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A relational view of causality in normal and abnormal development

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Abstract
An understanding of developmental phenomena demands a relational or coactive concept of causality, as opposed to a conceptualization that assumes that singular causes can act in isolation. In this article we present a developmental psychobiological systems view of relational (bidirectional, coactional) causality, in which it is proposed that developmental outcomes are a consequence of at least two specific components of coaction from the same or different levels of a developmental system. The levels are genetic, neural, behavioral, and environmental; the latter level includes the cultural, social, and physical aspects of an organism's environment. We show the applicability of this view to the understanding of the development of normal and abnormal behavioral and psychological phenotypes through illustrations from the existing animal and human literature. Finally, we discuss future possibilities and potential stumbling blocks in the implementation of a more fully realized bidirectional, coactional perspective in developmental psychopathological research.

The widespread use of analysis of variance as a statistical technique in psychological studies has led to an "analysis of variance mentality" in which it is believed that variables contributing to outcomes make independent contributions to such outcomes. This is especially clear in the practice of quantitative behavior genetics, which is based on the erroneous assumption that genes and environments make identifiably separate contributions to the phenotypic outcomes of development. Such a view is erroneous because animal experiments have shown repeatedly that it is not possible to identify the genetic and environmental components of any phenotype, whether psychological, behavioral, anatomical, or physiological (see the extensive review in Wahlsten & Gottlieb, 1997). This is not the same as saying one cannot pinpoint the participation of specific genes and specific environments in contributing to phenotypic outcomes. However, because genes and environments always collaborate in the production of any phenotype in a continuous interplay of bidirectional influences over time, it is not possible to say that a certain component (or a certain fraction) of the phenotype was caused exclusively by genes (independent of environmental considerations) and some other component (or fraction) was caused exclusively by environment (independent of a genetic contribution). An understanding of developmental phenomena demands a relational or coactive concept of causality as opposed to singular causes acting in supposed isolation (discussed at length in Gottlieb, 1991, 1997). Overton (1998) has presented a historical overview on the topic of dualistic conceptions of causality versus the more recent relational or coactive concept of causality. Overton (1998, pp. 114–115) refers to the former as the "split model" of developmental change:

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split positions assert the priority of individual elements over the relational whole. Consequently, split positions assign either/or explanatory values to the segregated individual elements. Traditionally, the elements are treated as "causes" and the two broad classes of elements used to explain change are "biological" causes or factors and "social-cultural" causes or factors. Thus, it is assumed within a split position that all change can be totally explained by one or the other, or by some additive combination of these two elementary foundational factors. (Anastasi, 1958; Schneirla, 1956, 1957)

Further, with respect to the erroneous separation of hereditary and environmental contributions to the phenotype by quantitative behavior geneticists, Wahlsten (1990) showed that the presumed absence of heredity–environment interaction is a statistical artifact stemming from the insufficient power of the analysis of variance to detect such interactions, not an empirical absence of gene–environment interactions. Also, the use of insensitive population-level measures to model individual development confounds population and individual conceptual levels of analysis (Robert, 2000). These same criticisms and shortcomings of the analysis of variance mentality apply equally to other issues in the study of human development beyond gene–environment interaction.

The purposes of the present article are (a) to present a developmental psychobiological systems view of relational (coactional) causality and (b) to show the applicability of this view to the understanding of the development of normal and abnormal behavioral and psychological phenotypes. Gradual appreciation of the utility of developmental systems thinking in biology as well as in psychology is documented in a recent book, *Cycles of Contingency,* edited by Oyama, Gray, and Griffiths (2001). In other contexts, minority voices are speaking out in the fields of psychiatry (Eisenberg, 1998; Munir & Beardslee, 1999; Robert, 2000), school psychology (Carlton & Winsler, 1999), mental retardation (Blair, 1999), and infant behavior and psychological development (Anderson, Hubbard, Campos, Barbu–Roth, Witherington, & Hertenstein, 2000), and even among behavior analysts (Watson, 1999), where the relevance of developmental–psychobiological or probabilistic–epigenetic thinking has only rarely been appreciated. The present approach takes the relational causal thinking of Sroufe (1989) and others at the social level and extends it to include the biological level (as do Reis, Collins, & Berscheid, 2000, pp. 852–853). The present approach is also compatible with the multilevel (social, biological) integrative analyses championed by Cacioppo, Berntson, Sheridan, and McClintock (2000), explicitly adding a bidirectional component to emphasize the reciprocity of influences across the social and biological levels of analysis.

