Preface

Bipolar disorder (BD) is both a common and highly disabling condition. It affects as many as one in 25 adults and between 420,000 and 2,072,000 children in the United States alone (Post & Kowatch, 2006). BD takes an enormous toll on an individual's quality of life and causes considerable stress and hardship for the family. People with the disorder spend as much as half of their lives in states of illness, mostly in states of depression rather than mania (Judd et al., 2002). As many as one in every six persons with BD dies by suicide, and almost half attempt suicide one or more times (Harris & Barraclough, 1997; Jamison, 2000). By 2020, the World Health Organization estimates that BD will be the sixth leading cause of disability among all medical disorders (Murray & Lopez, 1996).

In the 1970s and 1980s, with the advent of lithium, antidepressants, and later the anticonvulsant medications, many in the psychiatric community believed that the problem of BD had been solved. Advances in behavioral genetics offered incontrovertible evidence that the disorder was heritable, even if the phenotype varied from person to person or from generation to generation (Smoller & Finn, 2003). Early findings with positron emission tomography, structural neuroimaging, and neuropsychology studies suggested changes in the brain, particularly in frontal lobe functioning (e.g., Powell & Miklowitz, 1994). Thus, the disorder was seen as genetic and biological in origin, and its developmental origins commanded little attention. Moreover, psychotherapy was relegated to a supporting role relative to drug treatment and was seen primarily as a means to keep people on their medications. Nonetheless, patients continued to have frequent recurrences, residual symptoms between episodes, and decrements in functioning and quality of life (Gitlin, Swendsen, Heller, & Hammen, 1995).

Fortunately, there has been a shift in our thinking about BD in the past two decades. First, many more patients report a childhood onset than we originally thought: Recent studies have found that between 15 and 28% of adults with BD reported that the onset occurred before the age of 13, and between 50 and 66% reported onset before the age of 19 (Leverich et al., 2002; Perlis et al., 2004). Sec-

ond, an early onset has been found to be associated with a host of negative outcomes in adulthood, including lengthy episodes, multiple "polarity switches," a continuously cycling course, and a preponderance of mixed episodes, psychosis, and suicidal behaviors (Birmaher et al., 2006; Brent, Baugher, Bridge, Chen, & Chiapetta, 1999; Geller et al., 2002). Third, although at times seeming to appear overnight, BD has a lengthy prodrome, with behavioral and emotional dysregulation observable even in toddlerhood (Correll et al., 2007; Luby, Tandon, & Belden, 2009; Post & Kowatch, 2006; Radke-Yarrow, Nottelmann, Martinez, Fox, & Belmont, 1992). These findings have helped refocus our attention on BD as a neurodevelopmental disorder, much like schizophrenia.

The purpose of this book is to bring together what is known about the development of BD from the genetic, neurobiological, cognitive, and psychosocial perspectives. We have asked each of the authors, all of whom are highly regarded experts in the field, to consider BD from a *developmental psychopathology* perspective (Cicchetti & Rogosch, 2002; Cicchetti & Toth, 1998). What do we know about how BD symptoms emerge at different developmental stages? How do mood symptoms unfold in the context of dynamic interactions between risk or protective factors in the genetic, biological, psychological, familial, or sociocultural contexts? How do we explain the variability in outcomes among children who initially look very similar (multifinality)? In contrast, how do we explain why children with many different initial presentations can all develop into adults with the same disorder (equifinality)? Finally, how do we modify our pharmacological and psychosocial treatments to address the unique needs of persons with the disorder at different stages of development?

We begin the book with an overview of the developmental psychopathology framework and its application to BD (Cicchetti). This chapter explains the terminology and key assumptions used throughout the book. Cicchetti discusses the nature of person × environment interactions; the complex interplay among genetic, biological, psychological, and social factors as they unfold across development; and the multifactorial nature of BD.

The book is divided into five sections. Part I (Chapters 2–4) is devoted to the phenomenology and diagnosis of BD in children. Considerable disagreement exists on how to define the boundaries between pediatric BD and other childhood-onset disorders or even its boundaries with normal development. Meyer and Carlson offer an historical overview of the BD concept in children, urging the field to take a critical eye toward the premises of DSM-IV (American Psychiatric Association, 1994) in making diagnostic differential decisions. They review the developmental discontinuities between childhood and adult BD; the role of age at onset and puberty; and the distinctions among childhood, adolescent, and adult mania. Youngstrom, in applying key concepts of developmental psychopathology, encourages a highly scientific approach to determining what is and is not BD. One comes away impressed with the ease by which he moves back and forth from the scientific to the clinical-observational level. Both of these chapters will be of considerable value to clinicians and researchers who struggle with how to define BD in children.

Luby, Belden, and Tandon address the highly controversial issue of BD during the preschool years. Many readers will go into the chapter doubting the validity of bipolar diagnoses in very young children, but will be surprised at how their opinions change once acquainted with the considerable progress in this area.

Part II (Chapters 5–7) addresses the onset, prognosis, and course of BD in children, adolescents, and adults. Diler, Birmaher, and Miklowitz describe several longitudinal investigations of the course of BD in children and shed light on the continuities and discontinuities in symptom presentations across the lifespan. Their discussion of the Course and Outcome of Bipolar Youth study, the largest longitudinal study of bipolar spectrum disorders to date, answers many questions (and formulates many others) about the progression of the disease over time. Moving to late adolescence, Alloy, Abramson, Urosevic, Nusslock, and Jager-Hyman examine a cohort of college students who were deemed at risk for BD. Together with their later chapter in the etiology section (Alloy, Abramson, Walshaw, Keyser, and Gerstein), Alloy and colleagues present a cognitive vulnerability–stress formulation for understanding the onset and course of BD, as informed by their earlier work on unipolar depression. In many ways, their work provides the most direct test of a developmental psychopathology formulation, given their continuous measurement of cognitive predisposition, temperament, family history, and stress in students at risk for BD spectrum disorders.

Finally, Goldberg persuasively argues that the predictors of the course of BD in adulthood provide a window for understanding the development of the illness itself. His analysis of risk and protective factors includes personality structure; locus of control; resilience to stress; temperamental traits; and genetic, neurotrophic, and environmental considerations. Goldberg reminds us that symptoms comprise only one domain of outcome. Work functioning, social functioning, family relationships, and quality of life, while harder for us to measure, are often the most important outcome variables to patients.

Part III, on etiology (Chapters 8–12), discusses the many causes of BD from a multiple-levels-of-analysis perspective. In their methodologically rigorous chapter on genetic vulnerability, Willcutt and McQueen make clear what can and cannot be concluded from behavioral genetic and gene-mapping studies. The approach of parsing the effects of heritability, shared environments, and nonshared environments suggests directions for future research, notably the importance of identifying environmental variables with prognostic significance in genetically vulnerable samples. Fleck, Cerullo, Nandagopal, Adler, Patel, Strakowski, and DelBello review the rapidly growing area of neuroimaging (structural and functional neuroimaging, magnetic resonance spectroscopy, positron emission tomography, and diffusion tensor imaging). Although no diagnostically specific biological markers have yet been found, it is likely that these methods will increasingly be used to map the pathophysiology of BD and identify children at risk for the disorder.

Deficits in social cognition and response flexibility are discussed in a particularly erudite chapter by McClure-Tone, who explores how bipolar children and adults understand social relationships (e.g., why they view neutral faces as negative) and the neural correlates of these cognitive and interpersonal processes. Post

and Miklowitz address the interactive roles of life events, neuropathophysiology, family stress, and the onset of BD with reference to the "kindling" and stress-sensitization models. The role of childhood adversity (notably physical and sexual abuse) in the background of persons with BD is becoming increasingly apparent, with its downstream effects observable well after the onset of the disorder.

Part IV (Chapters 13–16) concerns the treatment of BD in youth and adults. As is true throughout the book, we asked the authors to approach treatment from a biopsychosocial perspective, whether the topic is psychopharmacology (Kowatch, Strawn, and DelBello; Thase), family-focused therapy or dialectical behavior therapy (Miklowitz and Goldstein), or multifamily or individual family psychoeducation (Mendenhall and Fristad). The evidence base for individual medications and psychosocial approaches is limited at this stage. Nonetheless, practice guidelines for the pharmacological and psychosocial management of early-onset BD are being articulated (Kowatch et al., 2005). It is likely that future guidelines will combine various forms of pharmacotherapy and psychotherapy at different phases of the illness or even during the prodrome. It is hoped that future investigations will use early intervention and prevention paradigms to elucidate the role of environmental/contextual and individual resilience variables in the onset of bipolar spectrum disorders.

