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ENDOPHENOTYPES IN THE GENETIC ANALYSES OF MENTAL DISORDERS

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■ **Abstract** Common mental disorders such as schizophrenia, bipolar disorder, and severe major depression are highly heritable, but differ from single-gene (Mendelian) diseases in that they are the end products of multiple causes. Although this fact may help explain their prevalence from an evolutionary perspective, the complexity of the causes of these disorders makes identification of disease-promoting genes much more difficult. The “endophenotype” approach is an alternative method for measuring phenotypic variation that may facilitate the identification of susceptibility genes for complexly inherited traits. Here we examine the endophenotype construct in context of psychiatric genetics. We first develop an evolutionary theoretical framework for common mental disorders and differentiate them from simpler, single-gene disorders. We then provide a definition and description of endophenotypes, elucidating several features that will make a proposed endophenotype useful in psychiatric genetic research and evaluating the methods for detecting and validating such endophenotypes. We conclude with a review of recent results in the schizophrenia literature that illustrate the usefulness of endophenotypes in genetic analyses of mental disorders, and discuss implications of these findings for models of disease causation and nosology. Given that in mental disorders as in behavior generally, the pathways from genotypes to phenotypes are circuitous at best, discernment of endophenotypes more proximal to the effects of genetic variation will aid attempts to link genes to disorders.

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INTRODUCTION

There is a growing recognition that common mental disorders, such as schizophrenia, bipolar disorder, and depression, are caused by numerous genetic and environmental factors, each of which have individually small effects and which only result in overt disease expression if their combined effects cross a hypothetical “threshold of liability.” Such complexity poses considerable challenges to traditional genetic linkage strategies, which are most effective in the context of diseases or traits influenced by a single major gene. The use of endophenotypes—intermediate phenotypes that form the causal links between genes and overt expression of disorders—promises to facilitate discovery of the genetic and environmental architecture of common mental disorders and thereby suggest novel strategies for intervention and prevention based on an understanding of the molecular mechanisms underlying disease risk and manifestation. The genes influencing liability to mental disorders are likely to impinge on multiple neural systems known to be impacted in these illnesses, including cortical and subcortical dopaminergic, serotonergic, and glutamatergic systems that mediate a number of neurocognitive and affective processes, such as attention, learning, memory, language, stress sensitivity, emotional regulation, and social cognition (Cannon et al. 2001, Heinz et al. 2003). Thus, promising endophenotypes for these syndromes may be found in measures of performance on neuropsychological tests sensitive to these brain systems or in more direct physiological or anatomical assessments of these brain systems (see Figure 1).

An assumption of the intermediate phenotype approach is that the genetic determination of a particular neural system dysfunction in a particular disorder is likely to be relatively less complex than that of the illness phenotype overall, given the latter incorporates multiple neural system dysfunctions and summarizes the influences of all susceptibility genes as well as environmental etiologic influences (Gottesman & Gould 2003). Also implicit in this formulation is that different genes or subsets of genes related to the overall illness phenotype may impact one or more of these brain systems differentially. It is thus imperative to dissect the overall psychiatric diagnostic syndrome into its more discretely inherited neurobehavioral subcomponents, or endophenotypes (Gottesman & Gould 2003). Endophenotypes vary quantitatively among individuals at risk for the disorder, regardless of whether the illness is expressed phenotypically, making clinically unaffected relatives of psychiatrically disordered patients informative for genetic linkage and association studies (Cannon et al. 2001) and enabling the use of relatively powerful statistical

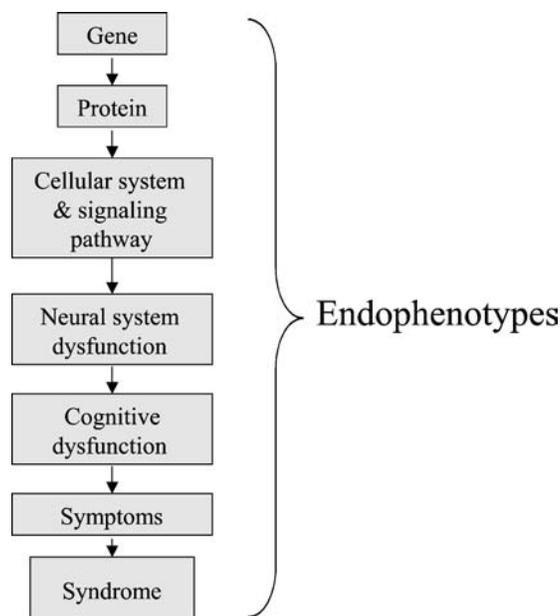


Figure 1 Levels of phenotypic effect in the cascade between a genetic sequence variation and a diagnostic syndrome. Candidate endophenotypic measures of liability to the syndrome may be found at any of the intermediate levels.

genetic methods for mapping genes of small effect, referred to as quantitative trait loci or QTLs (Abecasis et al. 2000).

In this chapter, we review the theoretical and empirical literatures in relation to the endophenotype construct in psychiatric genetics. We first provide a theoretical framework for common mental disorders and differentiate them from simpler, single-gene disorders. We then describe several features that should exist for a proposed endophenotype to be useful for genetic analyses, and we describe methods for detecting and validating such endophenotypes. Finally, we review recent results in the schizophrenia literature that illustrate the usefulness of endophenotypes in genetic analyses of complex psychiatric traits, and discuss implications of these findings for models of disease causation and psychiatric nosology.