Developmental Psychobiological Systems Metatheory: Probabilistic Epigenesis

As recounted in previous publications (Gottlieb, 1992, 1997), this conceptual scheme builds on the writings of Z.-Y. Kuo, T. C. Schneirla, and D. S. Lehrman. What were originally elegantly crafted critiques of nativistic thinking in psychology and ethology by those intellectual forebears eventually matured into a metatheoretical system characterized as the probabilistic epigenesis of development (Gottlieb, 1970). This system continues to be refined up to the present day with respect to human development under the rubric of developmental science (Cairns, Costello, & Elder, 1996; Tudge, Valsiner, & Shanahan, 1997). Developmental science itself grew out of developmental approaches and theories of human development that are called *ecological* (Bronfenbrenner, 1979), *transactional* (Dewey & Bentley, 1949; Sameroff, 1983), *contextual* (Lerner & Kaufman, 1985), *interactive* (Johnston, 1987; Magnusson, 1988), and *sociogenic* (Montagu, 1977; Valsiner, 1998). The metatheoretical developmental systems view that is consonant with these points of view and deepens their connection to biology is depicted in Figure 1. This bidirectional view was strengthened and encouraged by systems thinkers in biology (Bertalanffy, 1933/1962; Weiss, 1939/1969; Wright, 1968). The call for such a multilevel, systemic approach was recently sounded from within developmental psychopathology itself (Cicchetti & Cannon, 1999) and was advocated earlier for the training of clinical psychologists (Cicchetti & Toth, 1991). It is

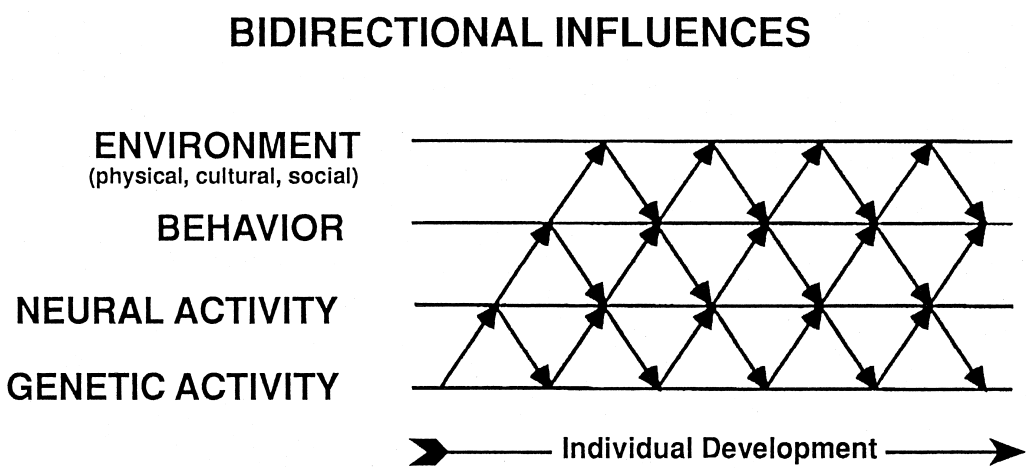

Figure 1. A systems view of psychobiological development. Reprinted from Gottlieb (1992) with permission. Copyright 1992 by Oxford University Press.

hoped that this article and this Special Issue of the journal will take us a step further toward that goal. (In this connection, also see the book edited by Hay and Angold, 1993, and the chapters by Sameroff, 1995, and Öhman and Magnusson, 1987.)

The core idea of probabilistic epigenesis is the bidirectionality of traffic among and within the levels shown in Figure 1. We would like to acknowledge concepts closely akin to probabilistic epigenesis, as they have been used in theories of human development, such as *bounded* or *deterministic indeterminacy* (Valsiner, 1998), *constructive epigenesis* (Bidell & Fischer, 1997), *nonobvious* or *nonlinear causality* (exemplified to some extent by Wachs' discussion of causal chains, 1999, pp. 236–240, and more explicitly in Lickliter, 2000 and Miller, 1997), and *equifinality* and *multifinality* (Cicchetti, 1990, p. 18; Cicchetti & Rogosch, 1996; Richters, 1997).[1] Because these issues involve the relational view of causality espoused here, more needs to be said about the coaction and nonlinearity of causes.

As originally put forward (Gottlieb, 1991), behavioral (or organic or neural) outcomes of development are a consequence of at least two specific components of coaction (e.g., person–person, organism–organism, organism–environment, cell–cell, gene–gene, nucleus–cytoplasm, sensory stimulation–sensory system, activity–motor behavior). The key concept to understand is that the cause of development (what makes development happen) is the relationship between the two components, not the components themselves. Genes in themselves cannot cause development any more than environmental stimulation in itself can cause development. When we speak of coaction as being at the heart of developmental analysis or causality, what we mean is that we need to specify some relationship between at least two components of the developmental system. The concept used most frequently to designate coactions at the organismic level of functioning is experience. Experience is thus a relational term. As documented previously (Gottlieb, 1976, 1997), experience can play at least four different roles in anatomical, physiological, psychological, and behavioral development. It can be necessary to sustain already achieved states of affairs (*maintenance* function); it can temporally regulate when a feature appears during development (or change thresholds; *facilitative* function); it can be necessary to bring about a state of affairs that would not happen unless the experience occurred (*inductive* function); and, as a subtype of induction, it can canalize development in one direction

1. The concept of equifinality comes from Driesch's (1908/1929) embryological studies and, to our knowledge, was first introduced into the psychological literature by Brunswik (1952).

rather than another (Gottlieb, 1991, 1997). Because developing systems are by definition always changing in some way, statements of developmental causality must also include a temporal dimension (*X* axis in Figure 1) describing when the experience or organic coactions occurred.

