposure to trauma or significant stressors. Below we consider other contributions to this heterogeneity in rates.

In conclusion, these reviews show there is clear evidence that is consistent with continuum models of schizophrenia signs and symptoms.

Sources of Heterogeneity in Phenotype Studies

When reviewing this research on rates of symptom phenotypes, it became apparent that several method, sample, and data-handling variables might account for some of the significant variance in the rate data. Therefore, a second set of analyses was undertaken to evaluate the contribution of cohort and design variables to variance in observed rates. These analyses were conducted on prevalence rates collapsed across hallucination, delusion, and psychosis phenotypes. Again, Monte Carlo permutation sampling was used to simulate outcomes that would have been observed if just one rate per cohort was available. Permutation sampling was conducted in the same manner as described above. Two independent permutation-sampling analyses were conducted.

The first permutation sampling was used to examine bivariate associations between prevalence rates and individual design and cohort variables. The latter included cohort variables (convenience sampling, response rate, mean age of cohort, percentage of males in cohort, and sample size), assessment variables (mode of assessment, number of items in assessment instrument, the proportion of items pertaining to delusions, and the reference interval or period), experience criterion variables (application of phenotype exclusion criterion, qualitative response criterion, quantitative criterion), and analysis variables (use of population weighting and reporting of mean endorsement versus any endorsement scores). Convenience sampling of participants was coded 1 = convenience sampling or 0 = any other method of recruitment. Mode of assessment was coded 0 = self-report, 1 = lay assessment, or 2 = professional assessment. Phenotype exclusions was scored using four levels: 3 = excluded experience judged to be inconsequential (i.e., having no impact on the respondent) or culturally appropriate, 2 = excluded experience attributable to drugs or general medical conditions, 1 = excluded experience judged to be realistic or as arising from misunderstanding of item content, or 0 = no reported exclusions. Quantitative response criterion refers to the number of affirmative item responses required for the phenotype to be judged present. Qualitative criterion represented frequency, severity, or probability criteria and was scored 0 = none or ≥ low frequency or none or ≥ low severity or no criterion, 1 = ≥ sometimes or ≥ medium severity or likely or possible probability, or 2 = ≥ often or ≥ high severity or ≥ definite or probable presence. Independent permutation samples were obtained for each variable.

On each permutation, point-biserial \( r \) was calculated for dichotomous variables and Spearman’s rho from rankings of the remainder. The median correlation coefficients were used to estimate \( r^2 \) and exact 95% margins and \( p \) values were derived from the distributions of \( r \)-values.

The second permutation sampling procedure was used to evaluate a weighted multivariate least-squares regression model of prevalence using cohort and design variables for which the observed bivariate \( p \) values were ≤0.10. In these analyses, the dependent measure was the arcsine-root transformed prevalence rates, and the independent variables were the ranks of the cohort and design variables; sample size was used as a weighting coefficient. Where there was a missing value for a dependent variable, the mean rank was used. The primary result of interest from these permutations was the multiple \( r^2 \).

Microsoft Excel was used to compute bivariate correlation coefficients and to obtain all Monte Carlo permutation samples. The R (R Dev. Core Team 2004) lm (linear modeling) command was used to run regression models.
Table 3 shows the results of the first permutation sampling procedure, giving $r$- and $r^2$-values for 15 cohort and design variables. To facilitate evaluation of the significance of these coefficients, we also computed Yule’s approximations of phi-coefficients from odds ratios (Bonett 2007) for the associations between psychosis experiences and demographic and non-genetic risk factors reported in an overlapping review (van Os et al. 2009). From Table 4, which gives these approximations, it is apparent that the most influential demographic risk factors (minority status, unemployment, having never been married) may account for up to 2.3% of variance in rates of psychosis experience. For non-genetic environmental risk factors, the most influential (cannabis, other illicit drugs) may account for up to 9.6% of variance in rates. Nearly half of the cohort and design variables may account for 10% or more of the observed variance in the psychosis prevalence rates; three account for 20% or more of this variance (Table 3). Rates are considerably higher in studies using smaller $n$, convenience sampling, and self-report assessment modes.

The second permutation sampling analysis used the combined pool of cohort and design variables to predict prevalence rates. The median multiple $r^2$ estimate obtained from 10,000 permutations was 0.54 (95% margins = 0.27 to 0.73), suggesting over half of the observed study heterogeneity is attributable to methodological factors. (The reverse transformed value of the median intercept was 0.067, providing an estimated median prevalence of psychosis experience of 6.7%.)

