The concept of endophenotypes in psychiatric disorders has been developed over the last few decades. In their 1967 paper on the genetics of schizophrenia, Gottesman and Shields used the term *endophenotype* to define an illness-related characteristic, observable through biochemical testing or microscopic examination. It is assumed that a valid and useful endophenotype is more closely related to one or more pathophysiological genes for the nosological category, compared with the entire spectrum of disorders included in the nosological category. The utility of endophenotypes in psychiatric research is now more appreciated because we have a more accurate understanding of the genetic complexity of operationally defined disorders in our current psychiatric nosology. Endophenotypes should be valid approaches to creating more homogeneous subtypes of current diagnostic categories. If endophenotypes can create more homogeneous subgroups of the traditional nosology of schizophrenia and affective disorders, then more rapid advances in understanding these disorders at the genetic, molecular level can be made. Improved pharmacotherapy would surely follow.

**Criteria for an endophenotype**

The criteria for an endophenotype have been derived from those proposed by Gershon and Goldin:

- The endophenotype must be associated with illness in the general population.
- The endophenotype should be a stable, state-independent characteristic (that is, it must be observable despite the fact that the patient may be in partial or complete remission).
- The endophenotype should be heritable.
- The endophenotype should segregate with illness within families.
Among kindreds in which the proband has the endophenotype, the endophenotype should be observable at a higher rate among unaffected family members compared with the general population. In what follows below, we consider aspects of endophenotypes.

**Diagnostic specificity for an endophenotype**

The first criterion for an endophenotype is typically proven by demonstrating that the endophenotype is more common among unrelated people with a given nosological diagnosis compared with the general population. A related issue is diagnostic specificity. Should a single endophenotype be specific to a given nosological classification, such as schizophrenia or bipolar disorder? While such a one-to-one correspondence might make for easier comprehension of results, our current nosological system, distinguishing schizophrenia and bipolar disorders, is constructed on the basis of symptom clusters and—to a lesser extent—the course of illness. The extent to which our current nosological classification system reflects biological distinctions is an unresolved matter. Recent research suggests considerable overlap between schizophrenia and bipolar disorder in family studies and molecular studies (for reviews, see references 3 and 4). No bipolar family study (that was conducted in an optimal manner) reports increased risk for schizophrenia among relatives of bipolar probands. Similarly, no schizophrenia family study reports increased risk for bipolar disorders among relatives of schizophrenia probands. However, several schizophrenia family studies report increased risk for recurrent unipolar depression and schizoaffective disorders among relatives of schizophrenia probands.5-8 Family studies of bipolar illness show that a spectrum of mood disorders is found among the first-degree relatives of bipolar probands: bipolar I, bipolar II with major depression (hypomania and depressive episodes in the same person), schizoaffective disorders, and recurrent unipolar depression.6-13 These family studies are consistent with some degree of overlap in susceptibility to recurrent unipolar depression and schizoaffective disorders for relatives of bipolar probands and relatives of schizophrenia probands. Kendler et al specifically noted an increase in risk for psychotic affective disorders among the relatives of schizophrenia probands. Thus, from this family study perspective, some endophenotypes may be shared between schizophrenic and affective disorders.

Kendler et al specifically noted an increase in risk for psychotic affective disorders among the relatives of schizophrenia probands. Thus, from this family study perspective, some endophenotypes may be shared between schizophrenic and affective disorders. Similarly, there is molecular evidence for genetic overlap in susceptibility to schizophrenia and to affective disorders (for a review, see reference 4). One promising candidate gene is the G72 locus on chromosomal region 13q32, the site of a confirmed linkage in bipolar disorder and schizophrenia.4 G72 is a primate-specific, brain-expressed gene that activates D-amino acid oxidase.14 D-Amino acid oxidase may control levels of D-serine, which regulates glutamatergic receptors.15 Chumakov et al identified a haplotype from G72 single nucleotide polymorphisms (without obvious functional significance) that were in linkage disequilibrium with schizophrenia in a French-Canadian sample. This has been confirmed in distinct schizophrenia populations, including Russian,14 German,16 Israeli,17 and Chinese,18 although different haplotypes have been associated in distinct ethnic populations. Similarly, in bipolar disorder, there have been several positive findings with distinct haplotypes in different populations, including American19,20 and German16 bipolar samples. Thus, from this molecular perspective, some endophenotypes may be shared between schizophrenic and affective disorders.