We are fortunate to be able to conclude the book (Part V, Chapter 17) with a first-person account by Stephen Hinshaw, a clinical psychologist whose father suffered from BD. Growing up with the disorder, along with his own training in developmental psychopathology, gives Hinshaw a unique view of the development of the illness, its risk and protective factors, and its effects on family members. His recommendations on how to address the stigma of BD in our treatments are quite timely.

We hope that the reader will come away from the book with an appreciation of BD as an evolving, dynamic process. As we learn more about this disorder, the nature of the interactions among genetics, biology, cognition, and the psychosocial context becomes more complex than originally believed. We hope that this book will encourage new researchers and clinicians to take on the challenges of understanding and effectively treating this fascinating condition.

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CHAPTER 1

A Developmental Psychopathology Perspective on Bipolar Disorder

Dante Cicchetti

The thesis proposed in this chapter is that the principles and tenets inherent to a developmental psychopathology perspective can serve to elucidate the understanding of bipolar disorder (BD) across the life course. A developmental psychopathology approach espouses the conviction that comprehending the genesis (i.e., origins) and epigenesis (i.e., the development of new, different abilities across each stage of the life span) of adaptation and maladaptation in their full complexity necessitates that we possess an understanding of the organization and integration of diverse biological, psychological, and social systems at multiple levels of analysis within individuals across different contexts and varying developmental periods (Cicchetti, 2006, 2008).

Developmental psychopathology represents a movement toward comprehending the causes and determinants, course, sequelae, and treatment of mental disorders through its synthesis of knowledge from multiple disciplines (Cicchetti, 1990; Cicchetti & Posner, 2005; Masten, 2006, 2007). The undergirding developmental orientation impels researchers to pose new questions about the phenomena they study. For example, with regard to bipolar illness, it becomes necessary to move beyond identifying features that differentiate children, adolescents, and adults who have and who do not have BD (e.g., affect dysregulation, attributional distortions) to articulating how such differences have evolved developmentally within a multilevel and dynamic social ecology (Miklowitz & Cicchetti, 2006b). Likewise, rather than being concerned with merely describing the symptoms of BD in children, adolescents, and adults (as would be the focus of the DSM-IV), the emphasis shifts to ascertaining how similar and different biological and psychological organizations contribute to the expression of depressive, hypomanic, or

manic outcomes at each specific developmental level. Because psychopathology unfolds over time in a dynamically developing organism, the adoption of a developmental perspective is critical in order to comprehend the processes underlying individual pathways to adaptive and maladaptive outcomes in persons with BD.

Although abnormalities in the broad domains of genetics, neurobiology, cognition, emotion, and interpersonal relations are present to varying degrees among individuals with BD (Goodwin & Jamison, 2007; Miklowitz & Cicchetti, 2006a), these diverse areas do not exist in isolation. Rather, they are complexly interrelated and mutually interdependent (Cicchetti & Cannon, 1999; Cicchetti & Tucker, 1994; Gottlieb, 1991, 1992; Gottlieb & Halpern, 2002; Thelen & Smith, 1998). Consequently, it is essential for researchers to strive to comprehend the interrelations among the biological, psychological, and social systems in order to delineate the nature of BD, including the discovery of ways in which the organization and integration of these systems may promote resilient functioning (Charney, 2004; Curtis & Cicchetti, 2003). Relatedly, because there are myriad risk factors associated with BD and its comorbid forms of psychopathology (Goodwin & Jamison, 2007), it is critical for researchers and clinicians to acquire a firm grasp of the multilevel biological and psychological processes and mechanisms that contribute to the emergence, maintenance, and recurrence of BD. Because of the continuities and divergences from normal functioning that are manifested in BD, empirical research on pathways to BD as well as prospective longitudinal investigations of its developmental course and sequelae also hold promise for advancing understanding of the relation between normality and psychopathology.

In this chapter, I begin by explicating why a developmental psychopathology perspective can be usefully applied toward enhancing our understanding of BD. Next, I discuss the parameters of developmental psychopathology, including the core principles of the discipline. Throughout this presentation, I highlight aspects of a developmental psychopathology approach that are especially relevant to the investigation and treatment of BD. I conclude by suggesting future directions for studying BD within a developmental psychopathology framework; moreover, I address social policy implications that emanate from investigating BD through the lens of developmental psychopathology.

What Is Developmental Psychopathology?

The integrative nature of a developmental approach to psychopathology was articulated by Eisenberg (1977), who stated that development "constitutes the crucial link between genetic determinants and environmental variables and between physiogenic and psychogenic causes" (p. 225). Development thus encompasses "not only the roots of behavior in prior maturation as well as the residual of earlier stimulation, both internal and external, but also the modulations of that behavior by the social fields of the experienced present" (p. 225). Not surprisingly, given the intimate link between the study of normality and psychopathol-

ogy, similar depictions of normative developmental processes have been espoused in the literature.

Whereas the term *developmental psychopathology* has frequently been equated with the study of mental disorders among children and youth, this perspective encompasses a much broader approach to studying development, normal and abnormal, across the life span (Cicchetti, 1990, 1993). A developmental analysis is necessary for tracing the roots, etiology, and nature of maladaptation so that interventions may be sensitively timed and guided as well as developmentally appropriate (Toth & Cicchetti, 1999). Moreover, a developmental perspective will prove useful for uncovering the compensatory mechanisms, both biological and psychological, that may be used in the face of significant adversity (Curtis & Cicchetti, 2003).

Developmental psychopathology is an integrative scientific discipline that strives to unify, within a life span framework, contributions from multiple fields of inquiry with the goal of understanding the mutual interplay between psychopathology and normative adaptation (Cicchetti, 1990, 1993; Cicchetti & Toth, 1991). A developmental analysis presupposes change and novelty, highlights the critical role of timing in the organization of behavior, underscores multiple determinants, and cautions against expecting invariant relations between causes and outcomes. A developmental analysis is as applicable to the study of the gene or cell as it is to the investigation of the individual, family, or society (Cicchetti & Pogge-Hesse, 1982; Davies & Cicchetti, 2004; Miklowitz, 2004; Werner & Kaplan, 1963).

Developmental psychopathologists seek to engage in a comprehensive evaluation of biological, psychological, and social processes and to ascertain how the transaction among these multiple levels of analysis may influence individual differences, the continuity or discontinuity of adaptive or maladaptive behavioral patterns, and the pathways by which normal and pathological outcomes may be achieved (Cicchetti & Schneider-Rosen, 1986). In practice, this entails comprehension of and appreciation for the developmental transformations and reorganizations that occur over time; an analysis of the risk and protective factors and mechanisms operating within and outside the individual and his or her environment over the course of development; the investigation of how emergent functions, competencies, and developmental tasks modify the expression of a disorder or lead to new symptoms and difficulties; and the recognition that a particular stressor or set of stressful circumstances may eventuate in different biological and psychological difficulties, depending on when in the developmental period the stress occurs.

Developmental Analysis

There are two interrelated goals inherent to a developmental analysis. First, a developmental analysis strives to investigate the specific evolving biological and psychological systems that are characteristic of individuals at varying developmental stages across the life span. This requires formulating questions about a

phenomenon in terms of what capacities are characteristic of an individual during a particular developmental period and how a given process or mechanism becomes manifested in view of those developmental capacities and attainments of the individual. Age-appropriate limitations in children's cognitive, emotional, and social development may make the expression of specific manic and depressive symptoms beyond their capabilities. Thus, the delineation of those characteristics relevant to the overt manifestation of BD at different ages can probably only be accomplished by means of longitudinal prospective studies that measure skills and capacities in a variety of biological and psychological domains. Consequently, to comprehend BD fully, researchers must consider developmental variations in cognitive, social cognitive, and emotional capacities, in addition to other psychological and biological domains of functioning, to ascertain how particular outcomes—normal, psychopathological, or resilient—are exhibited during varying periods of development. One would not predict that the developmental variations in internal cognitive structures would enable individuals with BD of different ages to use similar strategies to interpret, express, or defend against their affective experiences or internal emotional states. Likewise, cognitive difficulties associated with BD can lead to impairments in regulatory processes that affect, and are affected by, attention networks and executive functions (Dickstein et al., 2004; Klimes-Dougan, Ronsaville, Wiggs, & Martinez, 2006; Meyer et al., 2004). Thus, a developmental analysis is needed to highlight the processes most likely to contribute to vulnerabilities or strengths at each developmental level in persons with BD.