Because of the emergent nature of epigenetic development, causality is often not transparent or straightforward. In developmental systems, the coaction of *X* and *Y* often produces *W*, rather than more of *X* or *Y*, or some variant of *X* or *Y*. Another, perhaps clearer, way to express the same idea is to say that developmental causality is often not obvious. Prenatal causality is often nonobvious because the information, outside of experimental laboratory contexts, is usually not available to us. For example, the rate of adult sexual development is retarded in female gerbils that were adjacent to a male fetus during gestation (Clark & Galef, 1988). To further compound the nonobvious, the daughters of late-maturing females are themselves retarded in that respect—a transgenerational effect!

In a very different example of nonobvious and nonlinear causality, Cierpial and McCarty (1987) found that the so-called spontaneously hypertensive rat (SHR) strain used as an animal model of human hypertension is made hypertensive by coacting with their mother after birth. When SHR rat pups are suckled and reared by normal rat mothers after birth, they do not develop hypertension. It appears there is a hyperactive component in SHR mothers' maternal behavior that induces SHR pups to develop hypertension (Myers, Brunelli, Shair, Squire, & Hofer, 1989; Myers, Brunelli, Squire, Shindeldecker, & Hofer, 1989). The highly specific coactional nature of the development of hypertension in SHR rats is shown by the fact that normotensive rats do not develop hypertension when they are suckled and reared by SHR mothers. Thus, although SHR rat pups differ in some way from normal rat pups, their development of hypertension nonetheless requires coaction with their mother; it is not an inevitable outcome of the fact that they are genetically, anatomically, or physiologically different from normal rat pups. This is a good example of the relational aspect of the definition of experience and developmental causality offered earlier. The cause of the hypertension in the SHR rat strain is not *in* the SHR rat pups or *in* the SHR mothers but in the nursing relationship between the SHR rat pups and their mothers.

We now turn to the second purpose of the present article and show the applicability of a probabilistic epigenetic view by documenting the bidirectional, multilevel, coactional aspects of causality in the development of normal and abnormal behavior. With respect to the latter, it has long been appreciated that developmental psychopathology must be grounded in an understanding of normal development (Cicchetti, 1984; Sroufe, 1990).

Discriminating Relational Causality

As indicated in Figure 1, there are four levels of developmental analysis (genetic activity, neural activity, behavior, and the cultural, social, and physical aspects of the organism's environment). However, implementing a relational view of causality in theory and empirical research is not as straightforward as simply including several levels of analysis. The critical component is the specification of coactional processes and the identification of agents of coaction. For example, to think of aggression (or any other behavioral outcome) as being caused by genes is, of course, a split view. Less obvious split views include thinking of obsessive–compulsive disorder as a consequence of dysfunction of the corticobasal ganglia–neural circuit, or decreased serotonergic activity as causing depression, or excessive buildup of phenylalanine in the nervous system as the cause of mental retardation (phenylketonuria, PKU). Consideration of biological factors is an essential first step in order to begin a developmental analysis. However, a developmental analysis cannot stop there and will necessarily involve multiple features across multiple levels of the phenomenon. In this regard, the PKU example is particularly instructive. The developmental explanation of PKU involves both the genetic and environmental levels of analysis, as well as the neural level. PKU infants lack the

genes (or genetic expression) that normally produce an enzyme critical to metabolism, specifically, converting phenylalanine to tyrosine. The buildup of the former is toxic to the developing nervous system. The physical aspect of the environment is also involved in this disorder. Milk and other foods high in phenylalanine are necessary contributors to PKU through the diet of the infant. When the problem is detected in the neonatal period and the diet is suitably altered for a prolonged period into childhood or beyond, the prospect of mental retardation is avoided. Early on, McClintock (1979) recognized the developmental–theoretical significance of PKU in an article titled, "Innate behavior is not innate." Milder cognitive and other psychological deficits result from more subtle nutritional problems, particularly in children with existing micronutrient deficits such as iron-deficiency anemia (Wachs, 2000).

Another demonstration of relational causality in a different context supports the notion that aggression is not "caused by genes." In a study utilizing two lines of mice selectively bred for high and low aggression, Hood and Cairns (1989) examined the significance of the social rearing environment in contributing to the aggressive phenotype. The usual rearing environment of the mice involved social isolation from the termination of weaning (at 3 weeks of age) until they were first tested at around 6 weeks of age. As shown in Figure 2, when the mice are reared as usual in social isolation, there is a large difference in attack frequency between the two lines. However, when the mice are reared in social groups, the line difference disappears, implicating the influence of the social environment in the development of aggression, even in mice selectively bred for this attribute. In fact, in order to get the line difference in aggression, the selective breeding regimen necessarily includes a rigidly controlled rearing environment from generation to generation. Thus, the mice are being selected not only for their presumed differences in genetic makeup but also for their developmental response to the rearing environment, which is an example of relational causality.