### On Boundaries Between Normality and Abnormality

The second and third expectations concern continuity in population structure. In the face of the substantial body of correlational evidence that is available—particularly factor analytic studies—and the ubiquity of continuum viewpoints, we reasoned that evidence contrary to continuum viewpoint would be more informative than evidence in favor of it. We also

### Table 3 Contribution of method variables to variance in prevalence rates

<table>
<thead>
<tr>
<th>Variables</th>
<th>$r^2$</th>
<th>$r$</th>
<th>95% margins</th>
<th>$p$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cohort variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convenience sampling</td>
<td>0.20</td>
<td>0.44</td>
<td>0.29, 0.62</td>
<td>0.000</td>
</tr>
<tr>
<td>Response rate</td>
<td>0.10</td>
<td>0.31</td>
<td>0.13, 0.48</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean age</td>
<td>0.09</td>
<td>−0.31</td>
<td>−0.48, −0.11</td>
<td>0.001</td>
</tr>
<tr>
<td>Percent males</td>
<td>0.01</td>
<td>−0.12</td>
<td>−0.25, 0.03</td>
<td>0.058</td>
</tr>
<tr>
<td>Sample size ($n$)</td>
<td>0.24</td>
<td>−0.49</td>
<td>−0.61, −0.35</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Assessment variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mode</td>
<td>0.26</td>
<td>−0.51</td>
<td>−0.64, −0.36</td>
<td>0.000</td>
</tr>
<tr>
<td>Number of items</td>
<td>0.07</td>
<td>0.27</td>
<td>0.10, 0.44</td>
<td>0.001</td>
</tr>
<tr>
<td>Reference interval</td>
<td>0.16</td>
<td>0.40</td>
<td>0.22, 0.55</td>
<td>0.000</td>
</tr>
<tr>
<td>Proportion delusions</td>
<td>0.00</td>
<td>0.05</td>
<td>−0.14, 0.25</td>
<td>0.291</td>
</tr>
<tr>
<td><strong>Criterion variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phenotype exclusions</td>
<td>0.10</td>
<td>−0.32</td>
<td>−0.48, −0.15</td>
<td>0.000</td>
</tr>
<tr>
<td>Response criteria</td>
<td>0.08</td>
<td>−0.29</td>
<td>−0.30, 0.05</td>
<td>0.047</td>
</tr>
<tr>
<td>Qualitative criteria</td>
<td>0.00</td>
<td>−0.03</td>
<td>−0.20, 0.14</td>
<td>0.618</td>
</tr>
<tr>
<td>Composite</td>
<td>0.16</td>
<td>−0.40</td>
<td>−0.53, −0.23</td>
<td>0.000</td>
</tr>
<tr>
<td><strong>Analysis variables</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weighting</td>
<td>0.08</td>
<td>−0.28</td>
<td>−0.44, −0.12</td>
<td>0.000</td>
</tr>
<tr>
<td>Mean versus any endorsement</td>
<td>0.01</td>
<td>0.08</td>
<td>−0.12, 0.31</td>
<td>0.246</td>
</tr>
</tbody>
</table>

Note: The 95% margins are the exact $r$-values at the 2.5 and 97.5 percentiles, and the $p$-values are the exact proportion of $r$-values for which $r \leq 0$ or $r \geq 0$.

### Table 4 Odds of psychosis experience given risk factor exposure

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>OR (95% CI)</th>
<th>phi</th>
</tr>
</thead>
<tbody>
<tr>
<td>Younger age</td>
<td>1.02</td>
<td>(0.99–1.05)</td>
</tr>
<tr>
<td>Less education</td>
<td>1.24</td>
<td>(1.12–1.38)</td>
</tr>
<tr>
<td>Unemployment</td>
<td>1.63</td>
<td>(1.38–1.92)</td>
</tr>
<tr>
<td>Immigrant</td>
<td>1.20</td>
<td>(1.01–1.43)</td>
</tr>
<tr>
<td>Asian minority</td>
<td>0.56</td>
<td>(0.42–0.74)</td>
</tr>
<tr>
<td>Ethnic minority</td>
<td>1.81</td>
<td>(1.51–2.16)</td>
</tr>
<tr>
<td>Lower income</td>
<td>1.32</td>
<td>(1.14–1.52)</td>
</tr>
<tr>
<td>Not married</td>
<td>1.72</td>
<td>(1.46–2.02)</td>
</tr>
<tr>
<td>Male sex</td>
<td>1.12</td>
<td>(1.03–1.21)</td>
</tr>
<tr>
<td>Alcohol</td>
<td>1.93</td>
<td>(1.49–2.50)</td>
</tr>
<tr>
<td>Cannabis</td>
<td>2.59</td>
<td>(2.04–3.27)</td>
</tr>
<tr>
<td>Other drugs</td>
<td>3.59</td>
<td>(2.44–5.28)</td>
</tr>
<tr>
<td>Stress or trauma</td>
<td>2.15</td>
<td>(1.82–2.54)</td>
</tr>
<tr>
<td>Urbanicity</td>
<td>1.25</td>
<td>(1.17–1.33)</td>
</tr>
</tbody>
</table>

Note: OR, odds-ratio; CI, confidence interval. Adapted from van Os et al. (2009).
reasoned that only evidence which was derived using factor mixture modeling (FMM; Muthén & Asparouhov 2006) or coherent-cut kinetic (CCK; Waller & Mehl 1998) methods could provide a robust basis for rejection of a continuum model in favor of a model involving a nonarbitrary boundary between normality and schizophrenia. This is because, unlike factor analysis, cluster analysis, and latent class analysis, only FMM and CCK procedures provide for either outcome. In contrast, one can never use factor analysis to contrast categorical and continuum models; it always results in the identification of continua, regardless of the true latent structure. Similarly, latent class analysis will always result in the identification of categories, regardless of the true latent structure. More detail on these procedures and their limitations is available elsewhere (Linscott et al. 2009a,b; Meehl 2004; Muthén & Asparouhov 2006).