A THEORETICAL FRAMEWORK FOR SIMPLE VERSUS COMPLEX DISORDERS

Enthusiasm in the 1980s and 1990s for the prospects of rapidly locating the genes responsible for common mental disorders was high. Beginning in those early years and continuing today, the genes responsible for rare Mendelian disorders,

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so called because their inheritance follows the simple rules outlined by Gregor Mendel, have been found at a rapid pace; the molecular bases for over 1700 Mendelian phenotypes have been discovered to date. It is understandable that such success in rare disorders generated optimism for finding the genes responsible for disorders hundreds or thousands of times more common, including psychiatric syndromes such as schizophrenia, bipolar disorder, and major depression. However, early reports of genetic discoveries in these disorders repeatedly failed to replicate at levels above chance (Sklar 2002), turning the initial optimism to discomfiture and healthy reflection over why methods so successful with Mendelian disorders have failed to find any genes of major effect in common mental disorders (Weiss & Terwilliger 2000, Wright & Hastie 2001).

Much of the focus for explaining the failure of traditional linkage studies in the context of complex traits has been on genetic mapping methods (e.g., Risch & Merikangas 1996), but the phenotypes themselves deserve at least as much scrutiny. Mendelian disorders and common mental disorders are fundamentally different phenomena genetically. Each Mendelian disorder is the end product of the inheritance of only one or two mutations (rare alleles). Common mental disorders, conversely, are hundreds to thousands of times more common than Mendelian disorders, and the bulk of epidemiological evidence implicates the roles of an unknown but potentially large number of genetic and environmental factors affecting each disorder. Such a multifactorial framework is supported by the results of segregation and modeling analyses that indicate the genetic component of liability to common mental disorders is likely determined by many genes of small effect (Comings 2001, Comings et al. 2000, McGue et al. 1985, Risch & Baron 1984, Whitfield et al. 1998). Also supporting this perspective is the fact that mental disorders lie on a continuum of severity that ranges from “nonaffected” individuals to those with extreme forms of the disorder (Benjamin et al. 2002, Farmer et al. 2002), although a truly dichotomous trait may also be the result of the combined effects of numerous factors crossing some hypothetical threshold of liability (Figure 2) (Falconer & Mackay 1996, Gottesman & Shields 1967).

Evolutionary considerations may provide insight into why common mental disorders differ so fundamentally from Mendelian disorders (M.C. Keller & G. Miller, in preparation). Mendelian disorders are caused by mutations that cause major, unique, and thereby recognizable syndromes, but this is not the way mutations typically affect phenotypes. Most new mutations have minor, nonobvious effects (García-Dorado et al. 2004), and this is even more the case with the much larger number of old mutations that exist in the population. Indeed, divergence data comparing chimpanzee and human coding DNA indicate that each human harbors an average of at least 500 old, slightly deleterious mutations (Fay et al. 2001), along with perhaps 1–2 newly arisen and somewhat more detrimental mutations (Eyre-Walker & Keightley 1999). Obviously, these mutations do not cause catastrophic failures such as Mendelian disorders; they must affect traits in minor, probably quantitative, ways. It is, moreover, highly unlikely that each minor

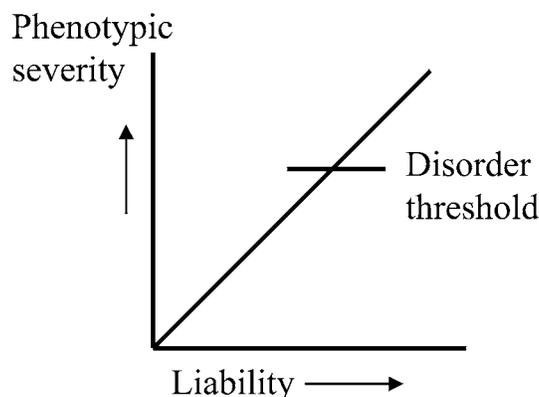


Figure 2 Liability threshold model of psychiatric illness. In this model, liability to disorder is determined by multiple genetic and environmental factors and is thus distributed continuously in the population. Phenotypic severity (degree of affection) is correlated with (and derives from) this underlying liability continuum. Diagnostic categories represent thresholds on the liability continuum, beyond which it is generally agreed that mental difficulties are impairing and require intervention. Subsyndromal degrees of affection are present in the population.

mutation affects only one trait; rather, any given trait will probably be affected by mutations at many different loci, and certain mutations will affect more than one trait (a phenomenon referred to as pleiotropy).

A given Mendelian disorder tends to be extremely rare because natural selection quickly weeds out such deleterious mutations. Such a Mendelian disorder nevertheless persists despite natural selection, albeit at a low frequency, because new mutations at the disease locus are continually introduced into the population. Evolutionary theory describes this process as a mutation-selection balance, and mathematical models can predict the equilibrium population frequency of deleterious mutant alleles at a locus, given the strength selection against them (which decreases their frequency) and the mutation rate at that locus per individual per generation (which increases their frequency).

A mutation-selection balance model would suggest certain mental disorders are much more common than Mendelian disorders because, in part, they have higher trait-level mutation rates, and the selection against each of these mutations is commensurately lower. Given approximately half of the genome is likely expressed in the brain (Sandberg et al. 2000), at least some of the 500 or so slightly deleterious segregating mutations in each individual should cause quantitative variation in low level biological processes (or endophenotypes) as well as the observable behaviors affected by them. As the cumulative effects of this mutational noise, combined with the effects of environmental insults, increase in a particular set of endophenotypes, maladaptive behaviors, and the probability of being diagnosed with a

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mental disorder, also increase. In other words, the relative commonality of certain mental disorders may simply reflect the much larger number of environmental and genetic factors that contribute to these disorders.

For virtually any model of mutation-selection balance, maladaptive alleles/mutations tend to be rare (minor allele frequencies less than 1%); deleterious disorders could only be hundreds of times more frequent than the mutation rate if they are affected by numerous genes. Thus, if a mental disorder such as schizophrenia has reduced Darwinian fitness as much as it appears to in modern industrialized societies (Haukka et al. 2003), a mutation-selection framework would implicate the role of perhaps hundreds of genes and, by extension, numerous endophenotypes. To the degree that this is not the case—for example, if fitness effects were much less severe in the ancestral past or if some susceptibility alleles were maintained by some balancing benefit—then fewer genes and less heterogeneity might be implicated (M.C. Keller & G. Miller, in preparation). Nevertheless, both evolutionary considerations and the slow progress in gene mapping suggest common mental disorders are considerably more etiologically complex than single-gene disorders.