Second, a developmental analysis seeks to examine the prior sequences of adaptation or maladaptation in development that have contributed to an outcome in a particular developmental period. In order to achieve this goal, it is essential that the current status of an individual's functioning be examined in the context of how that status was attained across the course of development. For example, given the multiplicity of biological and psychological processes affected by BD, directing attention to examining early developmental functioning (i.e., prior development) that may be theoretically related to later appearing BD organizations may prove to be very fruitful (Cicchetti & Sroufe, 2000; Cicchetti & Tucker, 1994; Sroufe, 2007). Accordingly, to obtain an understanding of the abnormalities in emotion regulation, close interpersonal relations, or the core negative attributions about the self that often exist in BD, researchers may begin by investigating the early development of these features, their developmental course, and their interrelations with other psychological and biological systems of the individual (Cicchetti & Sroufe, 2000; Leibenluft, Charney, & Pine, 2003; McClure-Tone, Chapter 11, this volume).

Normal and Abnormal Development

The field of developmental psychopathology is concerned with expanding its knowledge base by focusing on the extremes of adaptation and nonnormative

processes of development rather than on central tendencies and uniformities in normative processes of growth and development emphasized in classic developmental psychology. As such, developmental psychopathology underscores and highlights the dialectic between normal and abnormal development (Cicchetti, 1984, 1993, 2006; Cicchetti & Toth, 2009; Rutter, 1986; Rutter & Garmezy, 1983; Rutter & Sroufe, 2000). By virtue of its emphasis on comparing and contrasting abnormal development with normative developmental patterns, and investigating the similarities as well as differences between normality and psychopathology, the strengths and weaknesses associated with atypical development are underscored (Cicchetti, 1993; Karmiloff-Smith, 2007).

The central focus of developmental psychopathology is the elucidation of developmental processes and how they function as indicated and elaborated by the examination of extremes in developmental outcome. Such extremes contribute substantial diversity to the possible outcomes in development, thereby enhancing the understanding of developmental processes. Research in the field of developmental psychopathology is not limited to the investigation of mental disorders. Scientists working in the discipline of developmental psychopathology are interested in examining the entire range of developmental processes and functioning. Not only are the disordered extremes the subject of study, but also the subclinical range of functioning is viewed as being important to the goal of understanding the organization of normal and abnormal development. Individuals in the subclinical range of adaptation (e.g., children with cyclothymic moods) may be vulnerable to the subsequent emergence of psychopathology (e.g., the onset of bipolar I disorder) on the basis of the developmental organization of their biological, psychological, and social systems (e.g., negative attributional styles in the context of adverse family environments in which one or more parents have bipolar spectrum disorders). The investigation of processes that contribute to the later emergence of a disorder, such as BD, as well as processes that mitigate against disordered outcomes provides further insight into the full range of developmental phenomena.

Developmental psychopathology is especially applicable to the investigation of transitional turning points in development across the life span. This is due to its acknowledgment that disorders may appear for the first time in later life and because of its advocacy for the examination of the course of disorders once manifest, including their phases and sequelae (Goodwin & Jamison, 2007; Post, Weiss, & Leverich, 1994; Zigler & Glick, 1986).

Research Approaches within Developmental Psychopathology

The nature of the developmental process elucidates a clear perspective on how to conceptualize empirical research on the origins and course of later emerging psychopathology. Researchers conducting investigations aimed at identifying early precursors of later emerging BD face numerous conceptual and methodological challenges. Because of developmental changes in neurobiological and physiological systems, as well as parallel developments in cognitive, social cogni-

tive, socioemotional, and representational systems, investigators cannot presume phenotypic similarity between early precursors and later impairments (Carlson & Meyer, 2006; Youngstrom, Meyers, Youngstrom, Calabrese, & Findling, 2006). Consequently, studies of the early precursors of later psychopathology should conceptualize and measure features of early development that are theoretically related, but not necessarily behaviorally identical, to the emergence of subsequent BD.

Given the importance of a life span view of developmental processes and an interest in delineating how prior development influences later development, a major issue in developmental psychopathology involves how to determine continuity in the quality of adaptation across developmental time. Sroufe (1979) has articulated the concept of coherence in the organization of behaviors in successive developmental periods as a means of identifying continuity in adaptation despite changing behavioral presentations of the developing individual. Crucial to this concept is a recognition that the same behaviors in different developmental periods may represent quite different levels of adaptation. Behaviors indicating competence within a developmental period may indicate incompetence when evidenced within subsequent developmental periods. Normative behaviors early in development may indicate maladaptation when exhibited later in development. Thus, the manifestation of competence in different developmental periods is rarely indicated by isomorphism in behavioral presentation (i.e., *homotypic continuity*).

Additionally, it must be recognized that the same function in an organized behavioral system can be fulfilled by two dissimilar behaviors, whereas the same kind of behavior may serve two different functions (Werner & Kaplan, 1963) and that the same behavior also may play different roles in different systems. As a result, it is especially important to distinguish between similarities and differences in higher order organization of symptomatology (*molar level*) and component behavioral manifestations of symptomatology (*molecular level*) during different developmental periods. The reorganization of biological and psychological systems that takes place at each new level of development means researchers could not expect to see, for any symptom, behavioral isomorphism at the molecular level, even if there is isomorphism at the molar level. For example, individuals who experience recurrent bipolar depressions during the transition from preoperational to concrete operational thought may display excessive and inappropriate guilt, a loss of self-esteem, and a decrease in activity throughout the episode. Consequently, at a molar level, the depressive symptoms at the latter period (i.e., concrete operational) will be isomorphic to those of the earlier period (i.e., preoperational). Nonetheless, the particular manifestation of the guilt feelings, loss of self-esteem, and psychomotor retardation may change and develop during the transition, when the child's cognitive, representational, socioemotional, and behavioral competencies undergo a rather radical development across these developmental periods. In this way, there may be noteworthy differences at the molecular level.

Because development typically involves the organization through integration of previously differentiated behaviors, we can predict that the expression of bipolar illness may indeed be characterized by molar continuities but additionally by molecular discontinuities and changes. At the molar level, continuity will be preserved by an orderly development in the organization of behaviors; however, at the molecular level, the behaviors that are present at different periods may vary but the meaning may remain coherent (i.e., heterotypic continuity). Thus, a child who exhibits attention-deficit/hyperactivity disorder (ADHD) symptoms at age 7 and develops a bipolar, mixed episode at 15 may have the same molar organization but different molecular behaviors at different phases of development. We believe that the study of the development of the mood disorders over the life course is likely to be fruitful and to reveal the relationship between pathological processes and normal development only if the behavior of individuals with an affective disorder is examined simultaneously at the molar and molecular levels.

Furthermore, examining the course of adaptation once an episode of BD has remitted would benefit from the utilization of a developmental perspective. For example, the examination of the functioning characteristics of individuals previously diagnosed with BD who have returned to a nondisordered condition would provide additional valuable information about BD. It may be possible to identify core characteristics of functioning that remain stable but that no longer give rise to BD because of compensatory factors in the environment, within the individual, or through gene × environment (G × E) interactions that promote resilient adaptations (Cicchetti & Curtis, 2006, 2007). It is conceivable that research such as this might reveal that certain functioning characteristics that were causally relevant to BD in an earlier environment have become positively adaptive in a new context. They not only may not detract from but may actually facilitate successful adaptation. An example might be the personality trait of "novelty seeking" or "exuberance," which before the onset of BD might be associated with abusing drugs, keeping chaotic sleep–wake schedules, or conflict in family relationships. After multiple episodes, a person high in novelty seeking might be more willing to try innovative treatments, to use his or her high energy states in artistic and other creative endeavors, or to experiment with new social contexts that might provide protection against recurrences.

It also may be erroneous to assume that normalized behavior necessarily reflects improvements in processes that were once causal to the development of BD. Accordingly, a developmental psychopathology perspective encourages us to remain open to the possibility that at least some of the characteristics we typically view as functioning deficits in fact may be neutral or even advantageous. Stated differently, they may translate into assets or deficits depending on other characteristics of the individual or the environment. For example, in some contexts acting on impulse may lead individuals with BD to noteworthy and creative achievements, whereas in other contexts impulsive acts may result in persons with BD behaving in a dangerous fashion, resulting in self-destructive outcomes.