Therefore, our second hypothesis is that there is a nonarbitrary boundary between schizophrenia and normality. To examine this hypothesis we undertook a systematic search for CCK and FMM studies of schizophrenia signs and symptoms. We used the following approach.

We obtained the intersection of three sets of MEDLINE entries for research published from 1950 to (July) 2009: (a) entries containing one or more of the (truncated) keyword phrases “schizophren,” “schizoaffect,” “psychosis,” “psychotic,” or “schizotyp”; (b) entries containing one or more of “class,” “kind,” “type,” “subtype,” “taxa,” “taxon,” “taxonomic,” “taxonomic,” “categorical,” “categorial,” “continu,” “discontinu,” “discrete,” or “mixture”; and (c) entries containing “latent,” “underlying,” “structure,” “structural,” “hidden,” or “unobserved.” The resulting intersection set contained 1247 entries, of which 864 were nonreview human research papers. We read the title of each paper and, as necessary, the abstract and the paper itself to find reports on the latent structure of schizophrenia or schizophrenia-related phenotypes in general population samples.

We identified 15 reports that address an aspect of this issue, the majority of which described studies of self-report data from schizotypy questionnaires completed by university students (Blanchard et al. 2000, Fossati et al. 2007, Horan et al. 2004, Keller et al. 2001, Korfine & Lenzenweger 1995, Lenzenweger 1999, Lenzenweger & Korfine 1992, Linscott 2007). Several other similar studies examined primary health patients (van Kampen 1999), school children (Fossati et al. 2007, Linscott et al. 2006), or mixed-source samples (Meyer & Keller 2001, Rawlings et al. 2008). Two reports describe data from biological offspring of mothers with schizophrenia (Erlenmeyer-Kimling et al. 1989, Tyrka et al. 1995), but only the latter of these used measures of schizophreniarelated symptoms. One report examined data from endophenotype measures (attention and eye-movement variables) in a general population sample (Lenzenweger et al. 2007).

The 12 reports examining psychometric risk include 50 analyses conducted on 14 samples; only two of the analyses (Keller et al. 2001) involved an FMM-like analysis method. Of these 50 analyses, four yielded ambiguous results, 16 yielded results that are consistent with a dimensional interpretation, and the remaining 30 yielded results consistent with a categorical interpretation. However, 10 of these analyses, relating to 1 ambiguous result, 7 dimensional results, and 2 categorical results, were fundamentally flawed because of significant violations of test assumptions (Fossati et al. 2007) or serious biases inherent in the population sample (Rawlings et al. 2008). None of the studies involved representative epidemiological samples of the general population.

Among those unambiguous findings that clearly pertained to positive or negative features of psychometric risk, regardless of the sample or multiple analyses, 26 findings suggested risk for schizophrenia is categorical, whereas 13 suggested it is dimensional. The probability of observing this pattern of results, assuming outcomes were random and equally likely, is 0.015, suggesting this is not a chance pattern of findings. These findings included some sample-measure instances that were analyzed with more than one CCK- or FMM-related method,
providing multiple results to this analysis. However, taking a narrower set of findings—a single (unanimous, in the case of multiple analyses) finding per sample-measure instance, and excluding flawed analyses (Fossati et al. 2007, Rawlings et al. 2008)—did not change this pattern, with 15 observations favoring a categorical interpretation and 5 a dimensional interpretation, and a binomial probability test statistic = 0.015.

Taking all results consistent with a categorical interpretation, we separated estimates of the prevalence based on negative schizotypy and positive schizotypy scores, plotting cumulative relative frequencies (Figure 2). For the broader set of findings just described, this yielded median prevalence estimates for positive and negative schizotypy categories of 12% and 11%, respectively. For the narrower set, median prevalence estimates for positive and negative schizotypy were both 11%.

In summary, these findings are inconsistent with continuous population structure models. The weight of evidence suggests there is a nonarbitrary boundary between those with and without schizophrenia. Certainly, the prevalence estimates of the psychometric risk categories indicate that this nonarbitrary boundary is well below the threshold for schizophrenia, capturing approximately 11% of the population. Coincidentally, the median prevalence of psychosis or psychosis-like experience, reviewed above, is very similar to this estimate. Whereas the psychometric risk findings suggest some consistency between positive and negative attributes of psychometric risk, it is not clear that analyses of these data are detecting the same latent category of risk (Horrigan et al. 2004, Linscott 2007). Commenting on the same literature, Beauchaine et al. (2008) described evidence of nonarbitrary boundaries of psychometric risk for schizophrenia as one of the most well-replicated latent structure findings in psychopathology.

