Thinking clearly about the endophenotype–intermediate phenotype–biomarker distinctions in developmental psychopathology research

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Abstract

The endophenotype is central to modern developmental psychopathology studies. It is used in studies seeking to connect the genetic substrates of the panoply of major mental disorders with processes, tapped by laboratory and other assessment measures, in the genotype to a behavior/psychopathology pathway. Proposed originally by Gottesman and Shields (1972; Shields & Gottesman, 1973) 41 years ago, the endophenotype concept has gained widespread traction in psychopathology research since the Gottesman and Gould (2003) review. Other concepts broadly related to the endophenotype notion have also generated discussion in experimental and developmental psychopathology research. One is the intermediate phenotype, a concept proffered as a putative alternative formulation to the endophenotype. Another concept in this intellectual vein is biomarker. The terms endophenotype, intermediate phenotype, and biomarker have often been used interchangeably in the psychiatric literature, yielding conceptual confusion. However, these three terms are not fungible. The recent Research Domain Criteria proposal from the National Institute of Mental Health has emphasized selected underlying processes thought to be of developmental

Development and Psychopathology is celebrating 25 years of shaping the field of inquiry in developmental psychopathology, and the scholarship that fills the pages of this unique journal has impacted the field well beyond the borders of the developmental psychopathology vantage point. For example, one might only think of the concept of resilience and how this concept (a legacy of Norman Garmezy; Garmezy, 1996), which has been well represented in the pages of Development and Psychopathology, has become nearly

assume further that the underlying liability for an illness (or normal deviations in processes contributing to an illness) will manifest itself in some fashion before the emergence of its clinical signs and symptoms. In schizophrenia, taken as an exemple, this means the emergence of detectable pathological processes before the appearance of psychotic symptoms, even before prodromal features. One should be able to detect some internal manifestation of a genetic liability for schizophrenia, for example, within the at-risk person that (a) is not visible to common observation, (b) exists in situ (i.e., within the person), and (c) predates observable signs or symptoms of illness. These fundamental theoretical assumptions are embodied in the endophenotype concept (Gottesman & Gould, 2003; Gottesman & Shields, 1972; Shields & Gottesman, 1973).

The intellectual history undergirding the endophenotype concept

The endophenotype model has long characterized Irving Got-

constellations). Gottesman and colleagues (Chan & Gottesman, 2008, p. 964; Gottesman & Gould, 2003, p. 639; Gottesman & McGue, in press) proposed six explicit criteria that an endophenotype should meet (see Table 1).

One might reasonably ask what benefits accrue from the endophenotype concept and the identification and study of endophenotypes. A summary of what Gottesman and Gould (2003) described as the probable benefits of the endophenotype concept follows:

1. Physiological and more elementary-based endophenotypes may more directly reflect the activities of synaptic and other neuronal mechanisms than does the more complex illness itself, and therefore they are more likely to reflect genes with larger effect sizes.
2. Both the patients and their unaffected relatives may show a fairly extensive range of scores on the endophenotypes, making such measures ideal for quantitative trait linkage analysis. (The analysis of quantitative measurements related to the clinical phenotype will provide more statistical power to detect linkage compared with the smaller number of clinically defined [i.e., qualitative] psychiatric relatives/patients.)
3. To the extent that the biology of the endophenotype is understood or can be investigated via brain-imaging studies and infrahuman animal model research, candidate genes can be identified more systematically in the areas of linkage.
4. Endophenotypes (may) lend themselves directly to the use of animal models.

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). The single most important difference between the biomarker and the endophenotype is that a biomarker need not meet the heritability requirement of an endophenotype (see Figure 1). Thus, the term biomarker is not fungible with (or equivalent to) endophenotype.

Intermediate Phenotype: History, Prior Usage in Genetics, and Intended Usage in Psychopathology

The term intermediate phenotype has been used in some discussions related to psychopathology liability, biomarkers, and endophenotypes in psychopathology research. However, like the term biomarker, the intermediate phenotype concept is not fungible with endophenotype (Figure 1). The principal shortcomings of the intermediate phenotype center around the ambiguity that attends the meaning of intermediate in relation to phenotype, as well as a conflict with an established, prior technical definition in genetics.