Principles of Developmental Psychopathology

In this section, the major principles that are central to elucidating the understanding of both normal and atypical patterns of development are discussed and their relevance to the study of BD is highlighted. It is asserted that the incorporation of these principles into the design and implementation of longitudinal investigations from their inception will proffer a powerful framework for guiding and informing the future research agenda on the causes, sequelae, course, and treatment of BD.

The Mutual Interplay between Normal and Abnormal Development

A focus on the boundary between normal and abnormal development is central to a developmental psychopathology analysis (Cicchetti, 1984, 1989, 1993; Cicchetti & Toth, 1991, 2009; Rutter & Garmezy, 1983). Such a perspective emphasizes not only how knowledge from the study of normal development can inform the study of high-risk conditions and psychopathology but also how the investigation of risk and pathology can enhance our comprehension of normal development.

The study of BD from a developmental perspective can make many significant contributions to theories of normal development, primarily by contributing greater precision to existing theory and by forcing us to examine theories of development critically in relation to our knowledge about psychopathology. The results of such empirical and theoretical investigations may be the description of alternative developmental pathways that lead to the same or different outcomes of the developmental sequence and a weighting of the respective roles of biological, social, emotional, and cognitive factors in mental growth. Furthermore, before one is capable of identifying deviances that exist in a system, one must possess an accurate description of the system itself. Only when we understand the total ongoing development of normal systems can we fully comprehend developmental deviations as adaptational irregularities of those systems (von Bertalanffy, 1968). Because developmental change may be rapid or gradual, it is necessary to consider normative trends of developing skills in the social, emotional, and cognitive domains so as to be in a better position to evaluate deviation or maladjustment. In addition, it is critical to consider intraindividual variation in the overt manifestations of an episode of BD and individual protective factors or stressors that may inhibit or potentiate bipolar illness.

Thus, the application of knowledge of normal biological, cognitive/social cognitive, representational, and socioemotional development to the understanding of bipolar illness results in an articulation of how components of individual functioning in persons with BD contribute to their symptomatic presentation. For example, many of the internal processes implicated in existing theories of BD do not exist in isolation. Deficits in neurobiological, neurochemical, social cognitive, emotion regulatory, parent–child attachment, impulse control, executive functions, neuropsychological development and functioning, and other systems tend to covary significantly in children and adults with BD (see, e.g., Goodwin & Jami-

son, 2007; Miklowitz & Cicchetti, 2006a). This covariance, in turn, often renders difficult the important task of disentangling causal processes (Richters, 1997). In some instances, suspected causal processes actually may be the products of other covarying systems and only spuriously related to BD. In other cases, a process may indeed influence depressive, hypomanic, or manic behavior; however, the nature and extent of its causal influence may be masked or clouded by the influence of other interacting systems.

One strategy that could be used to help disentangle causal influences among multiple, interactive systems would be to identify and examine the functioning of individuals with BD who possess particular functioning deficits and not others. For example, individuals who have ongoing depressions between bipolar episodes could be compared and contrasted with individuals who have periods of complete remission between their bipolar breaks. Multiple processes investigated individually in this manner may provide significant insights into the distinctive roles they play in normal adaptation and into how those roles might change and require reconceptualization within a broader matrix of functioning deficits among persons with bipolar illness. Conversely, the examination of aberrations in the biological, cognitive, social cognitive, socioemotional, and other biological and psychological domains in individuals with BD contributes to a more complete comprehension of how these systems function in normal development (Cicchetti, 1984, 1993, 2006).

The Importance of a Life Span Perspective

Development extends throughout the entire course of life, and adaptive and maladaptive processes emerge over the life span. From infancy through senescence, each period of life has its own developmental agenda and contributes in a unique fashion to the past, present, and future organization of individual development, normal or abnormal. Thus, individuals with a mood disorder, such as BD, may move between pathological and nonpathological forms of functioning. Moreover, even in the midst of a disordered period, individuals may display adaptive as well as maladaptive processes so that it becomes possible to delimit the presence, nature, and boundaries of the underlying psychopathology.

With respect to the emergence of psychopathology, all periods of life are consequential in that the developmental process may undergo a pernicious turn toward psychiatric disorder at any phase. Many disorders have several distinct phases. The factors that are associated with the onset of a disorder may be very different from those that are associated with the cessation of a disorder or with its repeated occurrence. For example, a positive family history of BD is strongly associated with a higher risk of BD onset. In contrast, a positive family history of BD predicts a good response to lithium once an individual has developed the disorder (Grof, Alda, Grof, Fox, & Cameron, 1993).

In contrast to the often dichotomous world of mental disorder/nondisorder depicted in the extant literature, a developmental psychopathology perspective

recognizes that normality often fades into abnormality. Thus, because individuals with BD can have extended periods of normal functioning and also can move into a disordered period unexpectedly, being cognizant of the boundary between normal and atypical functioning is particularly relevant for persons with bipolar illness. For example, it is quite likely that during an acute episode individuals with BD may not recognize that they are in an illness phase. Therefore, strategies for helping them to detect signals of deteriorating functioning during the wellness stage is critically important. Family members, friends, and significant others also can be enlisted and may be helpful in the "detection" process.

Moreover, in developmental psychopathology, "adaptive" and "maladaptive" may assume differing definitions depending on whether one's time referent is immediate circumstances or long-term development, and processes within the individual can be characterized as having shades or degrees of psychopathology. With respect to bipolar illness, such a life span perspective suggests that, even when recurrent depression, hypomania, or mania have occurred, future remission and more adaptive functioning are possible (cf. Jamison, 1993, 1995; Jamison, Gerner, Hammen, & Padesky, 1980; Kraepelin, 1921).

Rutter (1989) has conjectured that key life "turning points" may be times when the presence of protective mechanisms are especially likely to help individuals redirect themselves from a risk trajectory onto a more adaptive developmental pathway. Likewise, Toth and Cicchetti (1999) have suggested that these periods of developmental transition may also afford opportunities when individuals are most amenable to profiting from therapeutic interventions. Whereas change in functioning remains possible at each transitional turning point in development, prior adaptation does place constraints on subsequent adaptation. In particular, the longer an individual continues along a maladaptive ontogenic pathway, the more difficult it is to reclaim a normal developmental trajectory (Cicchetti & Tucker, 1994; Sroufe, 1989). Furthermore, recovery of function to an adaptive level of developmental organization is more likely to occur after a period of pathology if the level of organization before the breakdown was a competent and adaptive one (Sroufe, Egeland, & Kreutzer, 1990).

Developmental Pathways: Diversity in Process and Outcome

Since the emergence of developmental psychopathology as an interdisciplinary science, diversity in process and outcome has been among the hallmarks of its perspective. As Sroufe (1990, p. 335) has asserted, "One of the principal tasks of developmental psychopathology is to define families of developmental pathways, some of which are associated with psychopathology with high probability, others with low probability." Even before a psychiatric disorder emerges, certain pathways signify adaptational failures that probabilistically forebode subsequent psychopathology (Gottlieb, 2007). An example comes from a 40-year follow-up of children who showed mild or moderate externalizing behavior, as rated by teachers when they were ages 13 to 15. By middle adulthood, these children had shown

greater rates of alcohol abuse, marital failure, occupational impairment, and psychiatric disorder than comparison children rated low in externalizing behavior (Colman et al., 2009).

It is expected that (1) there are multiple contributors to BD outcomes in any individual, (2) the contributors vary between individuals with BD, (3) there is heterogeneity among persons with BD in the features of their biological and psychological disturbances and underlying dysfunctions, and (4) there are numerous pathways to BD. Moreover, it is believed that there is heterogeneity among individuals who possess many of the risk factors for BD but who do not develop the disorder. In this regard, the principles of equifinality and multifinality, derived from general systems theory (Cicchetti & Rogosch, 1996; von Bertalanffy, 1968), are germane.

Equifinality refers to the observation that a diversity of paths may lead to the same outcome. This alerts us to the possibility that a variety of developmental progressions may eventuate in BD rather than positing a singular primary pathway to disorder. In contrast, *multifinality* suggests that any one component may function differently depending on the organization of the system in which it operates (Cicchetti & Rogosch, 1996; Wilden, 1980). Multifinality states that the effect on functioning of any one component's value may vary in a different system; thus, the same risk factor or starting point may eventuate in a wide dispersion of outcomes. Actual effects will depend on the conditions set by the values of additional components with which it is structurally linked. Consequently, the pathology or health of the system must be identified in terms of how adequately its essential functions are maintained. Stated differently, a particular adverse event should not necessarily be seen as leading to the same psychopathological or nonpsychopathological outcome in every individual with BD. Likewise, individuals with BD may begin on the same major pathway and, as a function of their subsequent "choices," exhibit very different patterns of adaptation or maladaption (Cicchetti & Tucker, 1994; Sroufe, 1989; Sroufe et al., 1990).