On Boundaries Among Psychopathologies

The third hypothesis is that there are nonarbitrary boundaries between schizophrenia and other psychopathologies or that there are nonarbitrary schizophrenia subtypes. As far as we could ascertain, only two reports address this hypothesis.
The first of these conducted a test of the hypothesis that deficit schizophrenia is a discrete class comprising approximately 30% of those with schizophrenia (Blanchard et al. 2005). The sample \((n = 238)\) was one ascertained for a treatment outcome study conducted by the National Institute of Mental Health. The primary analysis variables were asociality, alogia, blunted affect, and avolition during the past week. These were derived from ratings on the Scale for the Assessment of Negative Symptoms (SANS) and the Brief Psychiatric Rating Scale (BPRS) taken during the treatment baseline and at six-month follow-up. Carefully conducted CCK analyses yielded compelling evidence of a categorical latent structure, with a deficit class prevalence of 28%. Subsequent comparison of the deficit and nondeficit classes suggested members of the former were more probably male and never married, exhibited poorer social functioning across multiple relationship domains, and had higher BPRS scores, particularly on anergia and disorganization items.

Although the study was well executed, one potential interpretive problem stands out. Data from treatment outcome studies contain a clear source of systematic variance: Some participants receive the active treatment; others do not. Blanchard et al. (2005) demonstrated that treatment condition did not predict class membership. However, it is not treatment assignment that is the primary concern. Rather, treatment response—regardless of treatment condition—could have significantly affected the follow-up assessment and introduced a treatment response–related nonarbitrary boundary within the data.

The second major report in this area was less theoretically driven (Cuesta et al. 2007). It explored reality distortion, disorganization, and negative symptom variables in a sample of 660 consecutive admissions with one or more signs or symptoms of psychosis. The analysis variables were derived from a factor analysis of SANS and Scale for the Assessment of Positive Symptoms (SAPS) scores. Results from CCK analyses were quite ambiguous, supporting neither continuum nor categorical interpretations. This ambiguity appears to be attributable to a simple violation of the assumptions of the CCK methods they used: These methods require unidimensional monotonically related variables (Maraun & Slaney 2005, Meehl 1999). That is, if CCK methods are to be applied appropriately, the variables included in the analysis must all be more or less uniformly and non-negatively correlated (i.e., correlations among variables must all be \(\geq 0\) or \(\leq 0\)). If a class structure is present and some correlations among variables are positive and others negative, the variables likely tap into multiple different latent categories (Meehl 1999). This was the case in Cuesta et al. (2007): Reality distortion was negatively correlated with both disorganization and negative symptoms, whereas disorganization and negative symptoms were positively correlated.

In summary, there is a significant dearth of evidence on schizophrenia-related phenotype boundaries within psychopathology. One report suggests evidence of a nonarbitrary boundary between deficit and nondeficit schizophrenia; however, this may be attributable to a source of systematic error variance. A second applied CCK methods to symptom dimension scores in a manner that invalidated its results. Several other smaller reports appear in the literature but lack the detail required to judge the significance of the findings. For example, Bell (1997) reported disorganization symptoms are categorical, and Blanchard et al. (2005) also refer to having analyzed disorganization symptom scores but did not describe the results.

**Summary**

Theory and practice give rise to diverse expectations about the latent structure and experience of schizophrenia phenotypes. Extant research provides clear evidence of continuity between clinical signs and symptoms, whether positive or negative, and schizophrenia-like subclinical experience and behavior. However, a range of methodological and design variables affect observed rates. Evidence also suggests that differences among members of the general
population, in respect to these experiences and behavior, are not solely quantitative; evidence of a nonarbitrary, qualitative boundary exists. As far as we can tell, there have been no unbiased examinations of whether there are also nonarbitrary boundaries within the psychoses.

It was demonstrated that narrowing the focus onto specific symptom phenotypes in the general population might assist in elucidating boundary issues reflecting different aspects of continuity. It was also shown, however, that this strategy is vulnerable to systematic error variance introduced by cohort and design variables. Using studies of the prevalence of psychosis phenotypes, we show that this source of error variance can account for up to 10 times the variance explained by demographic risk factors and more than twice the variance explained by the most potent nongenetic environmental risk factor.

DOES DSM PROVIDE THE REQUIREMENTS OF A SCIENTIFIC CONCEPT ON WHICH PHENOTYPIC FINDINGS CAN ADVANCE?

Without dampening enthusiasm for continuum (van Os et al. 2000) and categorical (Linscott 2007) viewpoints, there are significant challenges and limitations inherent in the literature reviewed here. These include methodological explanations for evidence of continuity of experience; the influence of tradition on definitions of schizophrenia; calls for incorporation of genotype or endophenotype measures in classification; and limitations on the interpretation of evidence of boundaries derived from phenotype measures.

Continuity of Experience as an Assessment Artifact

There are two reasons for suggesting that continuity of experience may be an assessment artifact of sorts. Evidence that psychosis and other phenotypes of schizophrenia are more common than the disorder itself may be due entirely to the arbitrary nature of the threshold for its diagnosis, the diagnostic requirement of impairment in functioning, or both. Taking a different viewpoint, continuity of experience is evident because, for example, DSM is artificially restrictive, requiring the combination of two key features—or in some presentations, one—as well as significant compromise in functioning. Consequently, to say that the prevalence of schizophrenia is 0.7% is simply to say that the current-day arbitrary convention places the cut for the disorder above the 99th percentile of the general population (Crow 2008, Meehl 1973). Although this criticism undermines the logic of the argument that continuity is implied when phenotype prevalence is greater than diagnosis prevalence, the crux of the problem lies with the diagnosis, not the phenotype. Arguments for the continuum viewpoint are redeemed by the more compelling evidence that the phenotype, in subclinical forms, is associated with the same demographic and nongenetic risk factors as schizophrenia (van Os et al. 2009; see also Table 4).