PROPERTIES OF ENDOPHENOTYPES USEFUL IN GENETIC ANALYSES

The diagnostic categories of mental disorders in use today were initially formulated in the late nineteenth and early twentieth centuries by a small number of psychiatrists who relied on perceived similarities in behavioral syndromes and clinical outcomes to formulate these categories. Aware such categories reflected only observable behaviors rather than dysfunctions in distinct anatomical-physiological substrates, some of these pioneers, such as Bleuler (1911) and Jaspers (1923), argued disorders given singular labels, such as schizophrenia, were probably better thought of as a heterogeneous group of dysfunctions whose final pathways led to similarity in symptoms, course of illness, and other clinical features. Such phenotypic similarity in the presence of etiologic heterogeneity might be a result of true similarity, such that disruptions in different mechanisms lead to the same common outcome, or to the inability or impracticality of making finer-grained distinctions between slightly different behavioral syndromes. By analogy, dysfunctions in a number of different automobile mechanisms (spark plugs, battery cables, the distributor, the electrical system) might lead to similarly perceived symptoms, such as a car that fails to start. It would be difficult to distinguish which mechanisms are dysfunctional, or how heterogeneous a particular set of symptoms truly are, without the ability to look under the hood of the car.

The discernment of endophenotypes is beginning to allow clinical neuroscientists and neurobehavioral geneticists to look under the hood of the mind and discover which mechanisms may be dysfunctional for a given disorder. Endophenotypes are intermediate phenotypes, often imperceptible to the unaided eye, that link disease-promoting sequence variations in genes (haplotypes or alleles) to

lower level biological processes and link lower level biological processes to the “downstream” observable syndromes that constitute diagnostic categories of disorders (see Figure 1) (Gottesman & Shields 1972). For example, specific alleles may increase the risk of dopaminergic dysregulation in the prefrontal cortex, leading to deficits in working memory that may, in turn, increase the risk for schizophrenia (Goldman-Rakic & Selemon 1997b). If true, working memory and, at an even lower level, dopaminergic dysregulation in the prefrontal cortex would be two of many endophenotypes that form the complex, multilevel pathways linking specific “upstream” alleles to the downstream behavioral syndrome known as schizophrenia.

This mapping of the pathways that lead from genes through different levels of phenotypes can be described using a watershed analogy (Figure 3). Much like the numerous tributaries that eventually coalesce into a major river, many upstream microbiological processes (e.g., dopaminergic regulation in the prefrontal cortex)

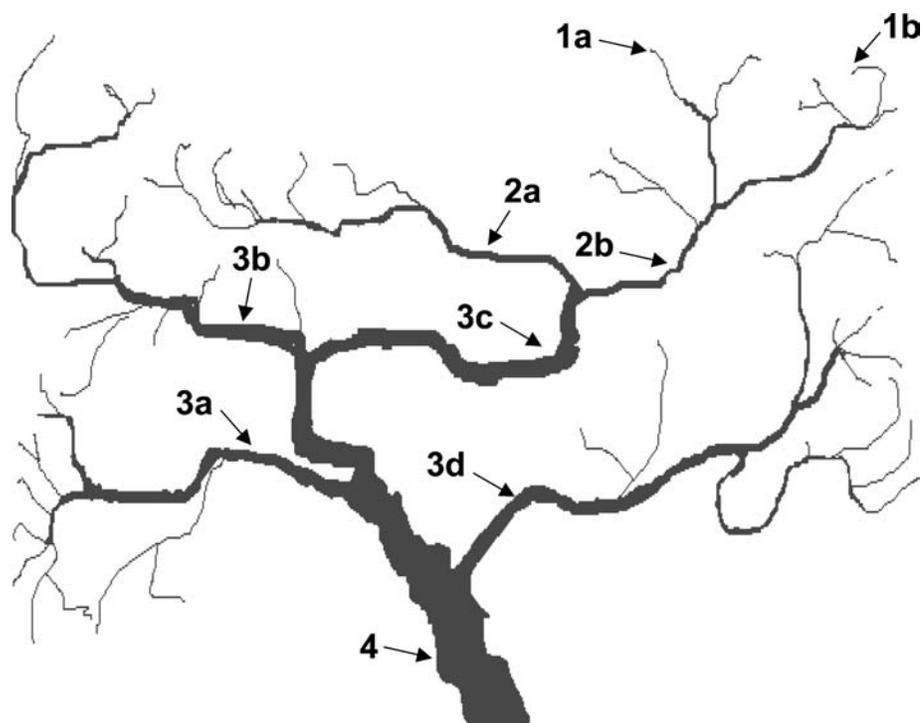


Figure 3 Watershed model of the pathway between upstream genes and downstream phenotypes. Specific genes (1a, 1b) contribute variation to narrowly defined endophenotypes such as dopaminergic regulation in the prefrontal cortex (2b). This and other narrowly defined endophenotypes affect more broadly defined endophenotypes, such as working memory (3c). Working memory in conjunction with several other endophenotypes (3a, 3b, 3d) affects phenotypically observable phenotypes, such as symptoms of schizophrenia (4).

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flow into (affect) further downstream macrobiological processes (e.g., working memory). A mutation at a locus that affects an upstream process disrupts not only that upstream process, but also every trait downstream of that process. A slightly harmful mutation that dysregulates dopamine in the prefrontal cortex may not affect brain function generally but will probably undermine specific downstream processes such as working memory and, through this, increase the risk for schizophrenia. Figure 3 illustrates this watershed model. A more accurate illustration, though less visually compelling, would allow upstream processes to affect more than one downstream process. In such a network model, the nodes most connected to other nodes would be equivalent to downstream processes in the watershed model.