For example, it is common for individuals with BD who were maltreated to become engaged in alcohol and drug use (Post & Leverich, 2006). These individuals with BD may engage in alcohol and substance use as a means of self-medicating and escaping from their traumatic experiences and their mood fluctuations. However, not all individuals with BD who were maltreated embark on a substance use pathway and instead will be able to engage in more direct competent means of dealing with their trauma histories, especially if they have the benefit of social supports and appropriate treatment.

Because of the diversity in processes and outcomes that characterize development, the developmental psychopathology approach to BD does not proffer a simple unitary etiological explanation. Although commonalities in pathways in different clusters of persons with BD may be delineated, it also is possible that BD is not the only outcome associated with each pathway. Although pathways may be discovered that are specific to BD in some individuals, there also are likely to be a range of dysfunctions and comorbid dysfunctions and disorders (e.g., anxiety

disorders, ADHD, substance abuse disorders, personality disorders), of which an affective disorder (e.g., BD) may be one. Thus, the empirical investigation of BD must be conceptualized within a larger body of inquiry into the developmental patterns promoting adjustment difficulties and psychopathology.

A pathways approach builds on knowledge gained from variable-oriented studies; however, attention is shifted to exploring the common and the uncommon outcomes as well as alternative routes by which outcomes are achieved by different individuals (cf. Cicchetti & Schneider-Rosen, 1986). Thus, what might be considered error variance at the group level must be critically examined for understanding diversity in process and outcome. The emphasis on person-centered observation highlights the transition from a focus on variables to a focus on individuals, and this transition is essential for demonstrating equifinality and multifinality in the developmental course.

The growing knowledge that subgroups of individuals manifesting similar problems arrived at them from different beginnings and that the same risk factors may be associated with different outcomes has proven to be critical not only because it has the potential to bring about important refinements in the diagnostic classification of mental disorders, but also because it calls attention to the importance of continuing to conduct process-oriented studies (Bergman & Magnusson, 1997; Richters & Cicchetti, 1993; von Eye & Bergman, 2003). The examination of patterns of commonality within relatively homogeneous subgroups of individuals and concomitant similarity in profiles of contributory processes becomes an important data analytic strategy. Moreover, the need to examine the totality of attributes, psychopathological conditions, and risk and protective processes in the context of each other rather than in isolation is seen as crucial for understanding the course of development taken by individuals. For example, the presence of BD in a child, adolescent, or adult would have different developmental implications depending on whether it occurs alone or in conjunction with other types of psychopathology. The meaning of any one attribute, process, or psychopathological condition needs to be considered in light of the complex matrix of individual characteristics, experiences, and social contextual influences involved, the timing of events and experiences, and the developmental history of the individual.

This attention to diversity in origins, processes, and outcomes in understanding developmental pathways does not suggest that prediction is futile as a result of the many potential individual patterns of adaptation (Sroufe, 1989). There are constraints on how much diversity is possible, and not all outcomes are equally likely (Cicchetti & Tucker, 1994; Sroufe et al., 1990). Nonetheless, the appreciation of equifinality and multifinality in development encourages theorists and researchers to entertain more complex and varied approaches to how they conceptualize and investigate development and psychopathology. Researchers on BD should increasingly strive to demonstrate the multiplicity of processes and outcomes that may be articulated at the individual, person-oriented level within existing longitudinal data sets. Ultimately, future endeavors must conceptualize and design research on BD at the outset with these differential pathways con-

cepts as a foundation (Richters, 1997). In so doing, progress toward achieving the unique goals of developmental psychopathology—to explain the development of individual patterns of adaptation and maladaptation—will be realized (cf. Sroufe & Rutter, 1984).

Individuals Play an Active Role in Their Own Development

There has been a growing recognition of the role of the developing person as a processor of his or her experiences. The environment does not simply create individuals' experiences; rather, individuals also choose and create their experiences and their own environments in a changing world (Scarr & McCartney, 1983). Individuals select, integrate, and actively affect their own development and the environment in a dynamic fashion (Cicchetti & Tucker, 1994; Wachs & Plomin, 1991). The principle of contextualism conceptualizes developmental processes as the ongoing interaction between an active, changing individual and a continuously unfolding, dynamic context (Cicchetti & Aber, 1998). Thus, maladaptation and psychopathology are considered to be products of the transaction among an individual's intraorganismic characteristics, adaptational history, and the current context (Boyce et al., 1998; Sroufe, 1997).

Various difficulties will constitute different meanings for an individual depending on cultural considerations (Garcia Coll, Akerman, & Cicchetti, 2000) as well as an individual's experiential history and current level of psychological and biological functioning. The integration of the experience, in turn, will affect the adaptation or maladaptation that ensues. Moreover, we now know that social contexts exert effects not only on psychological processes but also on biological structures, functions, and processes (Boyce et al., 1998; Cicchetti, 2002; Cicchetti & Tucker, 1994; DeBellis, 2001; Eisenberg, 1995; Nelson & Bloom, 1997). For example, persons at risk for developing BD who experience traumatic environmental adversity will possess a greater likelihood that their genetic vulnerability will get expressed and that the neural circuitry associated with aspects of BD will be activated (see Post & Miklowitz, Chapter 12, this volume).

Multiple Levels of Analysis

A "systems view" conceives development as being hierarchically organized into multiple levels that mutually influence each other (Gottlieb, 1992; Thelen & Smith, 1998). "Top-down" as well as "bottom-up" bidirectional effects are theorized to occur among the various levels. Accordingly, genetic activity ↔ neural activity ↔ behavior ↔ environment can serve as a schematic representation of this systems view. These bidirectional effects among levels of the system result in a probabilistic conceptualization of epigenetic development in all individuals, including those with a mental illness, such as persons with BD (Cicchetti & Tucker, 1994; Gottlieb, 1992). The probabilistic epigenesis perspective thus implies that individuals are neither unaffected by earlier experiences nor immutably controlled by

them. Change in developmental course is thought to be possible as a result of new experiences, reciprocal interactions between levels of the developing person, and the individual's active self-organizing strivings for adaptation (see also Cicchetti & Tucker, 1994). Thus, epigenesis is viewed as probabilistic rather than predetermined, with the bidirectional and transactional nature of genetic, neural, behavioral, and environmental influences over the life course capturing the essence of probabilistic experiences. Because development is a dynamic process, assertions about causality must include a temporal dimension that specifies and describes when the experience or coactions occurred (Gottlieb & Halpern, 2002).

Different levels of analysis—genetic, biological, social, psychological, familial, or cultural—constrain other levels. As scientists investigating BD learn more about multiple levels of analysis, researchers conducting their work at each level will need to develop theories that are consistent across all levels. When scientists in different disciplines function in isolation, they run the risk of formulating theories that will ultimately prove to be incorrect because vital information from other disciplines has either been ignored or is unknown. Just as is the case in systems neuroscience (Cowan, Harter, & Kandel, 2000), it is critical that there be an integrative framework that incorporates all levels of analysis about complex systems in the development of BD. As Miklowitz and Cicchetti (2006b) stated, "An interdisciplinary multiple-levels-of-analysis approach has the potential to become the guiding light in the next generation of studies on bipolar disorder" (p. 937).

It is now widely understood that individual risk factors seldom are powerful enough to exert sufficient influence to result in psychopathology (Sameroff & Chandler, 1975; Willcutt & McQueen, Chapter 8, this volume). Moreover, when they appear to have such effects, it is highly likely that they are surrogates for multiple, unobserved influences. Much more commonly, adequate prediction of either disturbance or resilience necessitates the consideration of multiple risk and protective factors and their interplay (Cicchetti & Rogosch, 1999). Moreover, the consequences of any risk factor depend on myriad other aspects embedded in the developmental context. For example, even abused and neglected children, who generally are confronted with an array of difficulties in addition to their maltreatment experiences, differ in their functioning depending on the level of community violence present in their lives; abused and neglected children who resided in settings high in extrafamilial violence exhibit the highest level of behavioral problems (Lynch & Cicchetti, 1998).