Second, evidence that psychosis and other phenotypes of schizophrenia are more common than the disorder may be due entirely to the facility of language—the item content of measures as a vehicle for creative portrayals of lesser phenotypes or euphemistic interpretations of clinical experience. Compare the contrasting hallucination-related content of instruments. DSM-IV schizophrenia may be diagnosed where “hallucinations consist of a voice keeping up a running commentary on the person’s behavior or thoughts, or two or more voices conversing with each other” (Am. Psychiatr. Assoc. 2000, p. 312). However, experience may be indicated with an affirmative response to the item “Did you at any time hear voices saying quite a few words or sentences when there was no-one around that might account for it?” (Johns et al. 2004, p. 300), “Over the past year, have there been times when you heard or saw things that other people couldn’t?” (Johns et al. 2004, p. 300), “No matter how hard I try to concentrate, unrelated thoughts always creep into my mind” (Bentall & Slade 1985, p. 528), or “Sometimes a passing thought
will seem so real that it frightens me” (Bentall & Slade 1985, p. 528). The first two questions are items in the Psychosis Screening Questionnaire; the others are items in the Launay-Slade Hallucination Scale (LSHS; Launay & Slade 1981). Each of these items was relied upon by authors of papers included in the systematic review of phenotype experience (Aleman et al. 2001; Bentall & Slade 1985; Johns et al. 2002, 2004; Larøi et al. 2004; Stefanis et al. 2004; Wiles et al. 2006).

What is the true significance of affirmative responses to these sorts of questions? A clear vulnerability conferred by these sorts of rating scales is tautological reasoning. Consider the LSHS (Launay & Slade 1981). The authors’ intention was to write some items that are clearly of a clinical nature (e.g., “I have been troubled by hearing voices in my head”) as well as items focused on related but milder experiences, as above. Moreover, the authors also used an item-analysis method to whittle down the content of the LSHS to produce a unidimensional instrument with items with differing completion probabilities (item difficulties). That is, the authors explicitly presupposed a latent dimensional structure to their instrument. A similar but more gross item-difficulty variation is evident in the Psychosis Screening Questionnaire. Finding that the prevalence of experience, measured with these and similar measures, is higher than the prevalence of schizophrenia is a simple consequence of instrument design. In itself, the tautology is not a fatal problem (Miller 2008). However, it leaves us pondering whether clinician- and self-report measures, such as those used in studies reviewed here, are the best tools available for rigorous testing of continuum versus category models of schizophrenia.

The Homogenizing Effect of Diagnostic Tradition

The flip side of the assessment-artifact criticism is that the field is intrigued by continuity because of the homogenizing effect of diagnostic tradition. According to many, advances in the understanding and treatment of schizophrenia go hand in hand with advances in the classification of the disorder (e.g., Bentall & Fernyhough 2008, Craddock et al. 2006, Intl. Schizophr. Consor. 2009, Jansson & Parnas 2007, Owen et al. 2007, Raedler et al. 2007, Stephan et al. 2006, Tsuang et al. 2000a, Uhlhaas et al. 2008, Yolken & Torrey 2008). However, tradition has a powerful influence over current-day diagnostic practice.

Consider DSM-IV (Am. Psychiatr. Assoc. 2000). By far the most frequently counted thing in schizophrenia research is evidence meeting or surpassing the APA’s criteria for schizophrenia, published in editions of the DSM (Am. Psychiatr. Assoc. 1980, 1987, 1994). Many more definitions of schizophrenia are available (Jansson & Parnas 2007), and the ICD (e.g., World Health Org. 2004) and Research Diagnostic Criteria (RDC; Spitzer et al. 1978) also feature prominently in contemporary literature. Nevertheless, DSM is the most commonly used instrument for diagnosis in schizophrenia research. Without a sea change in this field, this will continue to be the case. However, surveying its history, several observations give rise to the suggestion that DSM significantly constrains advancement in schizophrenia research and, more specifically, understanding of its nature and causes.

First, DSM was designed to serve as broad an array of interests as possible, although not equally well (Am. Psychiatr. Assoc. 1952, 1968). In the history of DSM, science has been both the latecomer and the poor cousin to clinical utility. Contrary to a claim in DSM-IV (Am. Psychiatr. Assoc. 1994, p. xvi), DSM nomenclature is not grounded in empirical evidence but rather in clinical utility, tradition, and consensus agreement (APA 1952, 1980, 1987, 1994; Crow 2008). Beneath these, of course, is the vital contribution of clinical experience of generations of clinicians schooled in psychiatric tradition. Other factors influencing its development, including the desire for consistency across revisions, administrative expediencies, reimbursement issues, and pedagogical merit, have been at least on par with scientific evidence.
Consequently, DSM-IV does very well in clinical practice and, no doubt, DSM-V will do even better; clinical utility is a key strength of DSM-IV. However, just as Crow (1990) savored the possibility that his propositions about psychosis would be demonstrated to be erroneous, a scientific epidemiology of schizophrenia desperately needs a conceptual model of schizophrenia that can be rejected and left behind. The DSM development and revision process is neither nimble nor quick enough to serve this purpose, nor is it focused on this purpose.