For endophenotypes to be useful in genetic analyses, they should have several properties (see de Geus & Boomsma 2001, Gottesman & Gould 2003). We propose six such properties below. The first two are probably necessary for any endophenotype to be useful in a genetic analysis. The last four, though not strictly necessary, are properties that should aid in the successful genetic dissection of behavioral traits.

1. Endophenotypes should be heritable.

For endophenotypes to aid in the genetic dissection of complex traits, they should be at least moderately heritable. There is no use in attempting to link genes to an endophenotype if differences in genes do not affect the variation in that endophenotype. Nevertheless, finding endophenotypes of very low heritability may be important for the development of treatments aimed at behavioral interventions or otherwise altering environmental conditions. However, the reverse logic does not hold: Environmental interventions may be crucial in altering the affects of even highly heritable disorders or endophenotypes as a result of the potential for gene-by-environment interaction. For example, the cause of phenylketonuria is purely genetic, but ameliorating its effect of causing mental retardation is achieved not through gene therapy but through altering the diets of those born with the genetic disorder.

2. Endophenotypes should be associated with causes rather than effects of disorders.

Endophenotypes should be part of the causal pathway from disease-promoting alleles to disorders (as shown in Figure 1) rather than effects (sequelae) of disorders or their treatment. To be useful in the development of effective interventions, the endophenotypes should optimally play a direct causal role in increasing risk for the disorder, but endophenotypes might be useful for genetic analyses even if they are markers of, or otherwise merely correlated with, phenotypes that do play a causal role in the disorder. The critical factor is that endophenotypes should not be consequences of the disorders or their treatment.

Two pieces of evidence can help ascertain whether endophenotypes are associated with causes rather than effects. First, within the same individual,

endophenotypes should be expressed in the deviant range before the manifestation of a disorder as well as afterwards. If the endophenotype is only deviant in those currently diagnosed with a mental disorder but not in those same people before such a diagnosis, then it is more likely the proposed endophenotype is related to an effect rather than a cause of the disorder. Second, assuming the endophenotype is heritable, the level of the endophenotype should correlate with an individual's level of genetic risk independent of his or her symptomatology or diagnosis. For example, within a given class of biological relatedness (e.g., monozygotic twins), the correlation on the endophenotypic trait between relatives discordant for the disorder should be as high as the correlation between two concordant relatives. Of course, it is possible a particular neural system dysfunction is influenced by the genetic and environmental causes of a disorder and also affected by the disease process or treatment, in which case, we would expect higher correlations for these traits among relatives concordant for the illness phenotype compared with those discordant for it, and relatively greater deviance on the trait when overt psychiatric illness is manifest compared with before or after such illness episodes.

3. Numerous endophenotypes should affect a given complex disorder.

As noted above, endophenotypes are expected to be less genetically complex than the disorders they affect. By genetically less complex, we mean either the number of genes that affect any one endophenotype will tend to be fewer in number than the total number of genes that affect the downstream disorder, or the effect size of a particular gene will be greater in relation to the endophenotype than to the clinical syndrome, or both. Endophenotypes also may involve fewer gene-gene and gene-environment interactions than the downstream disorder. Because polygenicity (Risch & Merikangas 1996) and nonadditive genetic variation (Purcell & Sham 2004) both decrease statistical power of genetic analyses and because endophenotypic traits vary quantitatively rather than categorically, genetic analyses of endophenotypes should be more powerful than analyses of the disorders they affect.

Endophenotypes that have a many-to-one relationship with complex disorders will generally account for only part of the risk for the disorder, meaning weak associations are not necessarily grounds for dismissing the importance of a proposed endophenotype. Indeed, distal, narrowly defined endophenotypes far upstream from the disorders they affect will tend to have the weakest associations with the downstream disorders, but these endophenotypes may also be the most tractable to genetic analyses. Similarly, endophenotypes that account for a substantial portion of the risk for a disorder may be the least tractable to genetic dissection. Thus, the genetic analysis of dimensions on which disorders lie (e.g., the schizotypal dimension for schizophrenia), although preferable to the analysis of discrete disorders (see below), is probably less useful than the genetic analysis of more narrowly defined endophenotypes.

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4. Endophenotypes should vary continuously in the general population.

Given it is easier to convey qualitative than quantitative information, the nosology of mental disorders developed in a way that was helpful for communication. However, as discussed above, it is unlikely common mental disorders, much less their underlying endophenotypes, vary in a discrete manner. Statistical analyses of continuous traits forced into categories have substantially less power than analyses conducted on the original scale. Rather than binning all nonaffected individuals into a single category, continuous measures allow for the discernment of differences (i.e., scaling of liability) in the nonaffected population. This can also allow for much more powerful linkage designs, such as “extreme discordant and concordant sibling design.” Therefore, analyses of endophenotypes that can be measured on continuous scales should be more powerful.

Another important advantage of analyzing endophenotypes that vary continuously in the nonaffected population is it greatly simplifies the sampling process (Almasy & Blangero 2001). Because it is not necessary to screen for the disorder to study the genetics of endophenotypes, the population from which samples can be drawn is much larger. Furthermore, population-based studies on such endophenotypes could circumvent many of the problems associated with ascertainment biases and the difficult and uncertain correction schemes that attempt to correct for these biases. Nevertheless, it is likely advantageous also to study the association of genetic markers with endophenotypes within populations with and/or at risk for psychiatric disorders, as such populations are expected to be enriched for the disease-promoting forms of genes that affect the endophenotypes in question, and these genes may account for a larger proportion of the trait variance in such endophenotypes among the psychiatrically disordered or at risk compared with general populations, making them statistically much easier to detect with a given sample size.

