The Cutting Edge

ENDOPHENOTYPE, INTERMEDIATE PHENOTYPE, BIOMARKER: DEFINITIONS, CONCEPT COMPARISONS, CLARIFICATIONS

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This Cutting Edge essay focuses on three concepts enjoying increasing usage in contemporary psychopathology research, namely endophenotype, intermediate phenotype, and biomarker. These concepts are likely to see a meteoric rise in use in studies of affective illness and anxiety disorders in the coming years. This is true especially given the recently NIMH proposed research diagnostic criteria (RDoCs), a newly re-configured nomenclature for psychopathology in the offing (e.g., DSM-5), and ever changing scene in genetics research strategies (candidate gene, genome-wide association, epigenetic). These concepts, however, are not fungible. A clear understanding of their specific meaning and the implications of these meanings for psychopathology research, going forward, is essential.

THE ENDOPHENOTYPE CONCEPT

The modern psychopathology research corpus supports the inference that most forms of mental illness (e.g., bipolar illness, schizophrenia, unipolar depression, anxiety disorders) possess an appreciable heritable substrate. This substrate contributes, in interaction with other genetic assets and liabilities as well as environmental and epigenetic inputs, to the overall liability for an illness. It is highly plausible to assume further that the underlying liability for an illness will manifest itself in some fashion before the emergence of its clinical signs and symptoms. In the study of schizophrenia, as an example, this means the emergence of detectable pathological processes before the appearance of psychotic symptoms,
even before so-called prodromal features. In short, one should be able to detect some internal manifestation of a genetic liability for an illness within the at-risk person that (a) is not visible to common observation, (b) exists in situ (i.e., in place, within (not outside) the person), and (c) predates observable signs or symptoms of illness.

THE INTELLECTUAL HISTORY UNDERGRIDDING THE ENDOPHENOTYPE CONCEPT

The endophenotype model has long characterized I. I. Gottesman’s thinking about the genetics of schizophrenia, and psychopathology more broadly. With James Shields, he proposed the endophenotype concept in the early 1970’s ([2,3], p. 172). The substantive background and intended meaning of the endophenotype was explicated in Gottesman and Gould.[4] The endophenotype concept reflects the impact of two major intellectual currents in psychological science and genetics. One current deriving from the insect genetics literature, that advocated the term endophenotype to denote a feature internal to an organism and visible upon microscopic examination (i.e., not an obvious, external feature).[5] The other current deriving from the theoretical and methodological psychological science work on latent hypothetical constructs, inspired by the seminal substantive distinction between “hypothetical constructs” and “intervening variables” made by MacCorquodale and Meehl (1961; see also ref.[7]). Well known to psychologists, the “hypothetical construct” model advanced the core idea that a theoretical concept (e.g., anxiety, depression, pain, love, open mindedness) could (a) exist at a latent level and (b) not be directly observable, but (c) be plausibly related via a nomological network to observable and measurable characteristics (e.g., signs/symptoms, test measurements, interview data). Using the example of schizophrenia, Gottesman and Shields[3] argued that endophenotypes should be considered internal phenotypes that might someday be detectable in families of schizophrenics “…either biological or behavioral (psychometric pattern), which will not only discriminate schizophrenics from other psychotics, but will also be found in all identical co-twins of schizophrenics whether concordant or discordant” (p. 336). The endophenotype is conceptualized as internal to or “within” the individual. Additionally, the endophenotype represents an unobservable latent entity (such as a hypothetical latent construct) that cannot be directly observed with the unaided naked eye; rather, an appropriate technology would be needed to “see” the endophenotype. Importantly, the endophenotype is not “hidden,” rather it can be viewed with the appropriate tools.

The endophenotype concept was prominently positioned for psychopathology research writ large by Gottesman and Gould.[4] However, it emerged originally in schizophrenia research (e.g., [2,8]; see also ref. [9,10] and was subsequently imported into research on other disorders, including anxiety and affective disorders. The endophenotype concept has clearly begun to gain traction in the study of anxiety and affective disorders. Discussions of endophenotypes in the study of major depression ([11]; see also the new major depression database—http://mdd.psych.ac.cn/biomarkBrowser.do), bipolar illness,[12] and anxiety—disorders[13] began in earnest in recent years. Specific examples of potentially exciting candidate endophenotypes in anxiety and affective disorders research are (a) threat-related attentional bias in anxiety,[14] (b) baseline activation and neural response patterns in depression,[15] (c) cortical thinning in depression,[16] (d) amygdala and medial prefrontal cortex neural response configurations in PTSD;[17] and (e) neurotrophic signal transduction pathways in mood disorders.[18]