Second, the APA’s (1980, 1987, 1994, 2000) assertion that DSM classifications have no conceptual meaning creates a significant conundrum. In this context, evidence of inadequate construct validity for a particular DSM classification is neither here nor there—perhaps even consistent with the goal to have an atheoretical classification system. It is not simply that the DSM schizophrenia concept cannot be rejected. Instead, there is no concept to reject.

This qualification also constrains interpretation of research findings. For example, there is abundant evidence that may be construed as validating DSM schizophrenia: Modeling analyses suggest the clinical phenotype of schizophrenia construct is multifaceted (Liddle 1987); longitudinal analyses suggest a small number of outcome profiles (an der Heiden & Häfner 2000); neuropsychological studies indicate strong associations with neuromotor, attention, memory, and higher-order impairments (Heinrichs & Zakzanis 1998); epidemiological studies indicate robust associations with exposure to stress-laden environmental factors (van Winkel et al. 2008)—we could go on and on. If DSM schizophrenia is atheoretical, these consistencies relate to a cluster of symptoms that co-occur yet possess no meaning.

Third, the level of attention given to the reliability of classifications combined with little or no attention to diagnostic validity is seriously problematic. The reliability of a measure (diagnosis) is readily improved by basic mechanical changes to the device, such as by reducing heterogeneous item content or increasing the number of items. DSM-I and DSM-II diagnoses were unreliable in part because these were single-item or prototype instruments. By replacing the single item, or prototype, with multiple items (criteria) and a basic algorithm for combining item data, as in DSM-III, the influence of observer variance in the threshold for diagnosis is significantly restricted and overall error variance is reduced, improving reliability. Improved reliability may be expected to have two effects. First, improved reliability engenders increased confidence in the authenticity of the associated latent construct. If this construct is an arbitrary classification, reliability contributes to its reification. Secondly, it strengthens the sense that the field can agree that it is looking at the same thing, from which some may infer that the field agrees on what it is looking at, despite the epistemic cautions.

In summary, despite its frequent use, DSM does not provide the basic requirements of a scientific concept on which the epidemiology of schizophrenia can advance (Cronbach & Meehl 1955). There is a significant gulf between the tradition on which DSM-IV schizophrenia is based and the knowledge that has accumulated in the recent decades, knowledge that could be employed to identify, examine, and reject more homogeneous disorder concepts.

One could counter that DSM does not necessarily constrain a scientific epidemiology of schizophrenia: Researchers could develop and test criteria in samples of patients with DSM-IV schizophrenia or in relatives of DSM-IV schizophrenia probands, and so on. However, this counterargument requires the assumptions that (a) the DSM-IV criteria correspond to empirical and not arbitrary boundaries, and (b) the research classification is a true subset of DSM-IV schizophrenia. Both these assumptions are untenable, as described in respect to schizotypia (Tsuang et al. 2000a) and deficit schizophrenia (Kirkpatrick et al. 2001).

Our focus on DSM also invites the criticism that other classification systems are more meaningfully construed. This is a fair criticism. In defense, however, although there are some dissimilarities among the available systems for
diagnosing schizophrenia, similarities outweigh these. In several studies, authors have examined the consistency of schizophrenia diagnostic systems (Bell et al. 1998, Gift et al. 1980, Peralta & Cuesta 2005). In the most recent of these, patients meeting the inclusion criterion of exhibiting one or more psychotic or negative symptoms were diagnosed using 23 systems for the classification of schizophrenia.

The resulting data were subject to factor analysis, and three dimensions were identified (Figure 3): a general schizophrenia factor that loaded heavily on 20 of the 23 systems; a Schneiderian factor that captured a contrast between the Schneider and Cloninger systems on the one hand, and Feighner, Kraepelin, Langfeldt, and DSM systems on the other; and a Bleulerian factor that captured a contrast between the Bleuler and Vienna systems on the one hand, and the ICD-10, DSM, RDC, and Schneider systems on the other. With the second and third factors having more contrasting loadings, the authors interpreted these results as indicating that there is a single general schizophrenia factor, analogous to the general intelligence factor, g (Peralta & Cuesta 2005).

A more mundane interpretation is that those who have developed diagnostic systems tend to hold roughly similar conceptions of schizophrenia, with some minor departures from a generalized or modal concept reflecting the impact of, for example, Schneider’s and Bleuler’s viewpoints, respectively. Thus, the underlying dimension is item difficulty conflated with the expressivity of schizophrenia; it is more difficult to obtain a diagnosis of schizophrenia with Feighner’s criteria than with Cloninger’s criteria (Jansson & Parnas 2007). In a similar vein, Faraone & Tsuang (1994) encourage the application of related statistical procedures to derive evidence of diagnostic accuracy for psychiatric classifications.

