Endophenotypes and child psychiatry†

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The search for an appropriate way to define psychiatric phenotypes in order to enhance the discriminative capacity of linkage and association studies is increasingly recognised to be of crucial importance for understanding the genetic basis of both child and adult psychiatry (Skuse, 1997; Leboyer, *et al*, 1998). There is plenty of evidence that conventional definitions of major psychiatric disorders, such as schizophrenia or manic–depressive psychosis, are unsatisfactory means of establishing just who in a pedigree or population study is carrying susceptibility genetic loci. These phenotypes are complex in the sense that they do not exhibit classic Mendelian recessive or dominant inheritance that could be attributable to any single genetic locus. They probably result from the presence of at least two (probably rather more) susceptibility genes, which either simply co-act in an additive fashion, as in classic polygenic models, or interact – a phenomenon known as epistasis. These genetic components may assort independently, and thus – unlike the disease phenotype – could be associated with Mendelian patterns of inheritance of (possibly cryptic) phenotypic traits. Accordingly, it has been suggested that a focus on associated traits, rather than syndromes, is appropriate and could in due course contribute to the redefinition of traditional psychiatric syndromes. This would lead, in turn, to a greater understanding of how genetic mechanisms and environmental influences jointly bring about phenotypic expression of conventionally specified disorders.

ENDOPHENOTYPES

Latent genetically influenced traits, which may be related only indirectly to the classic disease symptoms defined in ICD–10 or DSM–IV (World Health Organization, 1992; American Psychiatric Association, 1996), are known as endophenotypes (Gottesman, 1997). They reflect an underlying susceptibility to the disease phenotype (or some forme fruste of it). In psychiatry we are likely to be interested in endophenotypes that are measurable by neurophysiological or neuropsychological means, for reasons of specificity that will be discussed further.

Measuring susceptibility to illness

Crucial characteristics of any endophenotype include the fact that it can be measured before the explicit onset of the illness, and that it represents the genetic liability of non-affected relatives of probands with the disorder. For example, there seems little doubt that the range of learning and social difficulties reported in the families of autistic probands, a quintessentially highly heritable condition (albeit a genetically complex one), reflect vulnerability traits (Pickles *et al*, 2000). If the disorder is genetically complex, we might ask the question: could each genetic locus contribute to distinct aspects of the illness phenotype? It is possible that there may be separate susceptibility genes for the language impairments in autism and for the social deficits associated with the condition.

If the same susceptibility loci contribute to specific aspects of phenotypes in a variety of apparently nosologically distinct conditions, knowing this could illuminate some currently puzzling aspects of comorbidity. In the search for genes that predispose to the development of child psychiatric disorders, it may prove unproductive to seek the genetic components of relatively amorphous syndromes, or 'comorbid' disorders. Broad heritability can, of course, be established with the aid of twin studies, which give us useful but often non-specific information about the nature of the genetic components of complex disorders. For a deeper understanding of the genetic predisposition to psychiatric conditions, it may be more profitable to seek the genetic basis of endophenotypes that are common to a number of diseases or disorders. Creating heuristic models that link traits across neurodevelopmental disorder will, in due course, lead to the integration of disciplines. Because, ultimately, we need to learn how genes control the neurobiological development of neural systems, we need to be able to create meaningful animal models of psychiatric disorders (Hunter *et al*, 2000). Although uniquely complex human conditions such as schizophrenia or autism may never be mirrored in the mouse, using transgenic technology or mutagenesis to create animal models that display endophenotypes is a promising strategy that is already proving productive (Skuse, 2000).

Perturbations of neurobiological development

Neurodevelopmental disorders resulting in psychiatric phenotypes represent the endpoints of aberrant pathways of brain development. Genetically influenced dysfunction could have originated as early as during foetal life. In such cases it seems reasonable to assume that we should find evidence of endophenotypes in the early childhood of individuals with a given genetic susceptibility. The identification and definition of such characteristics would be of value for several reasons. First, in family-genetic investigations, one may be less likely to identify falsely as unaffected those individuals who are at genetic risk but who do not manifest the full illness phenotype. Second, the characteristics of the endophenotype may shed light on fundamental processes that are disrupted as a consequence of the inherited genetic susceptibility. Of course, we should bear in mind that susceptibility to an endophenotype does not necessarily imply that the genetic locus responsible for that endophenotype is involved in the disease process. The gene could be in linkage disequilibrium with the locus of interest. Such proximity would be useful for linkage or association studies, but is useless for gaining an understanding of the biological processes that lead to the disease phenotype.