DEFINING THE ENDOPHENOTYPE: EXPLICIT CRITERIA FOR VALIDITY

According to Gottesman and Gould,[4,19] an endophenotype is a measurable component, unseen by the unaided naked eye, that lies along (i.e., within) the pathway between disease (i.e., observable phenotype) and distal genotype. An endophenotype is not a risk factor, rather it is a manifestation of the underlying disease liability. Thus, an endophenotype is internal and not easily discerned without some technological assistance with appropriate sensitivity. An endophenotype may be neurophysiological, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature and it can include configurational self-report (e.g., inventory) data. The utility of an endophenotype is that it represents, in principle, a relatively simpler clue to genetic underpinnings than the disease syndrome (i.e., symptom constellations). Gottesman and colleagues ([4], p. 639; [20], p. 964) proposed six explicit criteria defining an endophenotype (see Table 1). Gottesman and Gould[4] articulated the benefits of the endophenotype for research.

<table>
<thead>
<tr>
<th>TABLE 1. Criteria for an endophenotype</th>
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<td>(1) The endophenotype is associated with illness in the population.</td>
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<td>(2) The endophenotype is heritable.</td>
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<td>(3) The endophenotype is primarily state-independent (manifests in an individual whether or not the illness is active) but may require a challenge to elicit the indicator.</td>
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<td>(4) The endophenotype is more prevalent among the ill relatives of ill probands compared with the well relatives of the ill probands (i.e., within families, endophenotype and illness co-segregate).</td>
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<td>(5) The endophenotype found in affected family members is found in nonaffected family members at a higher rate than in the general population.</td>
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<td>(6) The endophenotype should be a trait that can be measured reliably, and ideally is more strongly associated with the disease of interest than with other psychiatric conditions.</td>
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Adapted from Refs. [4] and [20]
THE BIOMARKER CONCEPT

In biomedical research, a biomarker (occasionally termed “bioindicator”) could be any measurable indicator of a disease. An elevated blood concentration of one or another substance in the blood that would be taken as indicative of the presence of illness, thus a “biomarker” (e.g., high cholesterol is a biomarker of cardiovascular ill-health). In other words, such a biomarker could be correlated with an aspect of the disease process, but not fall within the genotype to phenotype pathway and, therefore, may not be specifically embedded in the causal chain for the disease. A biomarker could also reflect a biologically detectable impact of an outside agent upon the organism. The National Institute of Environmental Health[21] defined biomarkers as “key molecular or cellular events that link a specific environmental exposure to a health outcome.”[22] Consider blood or urine lead (Pb) levels as examples of biomarkers of environmental lead exposure. Finally, perhaps casting the broadest net in the biomarker dialogue, the Biomarkers Working Group (2001) defined a biomarker as “a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” (p. 91). In all of these descriptions, it is evident that a genetic basis for the biomarker is not a necessary criterion. However, in comparison, an essential component of the endophenotype concept is that it is heritable. In short, a biomarker may or may not be subject to genetic influences.

The easiest way to remember the distinction between these two terms is that all endophenotypes are, by definition, biomarkers, but not all biomarkers are endophenotypes. Whereas an endophenotype must meet all the criteria presented in Table 1, a biomarker need only reflect some measurable deviation in the organism, reflective of either internal factors operating in either health/illness or the impact of an external agent. Thus, for example, a biomarker that is reflective of an environmental exposure will necessarily fail to satisfy those criteria of validity for an endophenotype that concern patterns of familial aggregation (e.g., elevated ammonia levels due to some forms of drug abuse). Thus, the term biomarker is not fungible with (or equivalent to) endophenotype.

THE INTERMEDIATE PHENOTYPE CONCEPT

The term “intermediate phenotype” has also seen increased use in some discussions related to liability for psychopathology. However, not unlike the term “biomarker,” the concept “intermediate phenotype” is also not fungible with endophenotype. This is because the term intermediate phenotype can be used in multiple ways, but only one of them approximates the intended meaning of an endophenotype. Weinberger and colleagues[23, 24] clearly state a preference for the term intermediate phenotype in their work. They argue it “implies a biological [italics added] trait that is in a predictable path from gene to behavior and because the phenotypes and mechanisms are not secondary, but probably primary” (p. 820). This definition, which does not specify heritability as a necessary feature, suggests that the biological trait in question could be a biomarker. More recently, however, Rasetti and Weinberger[24] state, “An intermediate phenotype related to mental illness is a heritable [italics added] trait that is located in the path of pathogenesis from genetic predisposition to psychopathology” (p. 340) and in defining the intermediate phenotype they explicitly reference[4] “endophenotype.” Weinberger and colleagues buttress their preference for the intermediate phenotype concept as they see their intended usage of the term as “analogous to its usage in other areas of complex medical genetics” (p. 820).