This alternative mundane interpretation proceeds from the fact that experts’ conceptions of schizophrenia are more proximal to Peralta & Cuesta’s (2005) observed data than the essence of schizophrenia (Figure 4). Outcome variance may be rooted in phenotype
variance. However, raw phenotype variance is readily altered or obliterated by transformations. Consider their DSM data: Observed data were binary, 1 indicating the presence of DSM-IV schizophrenia, 0 the complement outcome. In this context, the transformation rules derive from the DSM-IV task force that determined the schizophrenia classification: The task force, weighing the interests of stakeholders, determined the classes and the class rule sets; those developing assessment devices or determining interview content look to rule sets to guide instrument development; the interview content constrained the interviewer to focus only on those phenotypes relevant to the rule sets; the interviewer relies on complex cognitive efficiencies developed over the course of prior experience to weigh patients’ anamneses, converting these analogue signals to binary item outcomes; the interviewer and the individuals comprising the task force and developing the assessment device carry the influence of their training in psychopathology; the class rule set is applied to the binary item data. At what point does self-report of an ununderstandable comment on a religious deity convert to Criterion A1 = 1? It is also notable that DSM-III-R, DSM-IV, and ICD-10 are the systems on which the general schizophrenia factor loaded the most. Across the 23 systems, loadings based on the whole sample (n = 660) were significantly correlated with inter-rater reliability estimates derived using a subsample of n = 33 consecutive admissions, with r = 0.49, p = 0.02. For the 17 systems with the strongest loadings (i.e., ≥0.65), diagnostic agreement accounts for 90% of the variance in the loadings (Figure 3B).

A more compelling defense of generalization from DSM to other systems is provided by Jansson & Parnas (2007), who completed a systematic review of polydiagnostic research. Two of their conclusions are pertinent. Of the 40 or so diagnostic systems for schizophrenia, none has been demonstrated to have superior validity. More concerning, however, Jansson & Parnas (2007) observe “what is conspicuously lacking in the polydiagnostic studies is a serious and systematic reflection on the conceptual validity of [schizophrenia, that is] what we take this illness to be in the very first place” (italics in original; p. 1194).

**Statistical Limitations and Interpretation**

Evidence of correlation between two variables obtained on a sample does not imply a single
continuous population structure underlies the data. Nor would this imply the absence of a commingled (two- or more-group) population structure. Indeed, CCK methods, which can be used to test for latent categorical population structures, do not work when variables are not correlated (Waller & Meehl 1998). Similarly, methods such as factor analysis cannot rule out the presence of latent categories of people, and latent class analysis cannot rule out continuum models of schizophrenia (Linscott et al. 2009a). Very few methods provide exploratory and unbiased contrasts of continuum versus category models (Muthén & Asparouhov 2006, Waller & Meehl 1998).

Some of these methods have been used to demonstrate evidence of latent structures consistent with categorical viewpoints of schizophrenia. However, there are notable limitations of this evidence. Foremost among these is that demonstration of a latent categorical structure does not imply identification of a natural kind. Instead, all that can be said with any confidence is that the data appear to derive from a population in which there is a latent statistical discontinuity that happens to be large enough to be noticeable (Meehl 2004). Whether discontinuity or dimensionality derives from a disease etiology, research design (Beauchaine & Waters 2003), psychometric properties (Launay & Slade 1981), or some artifact (Blanchard et al. 2005) is a matter of interpretation.

In the bulk of studies that yield evidence of categorical latent structures, researchers have not gone nearly as far as they could to facilitate interpretation through convincing design and methodology. For example, the inventor of CCK methods envisaged that testing of latent structure models would be based on variables spanning a diversity of schizophrenia phenotypes, including anatomical features (e.g., dermatoglyphic asymmetry), neurological softsigns (e.g., dysdiadochokinesia), psychophysiological anomalies (e.g., as in smooth pursuit eye movements), impaired cognition (e.g., of attention), language disturbance (e.g., reduced referential cohesion), and self-report schizotypy questionnaires (Meehl 1973, 1990). Unfortunately, the majority of studies we identified examined only a single level of description, typically self-report of psychosis-like experiences.

Use of a broad range of variables has two distinct advantages. First, this strategy is much less vulnerable to artifacts that may be inherent in single measures that operate at a single level of description (e.g., the LSIS). Second, this strategy affords more compelling evidence that any latent class is meaningfully related to the construct researchers are presuming to measure. If the data derive from a single level (e.g., self-report or performance on a continuous performance test, but not both), confidence that the resulting class really represents schizophrenia and is etiologically meaningful is likely to be a function of how convinced one is in the construct validity of the measure. In contrast, if data span the range of phenotypes, endophenotypes, and even genotypes that are strongly associated with—albeit not pathognomonic of—schizophrenia, a clear CCK or FMM result would have a much less confounded interpretation.

Finally, it is unclear how these statistical methods handle nonlinear continua. That is, if the population structure of schizophrenia is continuous but the relationship between load for schizophrenia—whether genetic (G), environmental (E), or G × E—and expression of schizophrenia is not linear, at what point do these methods convert the nonlinear continuum to a class solution? This question is particularly important in light of polygenic accounts of schizophrenia (e.g., Intl. Schizophr. Consort. 2009) and arguments in favor of synergistic gene-environment interactions (van Os et al. 2008).