5. Endophenotypes should optimally be measured across several levels of analysis.

Endophenotypes for behavioral traits are expected to vary in terms of their proximity to the initiating genetic effects and to the overt psychiatric phenotype (see Figure 1). The endophenotypes likely to be of greatest use in psychiatric genetics are those that reflect different levels of analysis of a fundamental neural system or substrate (Cannon & Rosso 2002). In general, our confidence that a particular neural system dysfunction represents an endophenotype for a particular disorder will be higher when there is convergence in the genetic causation and phenotypic distribution of the dysfunction across the behavioral, neuroanatomical, neurophysiological, and neurochemical levels of analysis, as appropriate. Because certain endophenotypes are further downstream of the initial gene effects than others, it is likely many of the same difficulties that have emerged in attempts to map genes to mental disorders will also plague attempts to map genes to

endophenotypes. In such cases, it may be necessary to find phenotypes even further upstream.

A critical by-product of traversing these multilevel endophenotypes in humans is the facilitation of their translation into animal models of these diseases. The genes that affect a neural system in animals are much more likely than randomly selected genes to affect that system in humans (Crawley 2000). Therefore, once a neural endophenotype is discovered in humans, researchers can begin to discern the genes that affect the homologous system in animals, using methods that are much less constrained than those used in human research. Loci that affect variation in these systems in animals would be logical candidate regions to affect the endophenotype's variation in humans. It is not, by the way, necessary for these neural features in animals to be related to syndromes analogous to the human disorders in question, given the human syndromes are expected to reflect extreme variation across a number of neural systems whose substrates are expected to differ in complexity across the evolutionary continuum.

6. Endophenotypes that affect multiple disorders should be found for genetically related disorders.

Multivariate genetic analyses have revealed certain mental disorders are related to one another because of shared genetic influences. For example Kendler et al. (1992) showed generalized anxiety disorder and depression tend to run in families together as a result of shared genes between these disorders. Endophenotypes can help disentangle the causes of such genetic correlations. That endophenotypes should generally have a many-to-one relationship to complex disorders does not imply they will not occasionally have a one-to-many relationship with different disorders. In other words, certain endophenotypes may naturally affect more than one disorder, and discerning such endophenotypes is important for understanding genetic correlations between disorders and, ultimately, for finding the pleiotropic genes that affect nominally separate disorders.

METHODS FOR FINDING AND VALIDATING ENDOPHENOTYPES

The detection of endophenotypes involves understanding the causes of covariation between putative endophenotypes and disorders, much as dissecting the genetic architecture of singular disorders, using for example the classical twin design, involves understanding the causes of variation of a disorder. In addition, however, the detection of endophenotypes requires the causation work from endophenotype to disorder and not vice-versa. To this end, all methods used to find endophenotypes rely on the fact that endophenotypes should be correlated with genetic risk of a disorder irrespective of the presence or absence of that disorder. If a putative endophenotype occurs at increasingly higher levels in unaffected individuals as

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genetic relatedness to a patient increases, the link between the putative endophenotype and the disorder is likely causal and heritable. Otherwise, the putative endophenotype is likely nonheritable, an effect of the disorder, or both.

The family-study design is the primary methodology used for validating proposed endophenotypes. In this approach, samples of patients, their first-degree relatives, and demographically similar control subjects are compared with each other on anatomical, physiological, and/or functional indicators (for examples of this in schizophrenia research, see Bolte & Poustka 2003; Bramon et al. 2004; Calkins et al. 2004; Callicott et al. 2003; Ettinger et al. 2004; Kathmann et al. 2003; Keri et al. 2004; Maggini & Raballo 2004; Michie et al. 2002; Seidman et al. 2002; Tuulio-Henriksson et al. 2003; Winterer et al. 2003a, 2004; Wittorf et al. 2004). Evidence that the clinically unaffected first-degree relatives of patients show a level of deviance on the indicator that is intermediate between patients and controls is generally construed to be consistent with a genetic relationship with the disorder. Strictly speaking, however, genetic and environmental influences are confounded in this design. For example, a higher level of deviance among first-degree relatives could be a result of shared environmental effects (e.g., exposure to toxins in the environment that affect all family members) rather than genetic effects. The root of this confound is that there are rarely systematic genetic differences within nuclear families because parent-offspring and sibling-sibling genetic relationships are all equal on average. Although adoption studies could in principle be used in this context, they are logistically difficult and do not control well for similarity in the prenatal and early (preadoption) postnatal environment.

A design more feasibly implemented than the adoption study is the use of monozygotic (MZ) and dizygotic (DZ) twin pairs discordant for the disorder and matched control pairs (e.g., Cannon et al. 2000, 2002; Glahn et al. 2003; Johnson et al. 2003; McNeil et al. 2000; Narr et al. 2002; van Erp et al. 2004). If we assume MZ and DZ cotwins share intrauterine and family environments to equivalent degrees, the differences in genetic similarity between twin types are not confounded with environmental sources of variation. In this design, the proposed endophenotypic indicator can be evaluated for dose dependency with genetic risk for the disorder by comparing the unaffected MZ cotwins of patients, who share 100% of their genes with an affected individual, the unaffected DZ cotwins of patients, who share on average 50% of their genes with an affected individual, and normal controls, who represent the base rate of disorder-related genes in the general population. In addition, the nongenetic component to the proposed indicator can be isolated by subtracting the value of the unaffected from the affected cotwin among MZ pairs.

Although the comparison of unaffected MZ twins versus unaffected DZ twins versus controls is preferable to studies that only include first-degree relatives and controls, this design itself suffers from potential confounds that deserve examination. First, it is possible MZ unaffected twins show a higher level of deviance on a putative endophenotype compared with DZ unaffected twins as a result of environmental factors shared between MZ cotwins at higher levels than DZ cotwins. For example, MZ cotwins may be more likely to share peer groups than DZ cotwins,

and may therefore be more likely to share exposure to known mental disorder risk factors, such as drug use. Second, this design is not well suited to elucidating the genetic architecture of the pathway between the endophenotype and the disorder. For example, a DZ cotwin level of deviance exactly midway between the levels of deviance of MZ cotwins and unaffected individuals could be purely a result of additive genetic effects, but it could also be a result of many different combinations of nonadditive genetic effects combined with common environmental effects (Keller & Coventry 2005). Including additional first-degree relatives in addition to twins, such as unaffected siblings, parents, and offspring, (a design analogous to the extended-twin family design, see Truett et al. 1994) allows for a much better understanding of the makeup of the genetic correlation between endophenotypes and disorders.