As discussed elsewhere (11), the term intermediate phenotype can denote a number of meanings, all of which are plausible and all of which would differently impact research. First, the term intermediate phenotype has an established meaning in genetics related to “incomplete dominance” (also known as “partial dominance,” when known a priori that a true autosomal dominant gene is causal) or a form of intermediate genetic inheritance in which heterozygous alleles are both expressed to varying degrees, resulting in an intermediate phenotype that represents a combination of the parent phenotypes. Examples of intermediate phenotypes are a white flower and a red flower gives rise to a pink flower; in short-horn cattle, coat color may be red, white, or roan (roan is an intermediate phenotype expressed as a mixture of red and white hairs); and in humans, one form of familial hypercholesterolemia (in humans) represents an intermediate phenotype reflective of incomplete dominance. This technical definition of intermediate phenotype in the genetics field predates all discussions in the psychopathology literature.

Intermediate phenotype, using schizophrenia as an illustrative referent, could also be taken to mean any of the following: (a) “not quite or almost a recognized/established phenotype” (e.g., schizotypal personality disorder; prodromal schizophrenia states); (b) “lying between two established phenotypes” (e.g., schizoaffective disorder lying between schizophrenia and affective illness); (c) “a phenotype precisely halfway (i.e., Latin intermedia) between a genotype and phenotype” (plausible, but no known example); and (d) “a measurable, but unobservable phenotype falling somewhere between an illness genotype and phenotype” (e.g., eye tracking dysfunction in schizophrenia; this is a Gottesman and Gould[24] endophenotype). The intended meaning of intermediate phenotype as used by Weinberger and colleagues is essentially that concept defined by endophenotype. As can be readily seen, the concept intermediate phenotype has several plausible interpretations in addition to its longstanding technical meaning genetics. This variability in interpretation of the meaning of intermediate phenotype has sown some confusion already. For example, Insel and Cuthbert[25] suggested that endophenotype is appropriate to situations where
a specific process is studied (e.g., prepulse inhibition), whereas intermediate phenotype should be used for con-
structs such as “personality or clinical constellations” (p.
988). Insel and Cuthbert clearly recommend usage of “intermediate phenotype” quite different from that es-
poused by Weinberger et al.

CONCLUSION

The biomarker and intermediate phenotype concepts are not fungible with the endophenotype concept and should not be confused with the latter (see Figure 1). The concept/term endophenotype enjoys freedom from the terminological ambiguity necessarily associated with the term intermediate phenotype. The semantic and substantive considerations reviewed here favor en-
dophenotype as a concept for psychiatric genetics and psychopathology research (including RDoC efforts).[31]
The biomarker and intermediate phenotype concepts do have utility, however. The biomarker term captures the
domain of any biologically influenced factor or deviation in relation to psychopathology (including endopheno-
types). It may be useful in distinguishing between bi-
ological factors that occur secondary to an illness, but fall outside the realm of endophenotypes (e.g., state mark-
ers). Biomarker may have utility when discussing the biological impact of environmental or exogenous fac-
tors on the emergence of psychopathology. Intermediate phenotype may be best used to describe a subclinical variant of a form of major psychopathology—such as schizotypic psychopathology vis-a-vis schizophrenia—
the phenotype is visible to the unaided eye and it bears some resemblance to the classic phenotype of interest. Intermediate phenotype, in this usage, describes a dilute form of an established phenotype (or unit of analysis).

More conservatively, the term intermediate phenotype might be best reserved for describing incomplete or par-
tial dominance as it has been used in genetics for decades.

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The endophenotype approach may aid in parsing heterogeneity in all manner of laboratory data in future psychopathology studies, including affective and anxiety disorders. One could easily argue that heterogeneity rep-
resents the Achilles’ heel of psychopathology research, especially in genetic work. Going forward, endopheno-
types (when carefully chosen, see ref. [26]) can be put to use maximally in efforts to reduce heterogeneity[27] in laboratory data relevant to RDoC processes relevant to affective illness. Such heterogeneity reduction might also advance efforts seeking to develop diagnostic bio-

logically tests in psychiatry.[28] One can clearly image that reliable and valid endophenotypes may eventually


cer rites to achieve the precision one finds in the more mature sciences, such as chemistry or physics.[29, 30]

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REFERENCES

3. Shields J, Gottesman II. Genetic studies of schizophrenia as sign-
4. Gottesman II, Gould TD. The endophenotype concept in psy-
5. John B, Lewis KR. Chromosome variability and geographi-
cal distribution in insects: chromosome rather than gene varia-
tion provide the key to differences among populations. Science 1966;152:711–721.
6. MacCorquodale K, Meehl PE. On a distinction between hy-