What makes for a useful endophenotype?

The characteristics of potentially valuable endophenotypes, whether physiological, psychological, functional or structural in nature, are clear. First, they should be measurable reliably, both over time and by different observers. Good reliability in the measurement of psychiatric symptomatology has been the touchstone sought by psychiatric researchers

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for decades, arguably at the expense of validity. Second, they should be sensitive to genetic susceptibility, in that all those with the susceptibility locus should manifest the endophenotype. This is a demanding criterion, for without measuring the genetic locus itself, and knowing just what its characteristics are, one has to assume that those 'at risk' individuals without an endophenotype are not genetically vulnerable. Perhaps the closest we have yet come to such a variable concerns individuals at risk of Huntington's disease (an autosomal dominant condition with virtually 100% penetrance in which the single susceptibility locus has been identified). Gray *et al* (1997) studied a sample of individuals who were at genetic risk but who did not yet show any signs of the disease clinically. They were compared with people who presented for genetic testing but who turned out not to carry the gene for Huntington's disease. A highly selective deficit in the recognition of disgust was confirmed in those whom genetic testing proved to be Huntington's gene carriers. These people were free from clinical symptoms. They did not perform significantly more poorly than non-carriers on any of the background tests or any other face processing tasks, including the recognition of other basic emotions. Gray *et al* (1997) concluded that their finding strongly indicated the importance of the basal ganglia – whose development is compromised by the disease – in the neural system underlying the emotion of disgust.

Third, endophenotypes should be specific to the disorder in question. For example, deficits in smooth pursuit eye movements and a failure to inhibit the P50 auditory event-evoked response appear to co-segregate with the genetic risk of schizophrenia as autosomal co-dominant phenotypes (Adler *et al*, 1999). It is arguable that attentional and inhibitory deficits are central to this condition's psychopathology. However, it is important to discover whether these attention-associated eye movement abnormalities are specific to schizophrenia or whether they are a non-specific expression of attentional deficits that are found in association with many psychiatric disorders (Ross *et al*, 2000).

Longitudinal studies from childhood to adulthood

The ideal population on which to develop knowledge of childhood endophenotype characteristics that reflect vulnerability to adult psychiatric disorders would be, of course, children who are known for certain to be at risk of the disorder. In the absence of a genetic test, the next best solution would be to use contemporaneously gathered data from childhood in a sample of patients who presented with the disease of interest in adulthood. Using as their data source the Maudsley and Bethlem Royal Hospital item sheets, Cannon *et al* (2001, this issue) sought to find premonitory symptoms of serious adult mental illness among those who had attended the Children's Department between 1968 and 1989. They identified 93 children, most of whom presented in early adolescence, and who had a subsequent psychotic illness according to later hospital records (70% schizophrenia; 30% affective psychosis). These samples were compared with a carefully chosen sample of attendees who did not succumb to serious psychiatric disorder. Those who subsequently developed schizophrenia were, as children, more suspicious and sensitive than comparisons and they were more likely to be withdrawn and socially isolated. Children who later developed affective psychoses were more likely to have suffered from symptoms of depersonalisation, conversion hysteria or non-epileptic disturbances of consciousness, but the strength of association was not substantial. The predictive validity of the symptom complexes themselves was modest, at best, as the authors themselves acknowledge. Their value is in pointing us towards other measures that might be used in a prospective design and that could provide greater discrimination.

What should we measure?

Finally, we must always be wary of assuming that simple correlation indicates causation. For example, perhaps the 'real' endophenotype for schizophrenia merely increases children's vulnerability to social opprobrium (by rendering those possessing the susceptibility locus socially inept). Thus, a child's social withdrawal and suspiciousness could be interpreted as a rational response to a hostile environment, which is encountered especially outside the immediate family. With the exception of childhood autism and associated pervasive developmental disorders, remarkably little attention has been paid to the heritability of neurocognitive deficits that underpin the social manifestations of neurodevelopmental disorders. A reconceptualisation of psychiatric nosology is overdue, as neuroscience begins to create an intellectual framework for the exploration of mental function (Cowan *et al*, 2000).

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