A final method for finding endophenotypes is to use a longitudinal design to compare the level of deviance on proposed endophenotypes before and after disorder onset or an illness episode. Useful endophenotypes should show deviance at both times, and higher levels of deviance on these endophenotypes should be correlated with likelihood and severity of the eventual disorder.

ENDOPHENOTYPES IN SCHIZOPHRENIA

To illustrate the utility of the endophenotype approach in psychiatric genetics, we briefly review work in this domain as applied to schizophrenia. This section is organized according to the brain systems most commonly associated with schizophrenia, including the prefrontal cortex and medial temporal lobe structures and associated deficits in neurocognition. The relationships of known or suspected susceptibility genes for schizophrenia with each of these indicators are also highlighted. We focus principally on studies published in the past few years, supplementing these with earlier papers whenever necessary to provide the full context for a particular endophenotype.

Prefrontal Cortex and Working-Memory Deficits

The prefrontal cortex is more highly evolved in humans than in nonhuman primates and supports higher-order cognitive processes such as working memory, the strategic allocation of attention, reasoning, planning, and other forms of abstract thought (Goldman-Rakic 1995). Several lines of evidence suggest that working-memory deficits and associated abnormalities in prefrontal cortical structure and function are reflective of an inherited diathesis to schizophrenia and thus represent promising candidate endophenotypic markers for the disorder. Spatial working-memory deficits scale in severity with the number of relatives affected with schizophrenia within families (Tuulio-Henriksson et al. 2003). This familial pattern has been confirmed to have a genetic basis, as performance on an experimental test of spatial working memory was observed to decrease with increasing genetic loading for

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schizophrenia among twins discordant for schizophrenia and control twins (Glahn et al. 2003). These results replicated findings from a previous study of the same sample using an extensive battery of clinical neuropsychological tests (Cannon et al. 2000). Notably, in the latter study, multivariate methods were employed that accounted for the overlap in performance variation among the various tests; spatial working memory, divided attention, reaction time to visual targets, and intrusions during verbal memory retrieval were the only measures found to make unique contributions to the prediction of genetic loading for schizophrenia.

In parallel with these findings, structural abnormalities in polar and dorsolateral prefrontal regions on magnetic resonance imaging scan varied in a dose-dependent fashion with degree of genetic loading for schizophrenia in the same twin sample (Cannon et al. 2002). It has been suggested that a reduction of interneuronal neuropil (i.e., the dendrites and synapses that emanate from neuronal cell bodies) in the prefrontal region in patients with schizophrenia results in impaired working-memory functioning due to hypoactive dopaminergic modulation of pyramidal cell activity (Goldman-Rakic & Selemon 1997a). This prediction has been supported by a positron emission tomography investigation, which found increased dopamine D1-receptor binding in the dorsolateral prefrontal cortex of schizophrenic patients compared with controls, which also correlated with reduced working-memory performance in schizophrenia (Abi-Dargham et al. 2002). This result was interpreted as suggesting D1-receptor upregulation secondary to reduced prefrontal intracellular dopamine. Although the dopamine hypothesis of schizophrenia suggests elevated dopaminergic functioning in schizophrenia, this hyperdopaminergic state is thought to pertain only to the meso-limbic dopamine pathways in which a different class of dopamine receptors, particularly the D2 receptor, are relatively prominent. In contrast, the D1 receptor is relatively more prominent in the cortical dopamine system, which mediates spatial working-memory functioning, and there appears to be a reciprocal relationship between the levels of activity in the subcortical and cortical dopamine systems (higher than normal subcortical and lower than normal cortical dopamine function in schizophrenia). Notably, altered physiological activity in the prefrontal cortex during performance of a working-memory task has been observed in both patients with schizophrenia and their unaffected siblings (Callicott et al. 2003, Winterer et al. 2004).

Given abnormalities of working memory and prefrontal cortical structure and function are associated with genetic liability to schizophrenia, it should be possible to identify specific genes that underlie these disturbances. Weinberger and colleagues reported evidence of one such genetic influence—the methianine/valine polymorphism of the catechol-O-methyl-transferase gene (located on chromosome 22), with valine alleles promoting more rapid breakdown of synaptic dopamine leading to prefrontal hypofunction in patients with schizophrenia (Egan et al. 2001, Goldberg et al. 2003). The G-protein signaling subtype 4 (RGS4) gene, which has been linked with schizophrenia in a number of studies (Harrison & Weinberger 2005), was recently shown to be associated with reduced prefrontal cortical gray matter volume in schizophrenia patients and controls (Prasad et al. 2005). Another

potential susceptibility locus that may affect prefrontal function in schizophrenia is the Disrupted-in-Schizophrenia-1 (DISC1) gene on chromosome 1. Both the translocation breakpoint that cosegregates with schizophrenia in a Scottish pedigree (Millar et al. 2000, St Clair et al. 1990) and the peak linkage signal in the 1q42 region within the Finnish population (Ekelund et al. 2001, 2004; Hennah et al. 2003) are intragenic to DISC1, with several other linkage findings also pointing to this region (Curtis et al. 2003, Ekelund et al. 2000, Gasperoni et al. 2003, Hwu et al. 2003). DISC1 is expressed in neurons and supporting cells (glia) and is translated to a protein that impacts on neurodevelopmental and neurochemical processes thought to be involved in the pathophysiology of schizophrenia, including neurite outgrowth, neuronal migration, synaptogenesis, and glutamatergic transmission (James et al. 2004, Millar et al. 2002, Miyoshi et al. 2003, Morris et al. 2003). Recently, three haplotypes incorporating different blocks of single nucleotide polymorphic markers in the DISC1 and immediately adjacent transelin-associated-factor-X genes were found to be associated with schizophrenia (two under- and the other overtransmitted to affected cases) in a study of multiplex families from Finland (Hennah et al. 2003).