In addition, a particular vulnerability may not pose risk in the context of a protective condition. For example, Suomi (2000) has discovered that, relative to the long (l) allele, the short (s) allele in the serotonin transporter gene promoter region confers no detectable liability for rhesus monkeys reared by nurturant foster mothers; in fact, such animals become leaders of the group. Yet the same gene polymorphism may confer vulnerability for anxiety and behavioral pathology in monkeys raised without adults. In another interesting example, Baldwin, Baldwin, and Cole (1990) found that in high-risk families from low-socioeconomic backgrounds, levels of restriction and control in parenting (i.e., authoritarian par-

enting practices) were related to successful child outcomes, and that such parenting practices were more frequent in high-risk than in low-risk families showing child success. Accordingly, controlling forms of parenting may be a protective factor for one group but not for another. These examples also illustrate the probabilistic rather than the causal status of risk factors. Knowledge of the differential mechanisms that underlie disparate subgroups of disorders (i.e., equifinality) can help to enhance the specificity of prediction from risk factors to developmental outcome.

Over the course of the past several decades, there has been a growing acknowledgment that the investigation of developmental processes, both normal and abnormal, necessitates that scientists must utilize different methods and levels of analysis depending on the questions being addressed in their research. One of the most dramatic examples of this is the work on experience-dependent brain development (Black, Jones, Nelson, & Greenough, 1998; Greenough, Black, & Wallace, 1987). The viewpoint is now widely shared that neurobiological development and experience are mutually influencing (Cicchetti & Tucker, 1994; Eisenberg, 1995; Nelson & Bloom, 1997). Rather than adhering to a unidimensional belief in the deterministic role that unfolding biology exerts on behavior, it is now widely believed that brain function and its subsequent influence on behavior possesses self-organizing functions that can, in fact, be altered by experiences incurred during sensitive periods of development. Specifically, it has been demonstrated that social and psychological experiences can modify gene expression and brain structure, functioning, and organization, including patterns of neuronal and synaptic connections (Kandel, 1998, 1999). Such experiential conditions may interact with an individual's genetic makeup to alter processes, such as the timing of the initiation of transcription for a specific gene, the duration for which it does so, or whether the gene will be translated or expressed. These changes not only contribute to the biological bases of individuality but also play a prominent role in initiating and maintaining the behavioral anomalies that are induced by social and psychological experiences (Kandel, 1998).

The mechanisms of neural plasticity are integral to the very anatomical structure of cortical tissue and cause the formation of the brain to involve an extended malleable process that presents developmental psychopathologists with new avenues for understanding the vulnerability of the brain as a basis for the emergence of mental disorder. Perturbations that take place in the developing brain can trigger a cascade of growth and function changes that lead the neural system down a path that deviates from that usually taken in normal neurobiological development, resulting in the development of aberrant neural circuitry that contributes to these early developmental abnormalities, eventuating in relatively enduring forms of psychopathology (Black et al., 1998; Cicchetti & Cannon, 1999; Cicchetti & Thomas, 2008; Courchesne, Chisum, & Townsend, 1994; Nowakowski & Hayes, 1999).

To comprehend BD in its full complexity, all levels of analysis must be examined and integrated. Research in the area of resilience has begun to follow this

interdisciplinary, multiple-levels-of-analysis perspective (Cicchetti & Blender, 2006; Cicchetti & Rogosch, 2007; Curtis & Cicchetti, 2007; see also papers in Cicchetti & Curtis, 2007).

Resilience

Developmental psychopathologists are as interested in individuals at high risk for the development of psychopathology who do not manifest it over time as they are in individuals who develop an actual mental disorder (Cicchetti & Garmezy, 1993; Luthar, 2006; Luthar, Cicchetti, & Becker, 2000; Masten, 1989; Masten, Best, & Garmezy, 1990). Moreover, researchers in developmental psychopathology emphasize the importance of understanding the functioning of individuals who, after having diverged onto deviant developmental pathways, resume normal functioning and achieve adequate adaptation (Cicchetti & Rogosch, 1997; Masten et al., 1990).

Resilience has been operationalized as the individual's capacity for adapting successfully and functioning competently despite experiencing chronic adversity or after exposure to prolonged or severe trauma. Resilience is a dynamic developmental process; it is multidimensional in nature, exemplified by findings that individuals who are at high risk for or who have a mental disorder may manifest competence in some domains and contexts, whereas they may exhibit problems in others.

Research on the determinants of resilience also highlights the need to examine functioning across multiple domains of development. An example from BD is provided by Keck and colleagues (1998), who found that, after a manic or mixed episode, 48% of adults with bipolar I disorder had symptomatically recovered by 1 year. When recovery was defined as "functional," meaning the regaining of preepisode level of social–occupational status, the rate was only 24%. To provide a further example, consider a school-age child with BD who was formerly categorized as resilient based solely on an examination of his or her cognitive abilities. If that child manifests subsequent poor peer relationships over time, many would assume that the child is evidencing discontinuity from his or her earlier resilient cognitive functioning. In fact, we may be observing evidence of maladaptation that would have been observed much earlier had his or her peer relations been previously examined. Furthermore, the ability to function in a resilient fashion in the presence of biological, psychological, environmental, and sociocultural disadvantage may be achieved through the use of developmental pathways that are less typical than those negotiated in usual circumstances. Thus, an important question for researchers to address is whether the employment of alternative pathways to attaining competence renders individuals more vulnerable to manifesting delays or deviations in development. Although only prospective longitudinal investigations can fully address this issue, it is critical to ascertain whether these individuals are more prone to developing maladaptation or psychopathology in

later life. Given the nonstatic nature of the construct, we do not expect children identified as resilient to be immune to declines in functioning at each subsequent developmental period.

Investigations aimed at discovering the processes leading to resilient outcomes and on the processes underlying recovery of adaptive function offer great promise as an avenue for facilitating the development of prevention and intervention strategies (Luthar et al., 2000; Toth & Cicchetti, 1999). Through the examination of the proximal and distal processes and mechanisms that contribute to positive adaptation in situations that more typically eventuate in maladaptation, researchers and clinicians will be better prepared to devise ways of promoting competent outcomes in individuals at high risk for developing BD (Beardslee & Podorefsky, 1988; Luthar & Cicchetti, 2000).

Despite the attention paid to discovering the processes through which individuals at high risk do not develop maladaptively, the empirical study of resilience has focused primarily on detecting the psychosocial determinants of the phenomenon (Charney, 2004; Curtis & Cicchetti, 2003). For research on resilience to grow in ways that are commensurate with the complexity inherent to the construct, efforts to understand underlying processes will be facilitated by the increased implementation of multidisciplinary investigations designed within a developmental psychopathology framework. Research of this nature would entail a consideration of biological, psychological, and environmental/contextual processes from which varied pathways to resilience (equifinality) might eventuate as well as those that result in diverse outcomes among individuals who have achieved resilient functioning (multifinality) (see Cicchetti & Curtis, 2007). Along these lines, the investigation of multiple aspects of the processes underlying resilience can shed light on the nature of the interrelation among various developmental domains in individuals with BD. For example, how do cognition, affect, and neurobiological growth relate with one another at various developmental periods? When an advance or a lag occurs in one biological or psychological system, what are the consequences for other systems?

It is important that these issues receive focused attention from researchers, because the presence of capacities of one of these systems may be a necessary condition for the development or exercise of capacities of another system. For example, certain cognitive skills may be necessary for the development of particular affective expressions and experiences (Hesse & Cicchetti, 1982). Lags in these systems may then result in compensatory development, which may, in some instances, leave the child vulnerable to psychopathology. Over time, difficulty in the organization of one biological or psychological system may tend to promote difficulty in the way in which other systems are organized as hierarchical integration between the separate systems occurs. The organization of the individual may then appear to consist of poorly integrated component systems. As the converse of the effects of early competence, early incompetence will tend to promote later incompetence because the individual arrives at successive developmental stages

with less than optimal resources available for responding to the challenges of that period. Again, however, this progression is not inevitable but probabilistic. Changes in the internal and external environment may lead to improvements in the ability to grapple with developmental challenges, resulting in a redirection in the developmental course.