**The Promise of New Discoveries**

The restriction of focus to signs and symptoms measured by observation and anamnesis starkly contrasts with the opportunities afforded by
new discoveries. In many instances where evidence favoring a theory of schizophrenia is evident, authors remark on the potential for refining the nosology of schizophrenia through the use of alternative genotype or endophenotype criteria (e.g., Bentall & Fernyhough 2008, Craddock et al. 2006, Intl. Schizophr. Consort. 2009, Jansson & Parnas 2007, Owen et al. 2007, Raedler et al. 2007, Stephan et al. 2006, Tsuang et al. 2000a, Uhlhaas et al. 2008, Yolken & Torrey 2008). Whereas the clinical community is well served by DSM, DSM is not well suited to the construct validation process (Cronbach & Meehl 1955) that this research community hopes to see. Yet, scientific explorations of alternative diagnostic systems (Tsuang & Faraone 2002; Tsuang et al. 2000a,b) and endophenotypes as the basis of classification (Lenzenweger et al. 2007) have produced dramatic insights into the nature of schizophrenia. The consensus method for the assessment of neurocognition in schizophrenia (Green & Nuechterlein 2004) provides a sort of precedent for the development of a consensus diagnostic construct validation process.

CONCLUSIONS AND RECOMMENDATIONS

As it stands, the literature on the phenotypes of schizophrenia suggests discontinuous subpopulations underlie a continuum of experience. The symptom phenotypes may not be bound by the DSM thresholds but rather may blend imperceptibly with subclinical, statistically frequent experience. Assuming this continuum corresponds to a broader notion of schizophrenia, such as load or liability, the population may be composed of two types of people; those who are liable, some of whom may also have the disorder, and those who are not.

A raft of limitations and challenges points unequivocally to the need to move beyond self-report, observation, and anamnesis of psychosis, disorganization, and negative symptoms to address questions on the latent structure of schizophrenia. Cohort and design variables play a major role in evidence of an experience continuum. Tradition and clinical utility provide no guarantees of a scientific epidemiology of schizophrenia. With a few important exceptions (e.g., Erlenmeyer-Kimling et al. 1989, Lenzenweger et al. 2007), research into population structure has an entrenched focus on the same DSM-like phenotypes. Advancing understanding and treatment is widely understood to be linked to advances in nosology. There is a huge divide between findings formulated in contemporary theories of schizophrenia and the (nonevidence-based) way psychosis is conceptualized in DSM.

Thus, there is dire need for robust explorations of empirically grounded definitions of schizophrenia or schizophrenia subtypes; of inclusion of genotypes and endophenotypes as criteria for classification alongside psychosis, disorganization, and negative symptoms; and of classifications linked with candidate etiologies. Our expectation is that classifications that cater to a fuller picture of schizophrenia will also stimulate multimodal and multilevel research paradigms that are less vulnerable to the limitations we describe above.

Pragmatically, carefully constructed tests of specific hypotheses on the latent structure of schizophrenia are required. Large-scale, large-sample studies that endeavor to answer multiple questions simultaneously using variables spanning the breadth of psychopathology are expensive ways of finding out a hypothesis is wrong. Instead, the judicious selection of good (inevitably imperfect) variables, the avoidance of sample biases, and the application of unbiased analysis methods are critical. Initial explorations with modest samples can yield important insights (e.g., Blanchard et al. 2005) and may provide the impetus for larger studies. General population surveys of representative samples to test population structure questions will certainly demand much larger samples.
SUMMARY POINTS

1. Few authors have proposed explanatory models that imply or specify that schizophrenia exists as a discrete latent entity clearly demarcated from other states of psychopathology as well as from normality.

2. The prevailing viewpoint is that the fundamental processes underpinning schizophrenia are such that there is continuity of experience and population distribution.

3. Intermediate phenotypes of schizophrenia can be readily identified, are more prevalent than the clinical phenotypes, and are associated with many of the same environmental and nongenetic risk factors as the clinical phenotypes, implying continuity of experience.

4. Taxometric evidence suggests that although there is continuity of experience, the population structure of schizophrenia—defined broadly to include liability states—is not continuous with normality.

5. Significant methodological limitations constrain interpretations based on research into continuity of experience and population structure.

6. DSM-IV is an important clinical instrument and well suited to clinical practice, but it does not meet the basic requirements for a scientific concept on which the epidemiology of schizophrenia can advance.

FUTURE ISSUES

1. Many authors remark on the potential for refining the nosology of schizophrenia through the use of alternative genotype or endophenotype criteria, yet there is currently no consensus infrastructure promoting sound construct validation of refutable diagnostic concepts of schizophrenia.

2. Can continuity of experience, or more broadly, continuity of phenotype, be demonstrated using endophenotype indices, or more broadly, indices that are not based on anamnesis or observation?

3. Can taxonicity in population distributions be demonstrated with indices that span multiple levels of description for the schizophrenia liability?

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