As indicated in Figure 1, genetic activity is involved in all neural and behavioral outcomes, not just in some outcomes. We expect differences in gene activity in the nervous system over time, as a consequence of differences in social rearing experiences, as well as more or less concurrent differences in gene activity, depending on the immediate social–environmental context. Regarding the latter, for example, in male songbirds a certain kind of gene expression (*ZENK*) differs in subdivisions of the corticobasal ganglia, depending on whether they are singing to females, singing in the presence of other males, or simply alone (Jarvis, Scharff, Grossman, Ramos, & Nottebohm, 1998). The Hood–Cairns study demonstrates longer term differences based on social rearing, but the presumptive difference in genetic activity in the high- and low-aggressive lines has not yet been documented. However, in studies with peer-reared rhesus monkeys (reared without mothers), it has been possible to correlate actual structural genetic differences in a "serotonin gene" with neural differences. However, when rhesus monkeys are reared normally (reared by the mother instead of peers), the structural genetic correlations with neural function go out the window. In short, a specific polymorphism in the serotonin transporter gene is associated with different central nervous system (CNS) outcomes in rhesus monkeys as a consequence of their early social rearing histories. These unanticipated differences, discussed in more detail below, demonstrate the utility of including various levels of analysis in any study of development.

Serotonin acts as an inhibitory neurotransmitter in the CNS. Low levels of serotonin are associated with depression and alcohol abuse in humans. Correlates of low serotonin are not behaviorally specific. In rhesus monkeys, low concentrations of serotonin metabolites (collected from cerebral spinal fluid) are associated with higher levels of impulsive aggression and risk taking (e.g., taking long leaps; Suomi, 2000). Rhesus infants who develop the least secure attachment with their mothers are also the most likely to have deficits in their central serotonin metabolism. Because there is a positive correlation between maternal and infant serotonin level, a genetic deficit

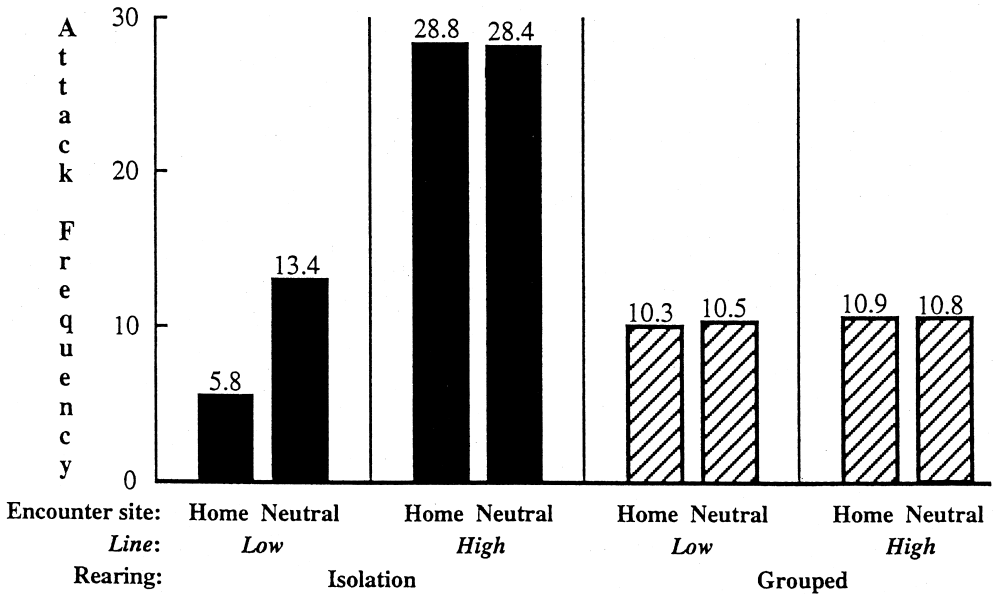

Figure 2. Failure to maintain selectively bred line difference in aggression when rearing environment changed from social isolation (usual rearing environment) to social grouping. Data reprinted from Hood and Cairns (1989) with permission. Copyright 1989 by Wiley. Figure reprinted from Gottlieb, Wahlsten, and Lickliter (1998) with permission. Copyright 1998 by Wiley.

could be involved, but it is possible that aberrant maternal care may also contribute to the serotonin deficit. To shed light on the genetic aspect, Bennett, Lesch, Heils, Long, Lorenz, Shoaf, Champoux, Suomi, Linnoila, and Higley (2002) genotyped the monkeys in Suomi's laboratory for a known polymorphism (long and short allele) in the serotonin transporter gene (5-HTT). The short allele confers low transcriptional efficiency to the 5-HTT gene promoter (relative to the long allele), so low 5-HTT expression may result in lower serotonergic function. However, evidence for this in humans is inconsistent, so the following difference in results with mother- and peer-reared monkeys may be pertinent to this inconsistency: when attempting to correlate the genetic polymorphism to serotonin metabolism in the rhesus monkeys, serotonin concentrations did not differ as a function of long or short 5-HTT status for the mother-reared monkeys, whereas, among the peer-reared monkeys, individuals with the short allele had significantly lower serotonin concentrations than those with the long allele (Bennett et al., 2002). Thus, the lowered serotonin metabolism was not simply a consequence of having the short allele but required a coaction with peer rearing in this instance. (Recall that, via internal mediators, social experience can penetrate to the level of gene activity, Gottlieb, 1998). Thus, the inconsistencies in the human literature are likely due to unknown but influential differences in the experiential histories of the populations under study.