Given what we know about the overlap in genetic susceptibility to schizophrenia and mood disorders,4 it is entirely possible that some endophenotypes may be characteristics of both types of disorder.

**Stability and heritability of an endophenotype: the P50 abnormalities as an example**

Ideally, an endophenotype should be a stable, state-independent parameter. An endophenotype should be an enduring characteristic of an individual, and should be present prior to the onset of illness. Thus, increased rates of an endophenotype for schizophrenia should be detectable when studying the young adult children of schizophrenic persons. The same statement cannot be made regarding an endophenotypic study of the prepubertal children of schizophrenic individuals because it is entirely possible that the endophenotype may not be manifest until after puberty. This is particularly relevant because schizophrenia is uncommon among prepubertal children, but becomes common in young adults. Increased rates of an endophenotype for schizophrenia should be detectable when studying the individuals who are acutely psychotic, as well as those in partial remission. Similarly, an endophenotype for bipolar disorder should be observable in the depressed, euthymic, or manic states.
These qualities render the endophenotype more easily demonstrable. Consider one outstanding example of an endophenotype, the P50 abnormality in schizophrenia. An abnormality of the P50 auditory evoked potential is considered an endophenotype for schizophrenia. The P50 wave is a positive deflection (recorded by scalp electrodes) occurring 50 ms after an auditory stimulus, typically a single click. When two such clicks are presented, with the second click occurring ~200 ms after the first, the amplitude of the P50 wave after the second click is reduced in comparison to the amplitude of the wave after the first click (Figure 1). This is considered to be an electrophysiological signature of sensory gating. In some individuals with schizophrenia, the amplitude of the p50 wave for the second click is similar to the amplitude after the first click. This is interpreted as a failure of sensory gating. This is shown in graphic form in Figure 1.

The P50 abnormality is found more often among individuals with schizophrenia, compared with controls, although this is not universally confirmed. The P50 abnormality is found more frequently among the relatives of persons with schizophrenia, thereby lending added confidence to this line of investigation. To summarize the P50 endophenotype literature, there is substantial evidence that the P50 abnormality in schizophrenia fulfills generally accepted criteria for an endophenotype. Variation in or near the α7-nicotinic receptor subunit gene may explain some of the genetic variance in the P50 measurement, and additional research with this endophenotype can be expected to yield new insights into this subtype of schizophrenia.

Stability and heritability of an endophenotype: cognitive deficits in schizophrenia as an example

A second endophenotype that has been studied extensively in schizophrenia is working memory. This term can be defined as the holding of information in the consciousness, in preparation for complex processing. Working memory can be assessed by multiple different mental tasks, such as N back, Wisconsin Card Sort, and reverse digit span. Deficits in working memory have been described as an endophenotype for schizophrenia (for a review, see reference 43). The fraction of individuals with schizophrenia who are designated as having abnormal working memory varies with the tests employed, the clinical population studied, and the definition of abnormal (e.g., 1.5 or 2 standard deviation units below the mean for controls). If consideration is given only to studies of large numbers of cases (~100) and controls, most reports describe 25% to 50% of persons with schizophrenia as falling in the variably defined “deficit range” for working memory. Several lines of evidence suggest that the working memory deficits are partly heritable. Twin studies of unaffected and discordant (for schizophrenia) monozygotic and dizygotic twin pairs indicate that genetic influences in the schizophrenia-related working memory deficits are prominent. In addition, multiple studies suggest that a
small fraction of the variance in working memory scores is explained by a functional variant in the catechol-O-
methyltransferase (COMT) gene, although this finding is not observed consistently. Working memory deficits are more common among the unaffected relatives (compared with controls) of schizophrenic individuals who have deficits themselves (for a review, see reference 8). The effect size for this observation is relatively small, such that substantial sample numbers are required to have adequate power. If only those studies that examined at minimum ~50 relatives and ~50 controls are considered, then there is a preponderance of data suggesting that unaffected relatives (of schizophrenic individuals) have some of the neuropsychological deficits seen in affected persons. However, one must be concerned with a negative publication bias and with the fact that a wide range of neuropsychological measures have been used, such as Wisconsin Card Sort, digit span, trailmaking, tests of verbal and spatial fluency, etc. The effect size is not large, as evidenced by the fact that multiple smaller studies have not found a significant difference between relatives of schizophrenic individuals and controls. The preponderance of data suggests that neuropsychological/cognitive deficits in schizophrenia are present more often among affected persons compared with controls. There are data to indicate that the measures are heritable. Finally, most of the larger studies find that nonpsychotic relatives of schizophrenic individuals score more poorly on various neuropsychological tests compared with controls. Thus, various measures of cognitive function are valid endophenotypes for schizophrenia, on the basis of the criteria noted above.