Three recent findings suggest the DISC1 locus contributes to alterations in prefrontal cortical function and altered working-memory performance in schizophrenia patients and their relatives. In one study, a marker located near DISC1 showed evidence of linkage and association with decreased performance on a spatial working-memory test among DZ twins discordant for schizophrenia (Gasperoni et al. 2003). In another study, decreased amplitude of the P300 cortical evoked potential response to detection of auditory oddball stimuli was observed in members of a Scottish pedigree showing translocation disruption of the DISC1 gene, regardless of their clinical status (Blackwood & Muir 2004). Although the P300 is registered across a broad expanse of the cortical surface, the frontal component of this response has been shown previously to be most strongly related to genetic risk for schizophrenia (Turetsky et al. 2000). Most recently, two haplotypes of the DISC1 and neighboring transelin-associated-factor-X genes were found to associate with increased risk for schizophrenia, reduced short- and long-term memory functioning, and reduced gray matter volume in the dorsolateral prefrontal cortex (Cannon et al. 2005).

Together, these findings strongly implicate genetic factors as playing a role in the abnormalities of prefrontal cortex and working memory in schizophrenia. Nevertheless, patients with schizophrenia have been found to show even greater disturbances in dorsolateral prefrontal cortex function and structure than their nonill MZ cotwins (Cannon et al. 2002). Thus, although genetic factors may cause patients and some of their first-degree relatives to share a certain degree of compromise in prefrontal cortical systems, nongenetic disease-related influences cause the dorsolateral prefrontal cortex to be further deviant in the patients, and this added measure of deviance in prefrontal cortical function may be among the processes associated with overt symptom expression among those genetically predisposed.

Temporal Lobe and Episodic-Memory Deficits

The medial temporal lobe structures (i.e., hippocampus, amygdala) and adjacent temporal cortex are involved in learning and recall of episodic information, auditory perception, emotion (especially the amygdala), and certain aspects of language processing (Squire & Zola 1996). Reductions in temporal cortical and hippocampal volumes are present in both patients and their healthy biological relatives (Narr et al. 2002, O'Driscoll et al. 2001, Seidman et al. 2002, van Erp et al. 2004, van Erp et al. 2002). From a neurocognitive perspective, impaired declarative memory processes that depend on the integrity of the hippocampus (Faraone et al. 2000) have been reported in both high-risk adolescents (Byrne et al. 1999) and nonpsychotic relatives of schizophrenics (Cannon et al. 2000, O'Driscoll et al. 2001, Seidman et al. 2002, Wittorf et al. 2004), suggesting they derive in part from an inherited genotype. Importantly, two studies have shown a significant relationship between deficits in verbal declarative memory and smaller hippocampal volumes in relatives of schizophrenia patients (O'Driscoll et al. 2001, Seidman et al. 2002). Among the many genes that may contribute to disturbances in structure and functioning of the temporal cortex and hippocampus in schizophrenia, *dysbindin*, *neuregulin*, and *G72* are particularly prominent candidates. *Dysbindin* has been shown to modulate excitatory glutamatergic neurotransmission in the medial temporal lobe and alter patterns of expression in neuronal tissue from patients with schizophrenia (Numakawa et al. 2004, Talbot et al. 2004), whereas *neuregulin* appears to have a complementary effect modulating inhibitory GABAergic transmission in the same regions (Numakawa et al. 2004, Talbot et al. 2004). *G72* interacts with D-serine, an important modulator of the glutamatergic N-methyl-D-aspartate receptor, which is critically implicated in long-term potentiation and thereby in learning and memory functions (Chumakov et al. 2002, Harrison & Weinberger 2005). Illustrating the possibility of pleiotropy in the context of endophenotypes, the *DISC1* gene also appears to influence hippocampal volume and long-term memory functions as well as prefrontal cortical structure and function (Cannon et al. 2005). In addition, a marker of an as yet unspecified susceptibility gene on chromosome 4q was shown to be linked to verbal learning and memory deficits in multiplex families from Finland (Paunio et al. 2004).

At the same time, however, hippocampal volume reductions and long-term memory deficits are specifically more pronounced in patients compared with their own healthy MZ cotwins (Cannon et al. 2000, van Erp et al. 2004). Thus, non-genetic, disease-related factors must also be involved. The hippocampus in particular is acutely vulnerable to hypoxic-ischemic damage (Vargha-Khadem et al. 1997, Zola & Squire 2001). Obstetric complications (i.e., oxygen deprivation) have been linked with hippocampal abnormalities in schizophrenia (McNeil et al. 2000). Specifically, in MZ twins discordant for schizophrenia, relatively small hippocampi in the ill twin were significantly related to labor-delivery complications and prolonged labor, both risk factors associated with fetal oxygen deprivation (McNeil et al. 2000). In a Helsinki birth cohort, schizophrenia probands who

experienced fetal hypoxia had smaller hippocampal volumes than in those who did not, a difference not noted within unaffected siblings and healthy comparison subjects (van Erp et al. 2002). At the same time, hippocampal volume differences occurred in a stepwise fashion with each increase in genetic load for schizophrenia (Seidman et al. 2002), suggesting, in patients with schizophrenia spectrum disorders, hippocampal volume is influenced in part by schizophrenia susceptibility genes and an interaction of these genes with fetal hypoxia. In a Finnish twin sample, there were pronounced shared and unique environmental effects on hippocampal gray matter volumes in schizophrenia (van Erp et al. 2004). Specifically, probands' hippocampal volumes were smaller than those of their nonschizophrenic MZ and DZ cotwins and healthy subjects, and probands' nonill cotwins' hippocampal volumes were smaller than those of healthy subjects, but nonill MZ and DZ cotwins of schizophrenic patients did not differ from each other. The intraclass correlations for hippocampal volumes among healthy MZ pairs were larger than those among healthy DZ pairs, but the intraclass correlations for hippocampal volumes among discordant MZ and DZ pairs were equivalent. Together, these findings indicate that although hippocampal volume in healthy subjects is under substantial genetic control, hippocampal volume in schizophrenic patients and their relatives appears to be influenced to a greater extent by unique and shared environmental factors.