Thus, the notion that the short allele of the 5-HTT gene is inevitably associated with a CNS deficit or defect is not true: the neural outcome depends on the developmental rearing history of the animal, as well as the particular genotype of the animal itself. This most likely also explains why there are inconsistencies in the human literature in finding anxiety-, depression-, and aggression-related personality traits associated with variations in the serotonin transporter gene. The association, or lack thereof, does not simply reflect genetic causality but developmental–relational causality (inconsistencies are reviewed in Bennett et al., 2002).

Implementing Relational Causality in Developmental Psychopathology

There are at least two big stumbling blocks to implementing a relational–causal perspective in human psychopathology. The first of these is that very often the pathological condition does not manifest itself until adulthood and therefore implicating social and other developmental factors can at best be done retrospectively. The other stumbling block is the widely held belief that debilitating psychopathological conditions are strictly a consequence of a "disordered brain." Although the model of mental disorders as "brain diseases" may help to reduce stigma and the tendency to blame individuals and/or families for disordered functioning (Hinshaw & Cicchetti, 2000), such a model represents a kind of neurogenetic determinism (Rose, 1995). The problem here, as indicated in Figure 1, is that social development, behavior, and physical aspects of the environment can contribute to the "disordering" of the brain through prior experiential influences that act directly on brain development and can also have disruptive influences on gene activity (Gottlieb, 1998). Because we, as a society and as a profession, are not willing to throw up our hands and give up the ghost in the face of these grave stumbling blocks, how is it that we might best proceed within the probabilistic–epigenetic framework?

Fortunately, at no time in the history of psychology and sociology have there been so many long-term longitudinal studies underway than at the present time. Another favorable feature is that, with the advent of a "developmental science" outlook, many developmental psychologists and life-span sociologists look with favor on those colleagues who can bring relevant biological expertise into the picture, both at the human level and in terms of animal models (e.g., Shanahan, Sulloway, & Hofer, 2000). As the value of a multidisciplinary study of the same or similar behavioral phenomena becomes evident, one would expect this cross-disciplinary cooperation to increase and become even more common for the benefit of our science, as well as humanity. We would like now to sketch, in broad terms, actual and potential fruitful collaborations that are in the spirit of relational (coactional) approaches to causality. It is clear from our perspective that the most promising approach to psychopathology must be both developmental (longitudinal) and cross-disciplinary, a message that will not be entirely novel to the readers of this journal. What may be somewhat novel in the message is that the relational traffic across the various levels of analysis (genetic, neural, behavioral, environmental) is bidirectional, an aspect of development that is more difficult to demonstrate or appreciate in human affairs than in animal models.

We already noted examples of coactional developmental processes related to hypertension, aggression, and serotonin concentrations in animals. To further illustrate existing research and future possibilities, we consider some of the ways in which pre- and postnatal stressors, in conjunction with factors at the same or different levels of the developmental system, yield variations in the patterns of stress response, as well as other developmental outcomes. We then turn to recent reviews of the neurobiology of mental disorders, schizophrenia in particular, as a starting place for conceptual models that represent a more fully realized coactional perspective.

Illustrative existing research: Responses to stress

A number of studies demonstrated associations between early life stress and later pathology, particularly mood and anxiety disorders. This link is thought to be based partly in differential hormonal response patterns to stress and novelty, response patterns that emerge in response to the environment and experience, and that, in turn, can alter the activity of multiple neurotransmitter systems. We described earlier how the outcome of a polymorphism in a serotonin transporter gene in rhesus monkeys can vary, depending on whether the monkeys experience mother or peer rearing. Recent work with mice underscores the inherently bidirectional nature of such processes and the fact that coactional development is not limited to early or "critical"

developmental periods. Cabib, Giardino, Calza, Zanni, Mele, and Puglisi–Allegra (1998) demonstrated in controlled experiments that chronic stress (operationalized as repeated restraint experiences) is associated with changes in brain dopamine receptor densities in mature mice but that the direction of development (i.e., increase or decrease in receptor density) varies according to the mouse strain (i.e., genotype). Because variation in dopamine receptor density and related differences in transmission have been implicated in certain pathologies (e.g., schizophrenia, see elaboration below), this finding is supportive of the idea that it is the coaction of stress, trauma, or other types of environmental insults with particular genetic constellations that ultimately results in different pathological profiles via neural structural changes and other intermediary mechanisms. This finding also underscores the point that neither particular genotypes nor particular environmental stressors are inevitably linked with particular pathological outcomes. This latter point about the probabilistic nature of development was also clearly demonstrated in a study by Crabbe, Wahlsten, and Dudek (1999), in which "rigorously equated" laboratory environments nevertheless were associated with different behaviors in knockout mice that theoretically lacked a specific "gene product." It is the particular combinations of environmental and genetic factors, and probably the timing of their coaction, that promote specific pathological outcomes.