The term intermediate phenotype is preferred by Weinberger and colleagues (Meyer-Lindenberg & Weinberger, 2006; Rasetti & Weinberger, 2011) because they argue it "implies a biological trait that is in a predictable path from gene to behaviour and because the phenotypes are not secondary, but probably primary" (Meyer-Lindenberg & Weinberger, 2006, p. 820). This definition suggests that the biological trait in question could be essentially a biomarker, as it leaves unclear the extent to which the intermediate phenotype concept requires heritability as a definitional criterion. However, Rasetti and Weinberger (2011) recently stated, "An intermediate phenotype related to mental illness is a heritable trait that is located in the path of pathogenesis from genetic predisposi-

Another plausible meaning of the term intermediate raises other problems. The word intermediate derives from inter (between) and medius (in the middle) and is typically defined as "being or occurring at the middle place, stage, or degree" (Webster), "lying or occurring in a middle position or state" (Stedman's Medical Dictionary), or "holding the middle place or degree between two extremes" (Oxford English Dictionary). If the word intermediate is used to mean midway, middle, or halfway, then a certain level of precision is suggested in locating a concept in some sort of semantic or conceptual hyperspace, what Meehl termed the nomological network (Cronbach & Meehl, 1955; Meehl, 1972). Adoption of this meaning of the word intermediate suggests that an intermediate phenotype demarcates a location precisely halfway between X and Y, or in this instance, halfway between the genotype (X) and phenotype (Y). This degree of precision in specifying the underlying topography spanning the distance from genotype to phenotype is simply not possible and cannot be assumed (Table 2, entry 4). Remaining simply at the level of observable phenotypes, one might consider the condition "schizoaffective illness" as halfway between schizophrenia and affective illness, which is not likely (Table 2, entry 3).

Alternatively, the term intermediate phenotype could plausibly mean a measureable phenomenon of some sort within the person that characterizes the observable phenotype in some manner. Thus, a phenomenon that falls somewhere between the unobservable genotype and the observable phenotype and affects the final phenotype (Table 2, entry 5). This meaning seems to be a bit closer to that implied by Weinberger and colleagues. However, this usage remains problematic

consideration. Thus, one can speak of working memory deficit as an endophenotype for schizophrenia, and such deficits do not need to appear visibly similar to schizophrenia signs/symptoms.

Finally, Weinberger and colleagues note their preference for the term intermediate phenotype is because the term is used elsewhere in medical genetics, outside of psychiatry. However, their intended meaning of the term intermediate phenotype conflicts with the formal definition of intermediate phenotype used in the general field of genetics (King, Mulligan, & Stansfield, 2012; Stern, 1973). The term intermediate phenotype is related to the technical concept of "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 (Table 2, entry 6; see Stern, 1973). The observable intermediate phenotype is a phenotype of an offspring expressing a mixture of the phenotypes of the parents. In this sense, the intermediate phenotype is a phenotype somewhere (but not exactly halfway) intermediate between the corresponding homozygote phenotypes. For example, in cross-pollination research, one could see a mating between a white flower and a red flower give rise to a pink flower. The palomino phenotype in horses (due to the incomplete dominance of a cream color gene for coat color) is an intermediate phenotype (with possible epigenetic inputs as well). In shorthorn cattle, coat color may be red, white, or roan (roan is an intermediate phenotype expressed as a mixture of red and white hairs). One form of familial hypercholesterolemia in humans represents an intermediate phenotype reflective of incomplete dominance. The low density lipoprotein receptor gene for hypercholesterolemia follows a pattern of autosomal dominance, such that heterozygous carriers express a certain degree of elevated cholesterol that is strangely predictive of early heart disease in later adulthood (in the early 40s and 50s). In contrast, carriers homozygous for the low density lipoprotein receptor gene mutation express severe hypercholesterolemia, typically emerging in childhood. Numerous examples of intermediate phenotypes in humans, using this technical definition of the term, can be found readily on the Online Mendelian Inheritance in Man website (http://www.ncbi.nlm.nih.gov/omim). Although this technical definition of intermediate phenotype appears not to be what is intended by those using the term in psychopathology genetics, this meaning of the term (i.e., intermediate phenotype) is established in genetics, predating the proposed use in psychopathology.