The role of biological factors in resilience is suggested by evidence on neurobiological and neuroendocrine function in relation to stress regulation and reactivity (Cicchetti, Rogosch, Gunnar, & Toth, in press; Gunnar & Vazquez, 2006), by behavioral genetics research on nonshared environmental effects (Rende & Waldman, 2006), and by molecular genetics research that may reveal the genetic elements that serve a protective function for individuals experiencing significant adversity (Cicchetti & Blender, 2006). To provide an example gleaned from the field of molecular genetics, research suggests that it is conceivable that the gene encoding high monoamine oxidase A (MAOA) activity and the l/l genotype of the serotonin transporter gene (5-HTT) gene may confer protection against the development of antisocial behavior in males who have been maltreated and against the development of depression in individuals who have been maltreated, respectively (Caspi et al., 2002, 2003). Consequently, the negative developmental sequelae associated with child maltreatment are not inevitable but appear to be the result of G × E interactions between risk (i.e., low-activity MAOA; the s/s genotype of 5-HTT) or protective (i.e., high-activity MAOA; the l/l genotype of 5-HTT) genes and maltreatment (see Cicchetti, Rogosch, & Sturge-Apple, 2007).

Several studies of early childhood adversity and the subsequent development of early-onset BD have suggested that adults with bipolar illness who had been physically or sexually abused during childhood not only displayed an earlier onset of BD than did nonabused adults with BD but also experienced a more severe and treatment-resistant course once the illness became manifest (Post & Leverich, 2006). In addition to the experience of early child abuse, it would be important to investigate whether the presence of risk alleles of genes implicated in BD were interacting with physical and sexual maltreatment to produce the severe outcomes (Hayden & Nurnberger, 2006; Serretti & Mandelli, 2008; Willcutt & McQueen, Chapter 8, this volume).

Children who develop in a resilient fashion despite having experienced significant adversity play an active role in constructing, seeking, and receiving the experiences that are developmentally appropriate for them. To date, research investigations that search for mechanisms of G × E interaction have yet to address the role that genetic factors may play in influencing how children who are developing in a resilient fashion have actively transformed their social environment (known as evocative gene–environment correlation) (Rende & Waldman, 2006; Scarr & McCartney, 1983). At the neurobiological level, different areas of the brain may attempt to compensate; on another level, individuals may seek out new experiences in areas where they have strength (Black et al., 1998; Cicchetti & Tucker, 1994). The effects of social experiences, such as child abuse and neglect,

on brain biochemistry and microstructure may be either pathological or adaptive. With respect to the experience of child maltreatment, depending on how the individual interprets and responds to the abuse, as well as the genetic elements that are expressed, the effects either may be pathological (the typical outcome) or may not preclude normative development (a resilient outcome) (Cicchetti & Rogosch, 2009; Cicchetti & Valentino, 2006). Thus, neither early neurobiological anomalies nor aberrant experiences should be considered as determining the ultimate fate of the individual with BD (the notion of probabilistic epigenesis).

A multilevel approach to resilience also affords an additional avenue for examining the biological and social constraints that may operate on aspects of the developmental process throughout the life course. Moreover, through investigating the multiple determinants of resilient adaptation, we are in a position to discover the range and variability in individuals' attempts to respond adaptively to challenge and ill fortune.

Translational Research

In recent years, the National Institute of Mental Health has emphasized the importance of translational research in the biological, behavioral, and social sciences (Cicchetti & Toth, 2006; Gunnar & Cicchetti, 2009). In the National Advisory Mental Health Council's (2000) report *Translating Behavioral Science into Action*, strategies for enhancing contributions of behavioral science to society more broadly were proposed. In this report, "translational research is defined as research designed to address how basic behavioral processes inform the diagnosis, prevention, treatment, and delivery of services for mental illness, and, conversely, how knowledge of mental illness increases our understanding of basic behavioral processes" (p. iii). Research examining basic biological processes, such as in genetic and neuroscience investigations on mental illness, also can be translated into preventive interventions and treatment initiatives (Cicchetti & Gunnar, 2009; Cicchetti & Thomas, 2008). The formulation of translational research in the behavioral and biological sciences is in direct accord with three of the key tenets of a developmental psychopathology perspective, namely the reciprocal interplay between basic and applied research, between normal and abnormal development, and a multiple-levels-of-analysis perspective (Cicchetti & Toth, 1991, 1998; Pellmar & Eisenberg, 2000). Research on resilience from a multilevel perspective is an excellent example of translational research because it also lends itself to informing prevention and intervention initiatives.

The principles of developmental psychopathology lend themselves to fostering translational research that has implications for society, policymakers, and individuals with BD and their families. The very subject matter of the field of developmental psychopathology necessitates thinking clearly about the implications of the work and devising strategies that will help to remedy the problems associated with BD. By developing relationships between researchers from dif-

ferent disciplines and policymakers, social policy initiatives also can build upon empirical evidence. Furthermore, if basic research on individuals with BD is designed with clinical and policy questions at the forefront, rather than as a post hoc afterthought, a true research-informed policy agenda would be achieved that could benefit the welfare of persons suffering from BD and their families.

For example, at what phases of development will psychosocial interventions have a maximal preventive effect among children at risk for BD and by what mechanisms? Basic neurobiological research could inform our understanding of when children at risk for BD develop facial emotion recognition errors (e.g., viewing neutral faces as negative) and the neural structures and circuitry with which these errors are correlated (i.e., amygdala/ventromedial prefrontal cortex circuits) (Rich et al., 2006). Results of such studies may suggest that certain forms of psychosocial intervention (e.g., psychoeducation, cognitive-behavioral therapy, or interpersonal therapy) can effectively teach emotion labeling skills, but only among children who have shown an ability to mentalize or infer emotional states in others. In turn, demonstrating that such interventions influence aberrant neural pathways and result in symptom improvement, in part mediated by improved emotion recognition, would inform our understanding of developmental pathways in the onset of BD.

Prevention and Intervention

The major objective of the field of prevention science is to intervene in the course of development in order to reduce or eliminate the emergence of maladaptation and mental disorder as well as to promote resilient adaptation in individuals at high risk for psychopathology (Ialongo et al., 2006). To achieve this laudable goal, it is essential that prevention scientists possess a complex, multilevel understanding of the course of normality to formulate an in-depth portrayal of how deviations in normal developmental processes can eventuate in maladaptation and mental disorder. Because of its focus on the mutual interplay between the investigation of normal and abnormal development, the field of developmental psychopathology is well poised to provide the theoretical foundation for prevention and intervention initiatives (Institute of Medicine, 1994).

Developmental psychopathologists believe that efforts to prevent the emergence of psychopathology or to ameliorate its effects also can be informative for understanding processes involved in psychopathological development (Hinshaw, 2002; Kellam & Rebok, 1992). For example, if the course of development is altered as a result of the implementation of randomized controlled prevention trials and the risk for negative outcomes is reduced, then prevention research helps to specify processes that are involved in the emergence of psychopathology or other maladaptive developmental outcomes (Ialongo et al., 2006). As a consequence, if randomized controlled prevention trials examine mechanisms of intervention action, then they can be conceptualized as true experiments in modifying the

developmental course, thereby providing insight into the etiology and pathogenesis of disordered outcomes (Cicchetti & Hinshaw, 2002; Hinshaw, 2002; Howe, Reiss, & Yuh, 2002; Kellam & Rebok, 1992). Thus, prevention research not only leads to support or lack of support for theoretical formulations accounting for the development of psychopathology, but it also can contribute to the knowledge base of strategies that can be implemented to reduce psychopathology and promote positive adaptation. Knowledge of developmental norms, appreciation of how developmental level may vary within the same age group, sensitivity to the changing meaning that problems have at different developmental levels, attention to the effects of developmental transitions and reorganizations, and understanding of the factors that are essential features to incorporate into the design and implementation of preventive interventions all may serve to enhance the potential for optimal intervention efficacy (Noam, 1992; Toth & Cicchetti, 1999).

Whereas much of the work on BD and other types of psychopathology is, of necessity, naturalistic and correlational in nature, given ethical constraints on randomly assigning developing persons to key environmental or psychobiological conditions, the gold standard for clinical intervention and prevention research is the randomized clinical trial. The experimental nature of such investigations provides an unprecedented opportunity to make causal inferences in the field (Kraemer, Wilson, Fairburn, & Agras, 2002). The types of independent variables manipulated in clinical or prevention trials may be several steps removed from crucial, underlying etiological factors, given that such trials are primarily concerned with the practical, clinical goals of alleviating suffering and promoting competence rather than isolating primary causal variables. Nonetheless, careful research design and assiduous measurement of ancillary, psychological, and biological process variables through which intervention effects may occur can shed light on theory-driven mechanisms underlying healthy and pathological development (Cicchetti & Gunnar, 2008; Hinshaw, 2002; Howe et al., 2002; Kraemer et al., 2002).