In a subsequent publication, Cabib, Orsini, Le Moal, and Piazza (2000) examined genetically bred strain differences in rats in response to amphetamine as a model of genetic susceptibility to addiction. They demonstrated that the response to amphetamine could be dramatically altered (i.e., aversion changed to preference) in mature rats through the experience of an ecologically meaningful event (food shortage), a change that is apparently mediated by glucocorticoid secretion and dopamine release. In discussing the inevitability of the coaction of genetic differences and environmental stressors, these researchers explicitly note that "the attempt to identify 'genetic' or 'environmental' causality as independent main effects is probably logically and procedurally flawed" (Cabib et al., 2000, pp. 464–465). The work of these and other researchers using animal models represents important first steps in coactional developmental analyses. However, their description and understanding of the genetic role are limited. A particular gene, or set of genes, has not been identified in the relationship. Instead, the use of inbred strains of animals has served as a proxy for assumed differences in gene structure, expression, and/or interaction.

As the relatively crude description above suggests, relational developmental processes can be subtle and difficult to specify. It is possible to find many examples of bidirectional associations that cross levels of the developmental system. However, identifying the existence of multilevel linkages is not the same as specifying the relational function that underlies them. For example, postnatal "handling" of rat pups (brief separations from their mother in the preweaning period) changes hypothalamic–pituitary–adrenal (HPA) responses to stressful stimuli (Ader & Grota, 1969; Meaney, Aitken, Sharma, Viau, & Sarrieau, 1989; Plotsky & Meaney, 1993). Handled rats show smaller increases in plasma adrenocorticotrophin (ACTH) and corticosterone levels during stress and a quicker return to basal hormone levels after termination of the stress. However, more extended periods of maternal separation are associated with completely opposite effects on HPA response to stress. These opposing patterns illustrate how experience may alter physiological and hormonal response; they also underscore the point that experiences may have similar elements and yet, in coaction with other factors, lead to very different physical and behavioral outcomes. However, in this example it is unclear what comprises the other "piece" of the coaction. Handling is thought to increase the number of glucocorticoid receptor sites, thereby enhancing the sensitivity of the feedback system. This enhanced sensitivity may consequently inhibit HPA activity. However, the initial step of this developmental cascade, that is, what coacts with handling to change the number of receptor sites, was not specified until more recently.

Gene(s) expression was a likely candidate, and greater genetic specificity has clarified the coactional process and allowed for a more fully bidirectional analysis (Meaney, DiOrio, Francis, Widdowson, LaPlante, Caldji, Sharma, Secki, & Plotsky, 1996).

The role of early stressors in sensitizing physiological systems was also demonstrated in humans. Heim, Newport, Heit, Graham, Wilcox, Bonsall, Miller, and Nemeroff (2000) studied the ACTH, cortisol, and heart rate responses to a standardized psychosocial laboratory stressor in women who had and had not experienced childhood physical and/or sexual abuse and who varied on diagnosis of current depression. The CNS corticotropin releasing factor (CRF) systems that are implicated in the physiology of depression and anxiety may also mediate the observed association between early life stress and adult mood disorders. Thus, Heim et al. (2000) tested whether there appeared to be sensitization or hyperactivity of CNS CRF systems in adult women who had experienced early life stress in the form of abuse. Although all women responded to the standardized stress protocol, women with a history of abuse, with and without current major depression, had significantly higher increases in ACTH concentrations. Abused women with current depression also had significantly higher levels of cortisol in response to the stressor. As the authors point out, the patterns of ACTH response in abused women look remarkably similar to the corticosterone responses of rats who were in the extended maternal separation group in the Plotsky and Meaney (1993) study. Like the animal models, this study demonstrates how experience (i.e., coaction) can result in pathological outcomes across levels of a developmental system. However, the specifics of the relational equation are yet to be detailed. Parallel effects for prenatal stressors have also been reported for humans and indicate the relevance of exposure to a teratogen during particular periods of gestation. For example, Selten, van Duursen, Van der Graaf, Gispen, and Kahn (1997) found that exposure to maternal stress (flood) when in utero was associated with later elevated risk for psychosis in the offspring, presumably partly as a function of maternal glucocorticoids crossing the placenta. Steroids are known to be involved in differentiation processes of the nervous system. Watson, Mednick, Huttunen, and Wang (1999) found parallel results linking prenatal exposure to maternal stress (earthquake) with adult depression in offspring; the underlying mechanism likely involves alterations in the HPA axis. These findings are consistent with earlier work suggesting linkages between maltreatment, depression, and dysregulation of the diurnal pattern of cortisol secretion among children (Hart, Gunnar, & Cicchetti, 1996; Kaufman, 1991).

Schizophrenia: Components of a coactional developmental model

It has been argued that a developmental perspective is inherent in psychiatry and psychopathology (Eisenberg, 1995; Munir & Beardslee, 1999). Epidemiological analyses have also supported a relational model (e.g., a combination of genetic factors and teratogens) for illnesses like schizophrenia (Cannon, Mednick, Parnas, Schulsinger, Praestholm, & Vestergaards, 1993). Unfortunately, however, research framed by a developmental systems orientation is generally lacking in the psychological, neurobiological, and epidemiological literatures (cf. Costello & Angold, 1996). In an introduction to a recent set of reviews of the neurobiology of mental disorders, Hyman (2000) sets the stage for useful first steps toward building "systems neuroscience" by reminding us that vulnerability to mental disorders is "genetically complex," involving multiple genes in epistatic interaction, and that genes must interact with nongenetic factors (e.g., physical or experiential aspects of the environment) in order to culminate in illness. In the same issue of *Neuron* (November 2000), Lewis and Lieberman (2000) propose a model of the pathogenesis of schizophrenia that provides suggestive possibilities regarding coactional processes that could be explored in a multidisciplinary program of research. Similarly, in an earlier lead article for a Special Issue of *Development and Psychopathology* that focused on neurodevelopment, Cicchetti and Cannon (1999) called for in-