In sum, the meaning of the word intermediate (as a modifier of phenotype) serves to reduce the clarity of the concept intended in intermediate phenotype, both as proposed and likely used. Of all the foregoing interpretations (see Table 2) of the term intermediate phenotype, all of which are entirely plausible, only the fifth interpretation in Table 2 is what Weinberger and colleagues seem to advocate as their intended meaning for the term intermediate phenotype. They provide evidence of a dysfunctional neural circuitry of putative relevance to schizophrenia and use it as an illustrative intermediate phenotype. That such dysfunctional neurocircuitry may be taken as an expression of schizophrenia liability and that dysfunction emerges somewhere between the genotype for schizophrenia and the clinical phenotype is plausible. Ironically, the intended meaning of intermediate phenotype in relation to the dysfunctional neural circuit example (Table 2, entry 5) is the precise definition of an endophenotype. Finally, although Weinberger and colleagues appear to advocate the use of the term intermediate phenotype as essentially synonymous with endophenotype, one is beginning to see others in the field using the term intermediate phenotype differently. For example, Insel and Cuthbert (2009) suggest that endophenotype is appropriate to situations where a specific process is studied (e.g., prepulse inhibition; Table 2, entry 5), whereas intermediate phenotype should be used for constructs such as "personality or clinical constellations" (Insel & Cuthbert, 2009, p. 988; Table 2, entries 1, 2, or 3). In this instance, Insel and Cuthbert recommended usage of intermediate phenotype is wholly different from that advocated by Weinberger and others, as well as different from the technical definition of the term in genetics. In short, this alternate interpretation of intermediate phenotype offered by Insel and Cuthbert (2009) provides evidence of the kind of confusion that attends the term.

Matters of Cause, Matters of Effect, Matters of Development, and Matters of Risk

There are additional concerns that should be brought to bear upon the distinctions among biomarker, intermediate phenotype, and endophenotype as concepts. These concerns are best framed as questions. If we assume a candidate measurement or putative disease process is reflective of a biomarker, intermediate phenotype, or endophenotype, we must ask ourselves the following: is this candidate measurement/process likely to be in the causal chain from genotype to phenotype? Is this candidate measurement/process reflective of the origin of the illness or the effect of the illness (in other words might it be an artifact of the illness)? Does a deviation on the candidate measurement/process predate the onset of the illness, and can it be detected earlier in development, even in the fetus, well before the onset of clinical symptomatology and signs of illness (even subtle symptoms or signs, such as those found in prodromal schizophrenia states)? Is the candidate measurement/disease process merely a variable that speaks to elevated risk for a disorder but, as a process, lies outside of the core pathological process(es) in the disorder/condition? (In many ways, these questions alert one to the correlation vs. causation distinction.) The endophenotype concept makes clear assumptions regarding its nature in the causal sequence involved in the pathogenesis of a given disorder. The definition of the endophenotype offered by Gottesman and Gould (2003) clearly places the construct within the gene–behavior

pathway. The endophenotype that is measured is therefore reflective of a developmental process that predates the onset of the disorder and is implicated in the cause of the condition or disorder. The endophenotype is not merely a risk indicator or

achieve the precision one finds in the more mature sciences, such as chemistry or physics (see Meehl, 1978).

The occasional need for specialized terminology in science

Related to the issue of clarity in language are concerns about creative use of language and in some instances the need to develop new concepts to capture the essence of a particular scientific concept. The latter is not unusual in science. This is an issue in the current context, because some may think that endophenotype is an unusual term that is crafted for a special purpose. That impression would be broadly correct because such a term was needed 40 years ago. There are instances in science when concepts are defined by a unique moniker, and this is done to convey a particular meaning that will be perceived immediately. In physics, special terminology emerged when thatsidegy

and/or processes should be either summarized or conducted so as to allow a separation of candidate biomarkers from endophenotypes, keeping in mind that endophenotypes are heritable yet many biomarkers are not necessarily so. Second, additional empirical study should be undertaken to demonstrate that putative endophenotypes do actually lie within the gene–behavior pathway in the causation of psychopathology. Such study would help to separate genuine endophenotypes from those indexes or processes that are merely statistically associated with illness occurrence (i.e., they are associated with elevated risk), but they are not genuinely in the causal pathway.

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