Research on BD has directed too little effort toward developing and evaluating psychosocial models of prevention that can be adjunctive to pharmacological treatment (for an exception, see Miklowitz & Chang, 2008). (For examples of efficacious preventive interventions for mothers with major depressive disorder and their young offspring, see Cicchetti, Rogosch, & Toth, 2000; Toth, Rogosch, Manly, & Cicchetti, 2006.) Rather than awaiting a full-blown disorder to emerge, risk markers that portend possible illness could be identified. Early identification and possible prevention could minimize the magnitude of the disease process and possible impairment. Prevention strategies become particularly relevant to the increasing diagnosis of the disorder in early childhood. As we progress with the ability to detect genetic and neurobiological markers of disease, prevention again emerges as an important future avenue to pursue. Such prevention strategies also could minimize the likelihood of the brain circuitry for BD becoming hardwired and increasingly recalcitrant to potential neuroplastic changes.

Conclusion and Future Directions

Although it is evident that research on BD has engendered greater clarity with respect to clinical description, etiology, pathogenesis, psychosocial and drug treatment, and development, there remains much to examine in the future. I discuss several empirical and practical issues that require greater attention as well as areas in need of enhanced theoretical integration (see Table 1.1 for illustrative examples).

To begin, a developmental psychopathology perspective underscores the importance of conducting ongoing prospective multiwave longitudinal studies that are properly designed and methodologically rigorous and that can provide an accurate portrayal of the life course trajectories of those afflicted with the varying subtypes of BD. Moreover, there is a strong need to be able to investigate BD before it emerges. What populations should be targeted to enhance the likelihood of observing BD at greater than population prevalence rates? What are the earlier precursors to BD across multiple levels of analysis? How can prodromal abnormal signs be identified within the framework of developmental psychopathology? A developmental perspective also would help to articulate and understand those factors that may contribute to the maintenance of BD over the life course, quite separate from those that might contribute to its etiology. In particular, a fuller comprehension of the role played by child physical and sexual abuse and child neglect in the development of BD is needed (Post & Leverich, 2006).

Another area that merits attention is the need to resolve the underlying structure and natural organization of BD. The DSM approach to diagnosing BD yields a phenotype that is characterized by considerable heterogeneity. Consequently, there exists great variability across the population of individuals diagnosed as having BD. This heterogeneity may reflect our flawed efforts to conceptualize a

TABLE 1.1. Future Research and Practical Issues on Bipolar Disorder: A Developmental Psychopathology Approach

- Research in the interdisciplinary field of developmental psychopathology examines processes underlying the interrelation between adaptive and maladaptive development over the life course. The principles of this discipline can be used to augment the understanding and treatment of BD.
- A multiple-levels-of-analysis perspective and an interdisciplinary developmental psychopathology approach must be incorporated into the research armamentaria of investigators studying BD.
- Investigations conceived within a developmental psychopathology framework must incorporate a multilevel perspective in the study of the processes leading to resilient adaptation in individuals with BD.
- Theory and empirical research on basic biological and psychological developmental processes must increasingly be used to inform prevention and intervention initiatives in BD.
- Scientific discoveries emanating from developmental psychopathology must be translated into practical social policy applications that contribute to reducing the stigma that exacerbates the burden of mental illness for individuals with BD and their families.

complex phenotype, variability in the underlying pathological process, the DSM decision to dichotomize a collection of dimensional symptom and trait variables, or all three. It is important to undertake latent structure statistical analyses of the BD phenotype; sophisticated data analytic methods now exist that enable researchers to sort individuals efficiently into meaningful relatively homogeneous clusters (e.g., finite mixture modeling; latent-class analysis).

Clinical features that run in families may aid in the categorization of more homogeneous phenotypes of BD. One such feature is polarity at illness onset, which is related to severity and course of BD. Kassem and colleagues (2006) discovered that sibling pairs with BD who were concordant for mania at illness onset were, on average, older, less likely to exhibit panic attacks or alcoholism, and more likely to display genetic linkage to chromosome 16p but no linkage to chromosome 6q. Thus, polarity at onset may be useful in the delineation of homogeneous subtypes of BD that may have distinct developmental courses.

Research in the area of endophenotypes also should be conducted. The endophenotype is a measurable component, unseen by the unaided eye, along the pathway between distal genotype and disease (Gottesman & Gould, 2003; Gottesman & Shields, 1972). Endophenotypes may be neurophysiological, endocrinological, neuroanatomical, cognitive, or neuropsychological in nature. Furthermore, the endophenotype is thought to represent a simpler clue to genetic underpinnings than the disease syndrome itself. The incorporation of endophenotypes will be extremely useful to advancing genomic, neuroimaging, neurobiological, and psychological investigations of BD.

Investigators and practitioners with a developmental perspective are interested not only in the differences between individuals with and without mental disorders but also in their similarities (Cicchetti, 1993; Zigler & Glick, 1986). Indeed, there are striking similarities between persons with bipolar illness and their well counterparts. For example, children and adults with BD, just as with persons who are nondisordered, experience a range of feelings, possess a need for connectedness with others, seek a sense of order in their worlds, strive for autonomy, and attempt to find meaning in their life experiences (Hinshaw & Cicchetti, 2000).

Individuals with BD typically shift from phases of normality to psychopathology and back. Almost all such individuals experience stages and phases of remission and relapse throughout the life span. Moreover, not only do persons with BD have periods of remission, but also an appreciable number manage to function in an adaptive and productive manner for prolonged periods of their lives. Accordingly, individuals with BD should not be reduced to their psychiatric diagnoses. Those persons with BD who have been successfully treated and those whose illnesses are in remission may be strikingly similar to persons who are without mental disorder. Unlike other psychotic spectrum disorders where impairment may be more chronic, individuals with BD may lead productive and fulfilled lives (see Hinshaw, 2005). As such, the stigma that commonly accompanies major mental disorders might be minimized if the public were sufficiently educated about the

resilience that is possible. The processes that promote resilience in BD should be a central focus of the next generation of research in BD.

In contrast to the viewpoint that mental disorders are "brain disorders" or "brain diseases," developmental psychopathologists conceptualize mental disorders in a more complex, dynamic systems fashion (Cicchetti & Cannon, 1999; Cicchetti & Thomas, 2008; Cicchetti & Tucker, 1994). Although the brain is clearly involved in all mental disorders, many other systems contribute and transact with the brain in dynamic fashion over the life course to bring about experience-dependent brain development (Greenough et al., 1987). The motivation underlying the promotion of the viewpoint that mental disorders are "brain diseases" may, in part, be to help reduce personal and family blame for aberrant behavior and emotion (Hinshaw & Cicchetti, 2000). Nonetheless, it is essential that researchers convey scientific truth to the lay public regarding the complex, multilevel, and dynamic processes that undergird the development of psychopathology in general and BD in particular. Whereas we believe that there are strong psychobiological predispositions to many forms of mental disorder, the concept of "brain disorder" may connote primacy or exclusivity for the biology and fail to underscore transactional processes. The increased emphasis on a multilevel, dynamic systems approach to psychopathology and resilience (Cicchetti & Blender, 2006; Cicchetti & Curtis, 2007; Masten, 2007), the growing attention paid to G × E investigations in the development of psychopathology and resilience (Cicchetti, 2007; Moffitt, Caspi, & Rutter, 2006; Rutter, 2006), and the application of a multilevel developmental psychopathology perspective to mental illnesses that have traditionally been studied nondevelopmentally (such as BD) will contribute to educating the public about the causes and consequences of mental disorder. The reduction of stigmatization toward persons with mental disorder, which can actually be exacerbated by simplified attributions like "brain disorder," will contribute to reducing the burden of mental illness for persons with BD and their families (Hinshaw, 2006).

Research in developmental psychopathology has enhanced our understanding of risk, disorder, and resilience across the life course (see, e.g., Cicchetti & Cohen, 1995a, 1995b, 2006a, 2006b, 2006c). Advances in genomics, G × E interactions, and epigenetics, growth in the understanding of neurobiology and neural plasticity, and progress in the development of methodological and technological tools, including brain imaging, hormone assays, and statistical analysis of developmental change, pave the way for multiple-levels-of-analysis research programs aimed at elucidating the development and course of BD (Cicchetti & Curtis, 2006; Masten, 2006). Moreover, the information that is emanating from the field of developmental psychopathology can be integrated into the conceptual base and measurement armamentaria of scientists from diverse disciplines, even if they do not consider themselves to be developmental psychopathologists. These knowledge gains not only will benefit the scientific study of BD but will also permit translation to informing developmentally based preventive strategies and

interventions that will contribute to reducing the individual, familial, and societal burden of BD.

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