Other Domains

Both schizophrenia patients and their first-degree relatives show deficits in the gating of the P50 electrophysiological response to repeated stimuli (Freedman et al. 2003, Winterer et al. 2003a). Deficits in the gating of the P50 response also appear in adolescents showing symptoms consistent with a heightened risk for imminent onset of psychosis (i.e., prodromal patients) (Myles-Worsley et al. 2004). The pioneering work of Freedman and colleagues has demonstrated a polymorphism in the alpha-7 nicotinic receptor gene is strongly associated with the P50 gating deficits (Freedman et al. 2003, Houy et al. 2004, Raux et al. 2002). Other promising intermediate phenotype candidates for schizophrenia include eye-movement dysfunctions (Ettinger et al. 2004, Kathmann et al. 2003, Ross 2003), related abnormalities of visual processing and attention (Calkins et al. 2004, Keri et al. 2004), and measures of EEG coherence and phase resetting (Winterer et al. 2003b, 2004).

IMPLICATIONS FOR MODELS OF DISEASE CAUSATION AND NOSOLOGY

The work reviewed above indicates there are several neural system abnormalities that meet criteria for representing an intermediate phenotype associated with genetic liability for schizophrenia. In the case of frontal and medial temporal lobe systems involved in working memory and long-term memory, respectively, there is convergent evidence of genetic mediation across multiple levels of analysis,

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including anatomical, physiological, functional, and behavioral. Together with abnormal gating of the P50 electrophysiological response to repeated stimuli, deficits in frontal and temporal lobe memory systems are also the endophenotypes showing the strongest evidence of linkage and/or association with genetic polymorphisms previously shown to be associated with schizophrenia.

Although encouraging, this slate of recent findings also raises some additional questions and challenges. First, are the genes mediating each neural system endophenotype at least partially distinct from each other? This is a key assumption of the endophenotype approach, yet empirical proof of this remains to be determined. A substantial degree of overlap appears likely for a number of the most promising genes associated with schizophrenia, including neuregulin, dysbindin, DISC1, G72, and RGS4, given these genes impinge on common cellular signaling pathways associated with glutamatergic and GABAergic neurotransmission. Nevertheless, each gene has a unique role in the biological cascades influencing these signaling pathways, and it thus seems likely these loci will differ in their magnitudes of influence across the brain systems affected in this disorder. A related question is, how do these genes (along with others that remain to be identified) coalesce in influencing liability to overt expression of schizophrenia? Are their effects additive or interactive? Do any of these genes confer increased susceptibility to neuronal damage following fetal hypoxia and other possible environmental etiological agents? The answers to these questions will depend on large-scale studies of genetically at-risk samples with and without environmental exposures and the use of sophisticated statistical modeling algorithms that can powerfully probe the resulting datasets for evidence of gene-gene and gene-environment interactions. Finally, are these endophenotypes and associated genes unique to schizophrenia, or are they shared by other forms of psychosis such as bipolar disorder and depression? Initial evidence indicates a number of the most promising loci, including DISC1, NRG1, RSG4, G72, also show evidence of linkage and/or association with bipolar disorder (Badner & Gershon 2002, Berrettini 2004, Ophoff et al. 2002, Potash et al. 2003), although it remains unclear whether these associations are limited to psychotic forms of bipolar illness.

CONCLUSIONS

The questions posed above raise considerable challenges for investigators attempting to unravel the genetic complexity of schizophrenia and other common mental disorders. Nevertheless, the nature of these questions indicate the field has moved considerably beyond the pessimism dominant in the literature only a few years ago concerning the failures of molecular genetics in psychiatry. We have entered a new era in which conjoint advances in molecular genetics and dissection of the psychiatric phenotypes are enabling rapid progress with multiple gene discoveries. These discoveries validate the dissection of each disorder into its more discretely determined neurobehavioral subcomponents, and, at the same time, create useful

tension for investigators to put the parts together again in explaining the necessary and sufficient conditions for overt illness manifestation.

Despite their utility in the context of etiological research on mental disorders, endophenotypes are not likely to have great utility in the clinical description of psychopathology. As the work reviewed above attests, the different categories of mental disorders probably do not reflect completely separate underlying neural system pathologies or genetic causes. However, at least in the short run, it is difficult to imagine the use of endophenotypic assessments in diagnostic or treatment contexts, even if they more realistically reflect variation in the underlying causes of illness. In the long run, it might be possible to specify diagnoses and treatments according to a "profile" analysis of multiple endophenotypic traits and/or their associated genetic determinants. For the time being, the diagnostic categories currently in use have utility in clinical contexts in terms of promoting communication and facilitating treatment and prognostic decisions. It may be nevertheless be useful to acknowledge the disorder categories as pragmatic simplifications to avoid their reification as reflecting nature carved at its joints.

In conclusion, although progress in identifying genetic variants that increase risk to common mental disorders has been slow, this is to be expected given the commonality of these mental disorders reflects, in part, the number of causes of these disorders. Identifying endophenotypes that underlie mental disorders provides an important and promising way forward, not only for genetic mapping, but also for the understanding of how environmental and genetic factors interact to influence disease susceptibility and expression, and for the development of new treatment and prevention strategies.

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