creased multidisciplinary work that would integrate neural, psychological, and social processes in order to better understand the development of mental disorders. In a companion article, Keshavan and Hogarty (1999) attempted to synthesize physical maturation processes of the brain with psychosocial factors to form a better integrated model of the timing of the onset of schizophrenia in late adolescence and early adulthood. Using these recent proposals as guides, we review and further speculate on some of the possibilities raised.

First, as noted by Hyman (2000), it is clear from both a philosophical and empirical perspective that genetic factors contribute to schizophrenia and that multiple, interacting loci are likely involved.[2] Findings based on genome scans or tests of candidate gene hypotheses suggest linkages with regions on more than half of the 23 human chromosomes; however, many of these have not been replicated and/or have not met more stringent linkage criteria (Pulver, 2000). Regions on chromosomes 13, 8, 22, and 6 currently look promising.[3] Genetic contributions could take multiple forms, such as associations with neurochemical process (e.g., dopamine hyperactivity) and/or structural brain abnormalities; these characteristics, in combination with early neurodevelopmental insults (e.g., exposure to infectious or toxic agents or elevated levels of glucocorticoids, hypoxia) and the psychosocial stressors of adolescence and young adulthood, may result in problems of neural connectivity across brain regions, which is thought to be a key factor among the proximal causes of schizophrenia.

Myriad possibilities exist for pre- and perinatal events that may help forge the neurobiological foundations for schizophrenia during brain development; the timing of such events may be a critical determinant of possible developmental paths. For example, there are factors that, when present at midgestation, disturb neuronal migration and differentiation. The guidance and motility of migrating neurons "involves complex interaction between the migrating neuron and the radial glial cell" (Nowakowski & Hayes, 1999, p. 409). A second trimester maternal influenza infection has been found to be associated with later schizophrenia (Mednick, Machon, Huttunen, & Bonnet, 1988; Watson et al., 1999), and particularly with a pattern of paranoid symptoms. Although evidence to date is circumstantial, influenza infection may disrupt and change the interactional neuron migration process, resulting in abnormality in cell position. Such positional abnormalities in the human cerebral cortex have been associated with some forms of schizophrenia (Nowakowski & Hayes, 1999).

After migration, neurons differentiate and establish synaptic connections. During this process, imbalances in neurotransmitters, sometimes as a result of stress responses, may contribute to faulty connections. Cortisol release, controlled by the HPA axis, is one biological response to stress. It is relevant to the development of schizophrenia because its release can coact with other factors to change neurotransmitter systems (e.g., by augmenting dopamine activity; Walker & Diforio, 1997). Prenatal events that were already mentioned, such as maternal viral infection, can "compromise the HPA system and potentiate the expression of abnormalities in dopamine neurotransmission" (Walker, Lewis, Loewy, & Palyo, 1999, p. 512). These system compromises can persist into adolescence and adulthood. With the increased activity of the HPA system during adolescence, hormonal change, in combination with increasing psychosocial stressors, may potentiate symptom onset.

In the frontal cortex, synaptic density peaks during childhood, declines during adolescence, and then stabilizes in adulthood. The prefrontal cortex, which is critical to executive functions, is the last region of the brain to completely mature, with maturation contin-

2. However, for a compelling argument that genes are a relevant, but not foundational, factor in the "construction" of schizophrenia, see Robert (2000). Further attesting to the important participation of nongenetic influences in the development of schizophrenia is the low concordance rate in monozygotic twins (approximately 28%: Torrey, Bowler, Taylor, & Gottesman, 1994).

3. As in all other mental and physical disorders, a lack of gene activity, as well as the positive contribution of mutated genes, may be involved in the search for "candidate genes" in schizophrenia (Gottlieb, 1998, p. 798).

uing through adolescence. Schizophrenia may be related to pathological alterations in the pruning and myelination processes of the brain. It has been suggested that biological and psychosocial events during and after puberty play key roles in producing the alterations. For example, late pubertal timing (estrogens) may contribute to "a failure to shut down the synaptic pruning process associated with puberty" (Keshavan & Hogarty, 1999, p. 532), thereby contributing to the excessive pruning that may be one neurological predecessor of schizophrenia.

As with other correlates of pubertal timing, psychological processes are also involved. Wrestling with multiple facets of physical and psychological identity and the related steps of establishing emotionally intimate friendships and romantic relationships are key developmental tasks of adolescence and young adulthood, the periods during which schizophrenic symptoms are likely to begin (Keshavan & Hogarty, 1999; Masten & Coatsworth, 1998). However, little work has been done to examine how an individual's efforts to accommodate these changes and meet the challenges of these tasks, particularly in the context of previous neurodevelopmental insults or psychosocial challenges (e.g., insecure attachment), may function to enhance or diminish risk. Impairments in attention may be one cognitive deficit resulting from disarrayed cell positioning and nonoptimal neural connections. Although such impairments are often subtle, their significance may increase at adolescence when individuals are faced with negotiating complex social relationships. A reduced capacity to process social information in the context of an increasingly challenging set of social situations may result in social incompetence and isolation (Cornblatt, Obuchowski, Roberts, Pollack, & Erlenmeyer–Kimling, 1999), thus setting the stage for the appearance of schizotypal symptoms during adolescence and early adulthood.