**Promising endophenotype candidates lacking heritability data**

Several potential endophenotypes for affective disorders and schizophrenia lack sufficient heritability data. For example, multiple central nervous system imaging studies have revealed a failure to appropriately activate dorsolateral prefrontal cortex while performing a Wisconsin Card Sort task in some individuals with schizophrenia (for a review, see reference 68). This promising endophenotype lacks sufficient heritability data at present. Although there is some evidence that a COMT functional variant is correlated with the endophenotype, there is a need for substantial data on normal monozygotic and dizygotic twins. One potentially useful endophenotype for affective disorders may be the magnetic resonance imaging finding of subcortical (white matter) hyperintensities in schizophrenia. Although heritability is considered to be one criterion for an endophenotype, this may not be an essential characteristic of all valid endophenotypes. For example, it has been hypothesized that viral infections in utero may be an environmental risk factor for schizophrenia, although many studies have been unable to confirm this association (for a review, see reference 88). While this may be a valid endophenotype, it is difficult to consider this as a heritable characteristic, because the increase in risk after in utero infection has been documented for influenza and for rubella. Thus, some endophenotypes may not have heritable components, but may be valid means for creating subgroups of cases. This does not mean that any means to create subgroups of patients represents an endophenotype. To subgroup schizophrenia patients as having suffered an in utero viral infection, one must first develop some biochemical test to determine if a given schizophrenic person has experienced such an infection. Once that test is in place, one can then attempt to define whether a particular genetic background of schizophrenia risk is more common among these unique cases.
Bases genéticas para los endofenotipos en los trastornos psiquiátricos

Este artículo revisa el concepto de endofenotipo, con especial atención a la heredabilidad como también a la especificidad diagnóstica. Un endofenotipo no requiere necesariamente ser heredable, como ocurre por ejemplo en la posible influencia de infecciones virales intrauterinas para la esquizofrenia. Sin embargo, la heredabilidad es una característica útil para un potencial endofenotipo, pues se puede estudiar en relación con un posible gen candidato. Se debe tener en consideración que los métodos tradicionales para demostrar la heredabilidad, como los estudios en gemelos, se pueden complementar con estudios de secuencias de ADN, que sugieren heredabilidad. Los endofenotipos no requieren ser específicos para determinadas clases nosológicas o trastornos psiquiátricos, ya que estas clases no reflejan categorías biológicas. Se resumen las evidencias para dos endofenotipos útiles en la esquizofrenia, como son las anormalidades de la onda P50 y los déficits cognitivos.

Bases génétiques des endophénotypes dans les troubles psychiatriques

Cet article passe en revue le concept d’un endophénotype avec une référence particulière à l’hérédité aussi bien qu’à une spécificité diagnostique. Un endophénotype n’est pas nécessairement à transmission héréditaire, par exemple, l’infection virale in utero, endophénotype possible pour la schizophrénie. Toutefois, l’hérédité est un caractère utile pour un endophénotype potentiel, car il peut être étudié avec un gène candidat plausible. Il faudrait noter que les méthodes traditionnelles de démonstration de l’hérédité, par exemple les études concernant les jumeaux, peuvent être complétées de l’étude des séquences d’ADN, suggérant l’hérédité. Il n’est pas nécessaire que les endophénotypes soient spécifiques d’une classe nosologique donnée de troubles psychiatriques, ces classes ne reflétant pas des catégories biologiques. Nous allons résumer les arguments pour deux endophénotypes utiles pour la schizophrénie, le P50 et le déficit cognitif.

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