

Bringing Genetics Back to Psychiatric Endophenotypes

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The concept of endophenotypes, introduced almost 4 decades ago, has become increasingly important in the study of complex neuropsychiatric diseases. Endophenotypes are measurable, but not overtly observable, constructs in the pathway from genetic variation to psychiatric disorder. As originally conceptualized, endophenotypes must: 1) be associated with illness in the population; 2) be heritable; 3) be state independent, although they may need to be elicited by a challenge; 4) cosegregate with illness within families; and 5) be found in unaffected relatives of probands at a higher rate than in the general population (1). Initially, scientists had hoped that investigating endophenotypes would hasten the identification of the genetic origins of various disorders, but this has not proven to be the case. This difficulty in identifying the genetic foundations of psychiatric disorders is due, in part, to the restrictive nature of the definitions included in the *International Classification of Diseases, 10th revision*, and the *Diagnostic and Statistical Manual of Mental Disorders-IV*, which are not based on etiology or pathophysiology (2). But it is also due to the fact that investigators have departed from the original criteria for endophenotypes noted above and have considered as a possible endophenotype virtually any neural, cognitive, or affective abnormality associated with a mental illness, regardless of its genetic links. This overgeneralization has impeded the study of endophenotypes in promoting the discovery of genes underlying psychopathology.

In this issue of *Biological Psychiatry*, Glahn *et al.* (3) present work that both returns to the original conceptualization of endophenotypes (with, arguably, one notable exception described below) and provides a formal, mathematical procedure for identifying endophenotypes that may promote gene discovery in psychiatry. In the context of major depressive disorder (MDD), these researchers define and test the usefulness of the endophenotype ranking value (ERV), an index for measuring the strength of association with genetics of endophenotypes implicated in psychiatric illness. The ERV is a straightforward index that increases with increasing values of three constructs: 1) the heritability of the psychiatric illness; 2) the heritability of the endophenotype; and 3) the genetic correlation between the illness and the endophenotype. In this formulation, a putative endophenotype that is associated with a heritable disorder and that is itself heritable will receive a high ERV, provided that it has high genetic correlation with the disorder; thus, the ERV returns genetic linkage to the conception of the endophenotypes and also maintains the requisite links between the endophenotype and the illness.

Glahn *et al.* (3) calculated ERVs for a large set (more than 11,000) of behavioral, neural, and transcriptomic factors that were assessed in a sample of 1122 Mexican-American persons. They then performed quality tests on the ERV index by conducting univariate and bivariate linkage analyses of the endophenotypes from each of these three categories that have the highest ERVs: the Beck Depression Inventory (BDI) scores, the bilateral diencephalon volume, and the RNF123 transcriptional endophenotype, as well as the inci-

dence of MDD itself. From univariate analyses, the authors found a genome-wide significant quantitative trait locus (QTL) on chromosome 7 for diencephalon volume and a strong but not genome-wide significant QTL at chromosome 4p15 for MDD. BDI and RNF123 did not show strong evidence for QTLs, although bivariate analyses of MDD with RNF123 strengthened the significance of the QTL at chromosome 4p15. Follow-up tests of pleiotropy identified the influence of MDD, RNF123, diencephalon volume, and, marginally, BDI at this same locus. Parenthetically, it may not be surprising that BDI scores were only marginally significant in these analyses. One may recall that one of the original criteria for an endophenotype is that it is state independent. Clearly, BDI scores do not meet this criterion; indeed, they are often used to indicate improvement in the depressive state. In fact, only 86 of the sample of 1,122 participants Glahn *et al.*'s were clinically depressed at the time of the assessment and, presumably, had elevated BDI scores.

Nevertheless, we find the results of Glahn *et al.* (3) to be compelling from the perspectives of structural and functional neuroimaging of MDD. As the authors point out, the volumes of the hippocampus and amygdala were among the top-ranked neuroanatomic endophenotypes. In this context, it is important to note that structural aberrations of the hippocampus and amygdala are among the few neural anomalies in MDD to be confirmed as reliable in systematic meta-analyses of neuroimaging data. Specifically, these analyses have shown the volumes of the hippocampus (4) and the amygdala (5) to be reliably reduced in MDD.

We think it is particularly noteworthy that Glahn *et al.* (3) found that diencephalon volume not only was the top-ranked neuroanatomic endophenotype but also was the only single endophenotype that was associated with a QTL at genome-wide levels of significance. The diencephalon is a part of the forebrain sitting atop the midbrain and comprising the thalamus (most prominently) as well as the hypothalamus, pineal gland, and several perithalamic structures. A growing appreciation of the roles of thalamic structures in regulating attention, affecting reward responsiveness, and influencing autonomic functioning has kindled a renewed interest in the role of these structures in MDD. This interest is further strengthened by results of positron emission tomography studies of resting-state regional neural activity in MDD that show the pulvinar nucleus of the thalamus to be overactive in MDD (e.g., [6]). In fact, neuroanatomic and functional neuroimaging studies provide compelling evidence that the pulvinar nucleus plays a central role in the maintenance of MDD. Recent conceptualizations of pulvinar function implicate the involvement of this structure in emotional attention and emotion awareness (7), both of which have been found to be aberrant in MDD. Furthermore, investigators have found consistently that the amygdala, insula, and dorsal anterior cingulate cortex, the primary nodes of the brain's salience network (8), are strongly activated in response to negative stimuli in MDD (9). Importantly, these structures have strong bidirectional connectivity with the pulvinar nucleus (7). Given this role of the pulvinar nucleus in the emotional attention and awareness and its connectivity with these three structures of the salience network, we posit that elevated baseline pulvinar activation serves to potentiate salience network response to negative stimuli in MDD.

Further supporting the usefulness of the ERV of Glahn *et al.* (3) is the growing interest of clinical neuroscientists in another diencephalic structure, the habenula, a neural region that has been

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found to be characterized by reduced volume and increased activation in MDD. In addition, stimulating the habenula with implanted electrodes has been found to result in the remission of treatment-refractory depression. Of particular interest with respect to the study by Glahn *et al.* (3), however, is the fact that the habenula represents a point of convergence of their findings. This structure receives projections from the amygdala, which Glahn *et al.* found to have a high ERV ranking, and sends projections to serotonergic and dopaminergic regions, such as the dorsal raphe nucleus and ventral tegmental area (see [10] for a full review). The fact that the ERV analysis by Glahn *et al.* (3) resulted in high ranks for the transcriptional endophenotypes PDXK and MARK2 highly, which influence serotonergic and dopaminergic functioning, is intriguing and indicates that it may be profitable to conduct additional bivariate linkage analyses that incorporate diencephalon volume and these transcriptomic factors.

We believe that the study by Glahn *et al.* (3) is important in developing and describing the ERV and in demonstrating that it can be used to identify possible endophenotypes for recurrent MDD. As we noted above, interpreting the high ERV for the BDI may be difficult, given the state-dependent relation of this construct and its high overlap in variance with MDD, which itself had high univariate linkage scores. Indeed, Hasler and Northoff (2) argued that the most important feature of a good endophenotype is its simple genetics, that is, that the association of the endophenotype is stronger with risk genes than it is with the disease phenotype. The analyses by Glahn *et al.* (3) move us in the right direction, indicating that MDD, even as currently defined, may have strong genetic linkage. And equally important, the ability of the ERV method to identify neural factors that are, independent of this analysis, of increasing interest to clinical neuroscientists attests to the validity and usefulness of this method and highlights the importance of integrating basic neuroscience with the search for psychiatric endophenotypes.

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