Prospective research comparing multiple facets of the psychosocial experiences of at-risk individuals who do and do not eventually manifest schizophrenia as young adults is needed to understand the coactive processes that contribute to these developmental outcomes. It is likely that the characteristics of socialization, social interaction, and the competency of social cognition are key elements contributing to positive or negative developmental trajectories (Keshavan & Hogarty, 1999). For example, a study of adopted offspring of schizophrenic mothers parallels findings described earlier for hypertensive rats. Offspring of schizophrenic mothers raised in "disturbed" families experienced a relatively high incidence of mental disorders (e.g., psychoses), whereas offspring raised in "healthy" families showed a relatively low incidence (Tienari, 1991). The latter group actually fared better than adopted offspring of normal mothers who were raised in "conflicted" family settings, suggesting important coactions between components of socialization and genetic processes.

Some individuals may be more affected by environmental stressors that occur during adolescence, and the presence of obstetric complications (e.g., pre-eclampsia, premature ruptured membrane) or other earlier environmental insults may increase the likelihood that schizophrenic symptoms are expressed in response to adolescent stressors (Marcelis, van Os, Sham, Jones, Gilvarry, Cannon, McKenzie, & Murray, 1998). These may represent selectional, as well as coactional, processes. That is, some aspects of schizophrenic vulnerabilities may change the probability of exposure to particular contexts, with such exposure providing the opportunity for environmental coactions to occur.

Conclusions

Although more voices are being raised in support of psychobiological approaches to development and the use of developmental systems metatheory (e.g., Cacioppo et al., 2000; Robert, 2000), it is clear that coactional processes are complex and we often cannot specify even two of the multiple players in developmental relationships. To further develop such an approach to understanding normal and pathological development, our research must incorporate certain methodological factors more consistently. First, more longitudinal studies that compare low and high risk individuals

over time are needed. Given the lag times between contributing coactional relationships and ultimate clinical outcomes (such as in schizophrenia), long-term prospective follow-up may often be necessary. Second, given the multiple pathways that may lead to the same outcome and the multiple outcomes that may ultimately be produced from similar biological "starting points," it is helpful to construct large samples, where possible, in order to examine individual differences in relational processes (Cicchetti & Cannon, 1999). For example, although a survey design is not necessarily ideal for studying developmental issues, large-scale longitudinal surveys, such as the National Longitudinal Study of Adolescent Health (Bearman, Jones, & Udry, 1997), which collect biological, psychological, behavioral, spatial, and contextual data (i.e., span several levels of analysis), can offer fruitful opportunities for exploring normal and pathological outcomes over time and for examining hypotheses of relational causality. Such data sets allow for the opportunity to see differential social and contextual exposures over time that result from both chance and self-selection, in addition to "snapshots" of social interactions that may be contrived and observed in laboratory settings (Cacioppo et al., 2000). Social interactions, as illustrated in both animal and human research noted earlier, are central to developmental processes through the routes of repeated stressors and cognitive and affective processes. Technical advances in biological measures, as well as in procedures such as experience sampling and ambulatory recording, facilitate such research both within and outside of the laboratory setting.

A third methodological consideration is that a variety of indicators of deviance may aggregate in individuals who will ultimately develop mental illness. At the same time, there may be consistent, cross-individual contributors to illness, even in the face of variable relational processes. Therefore, the use of both person-centered and variable-centered analyses are appropriate. Fourth, transdisciplinary research efforts, in which collaborating scientists trained in different disciplines share views about both the definition of research problems and the analytical methods that may be appropriately applied, given substantive theory and metatheory, will be necessary to explore and specify coactional processes that cross levels of the developmental system. For an early statement of the value and necessity of transdisciplinary centers in which a number of disciplines home in on the developmental study of particular topics (i.e., a National Research Center in Developmental Studies; see Kuo, 1970, p. 191). Within developmental psychopathology, similar recommendations for "collaborative, multidisciplinary multidomain studies on normal, 'high risk,' and psychopathological populations" have been voiced by Cicchetti (1990, p. 20; see also Cicchetti & Lynch, 1995) and, more specifically in terms of clinical training, by Cicchetti and Toth (1991). Research that is driven by assumptions of independent or simple additive contributions to developmental outcomes or that focuses on a single level is inherently blind to coactional processes crossing levels of the developmental system (Cacioppo et al., 2000). Unfortunately, present institutional structures of universities and departmental expectations about scientific achievement and recognition within a single discipline ultimately work against transdisciplinary research that integrates multilevel analyses, especially for younger scientists who are seeking promotion and tenure within unidisciplinary departments. Hopefully, increasing recognition of the value of interdisciplinary collaboration will mitigate such structural and historical constraints on the advancement of developmental science.

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