

Chapter 2

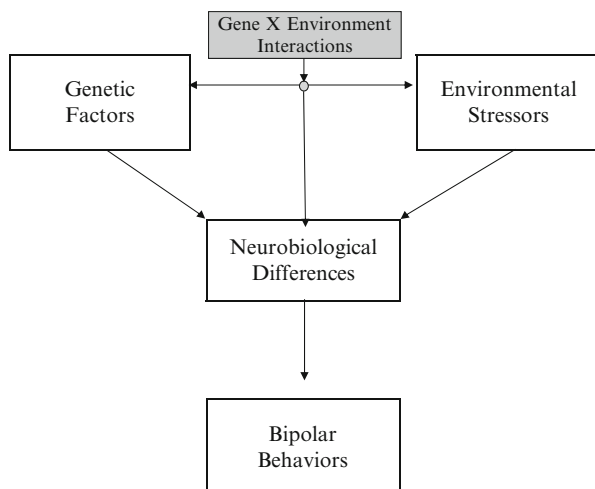
Etiology

The exact cause, or rather the causes, of bipolar disorder are not known and most researchers now agree that there is no single etiological factor that accounts for all instances of the disorder. Rather it would appear that several factors combined lead to the behavioral manifestations, or symptoms, collectively referred to as bipolar disorder (National Institute of Mental Health [NIMH], 2008). As illustrated in Fig. 2.1, this disorder is thought to be a neurobiological disorder (associated with certain brain regions and the dysfunction of certain neurotransmitters). In turn, these brain differences are thought to be associated with genetic factors, external environmental stressors, and/or the interactions among these variables (Bressert, 2007).

Prior to considering the complexities of genetic, environmental, and neurobiological research on bipolar disorder in youth, we need to consider the bigger picture of conceptualization of mental health conditions in general. The diathesis-stress model is the dialectical model (the widely accepted nature vs. nurture model of thinking), which states that individuals possess predispositions and vulnerabilities for illnesses (e.g., Zuckerman, 1999). The number and degree of these vulnerabilities varies greatly in a population and is not known. It appears that this variability is determined by multiple genetic, neurobiological, and environmental factors. Vulnerability or predisposition is one's potential for having a disorder (referred to as genotype). Whether this potential is ever actualized into an illness (phenotype) depends on other various factors or *stresses* that also vary greatly. It is the interaction between one's predisposition and stresses that triggers the actualization of the illness. The more and the stronger predispositions that one has, the less amount of stress this person needs to experience an outbreak.

Applying this model to early-onset bipolar disorder, we can assume that a child begins developing the disorder when a critical amount of stress triggers the otherwise dormant predispositions. Importantly, the stressors that trigger the predispositions for early-onset bipolar disorder (e.g., stimulant medication leading to escalation of mania; Delbello et al., 2001; Reichart & Nolen, 2004) may not be the same stressors that keep it in place (e.g., high-level of conflict families; Birmaher,

Fig. 2.1 Bipolar disorder is thought to be a neurobiological disorder. These brain differences are thought to be associated with genetic factors, external environmental stressors, and/or the interactions among these variables



Arbelaez, & Brent, 2002). Research is limited in identifying which stressors serve which function because of the tremendous heterogeneity of the early-onset bipolar disorder population.

There is evidence pointing to a biological basis for bipolar disorder (e.g., Pavuluri, Birmaher, & Nalor, 2005; Youngstrom, Birmaher, & Findling, 2008). Nonetheless, over the past two decades, mental health scientists and practitioners are shifting toward a systemic conceptualization and the above described diathesis-stress model. Scientists and practitioners are moving away from the medical model, which assumes that since the disease is present on a cellular level somewhere in the organism, the clinician's task is to locate the cells that are affected and administer treatment. According to this medical model (a) each cell is genetically programmed to progress according to a given trajectory; (b) diseases are fought via biological defense mechanisms; and (c) when and if the cell is assisted in fighting the disease with appropriate medical treatment, the cell utilizes medication to booster its natural arsenal and then gets back on genetic program. In case of mental health, psychosocial factors seem to play a very important role and psychological health is not as strongly influenced by genetic factors as is physical health. Therefore, as discussed in other books within this series (e.g., Brock, Jimerson, & Hansen, 2006, 2009), when discussing causes for mental health disorders it is imperative to attend to interactions between environment and genetic predisposition.

Again, even though research pinpoints various biochemical and neurophysiological factors in bipolar disorder, there is no biological or medical diagnostic test to reliably identify this disorder. Consequently, treatment protocols are highly dependent upon individual profiles. Multidisciplinary teams from biology, medicine, psychology, and other disciplines are continuously working to learn more about causes, triggers, and correlates of bipolar disorder in youth, find valid and reliable diagnostic tools, and establish empirically validated treatments (e.g., Faust, Walker, & Sands, 2006). The discussion that follows offers a brief review of what is currently

known about the genetic, environmental, and neurobiological factors considered to play a causal role in bipolar disorder (with particular attention to early onset bipolar disorder).

Genetics

It has been suggested that the strongest biological factor to play a causal role in the development of bipolar disorder is genetics (Kato, 2008). Furthermore, the role of genetics may be particularly strong among individuals with early-onset bipolar disorder (Faraone, Glatt, Su, & Tsuang, 2004). Research that has examined the role of genetics in the development of bipolar disorder can be classified as family, twin, and molecular genetic studies.

Family Studies

Among the first studies conducted to establish the heritability of bipolar disorder were family studies. This research examined whether there is an increased incidence of bipolar disorder among the family members of bipolar patients. From their review of this research Althoff, Faraone, Rettew, Morley, and Hudziak's (2005) concluded that the "preponderance of evidence is that adult-onset bipolar disorder has clear familiarity" (p. 599). Further, they conclude that the familiarity of early-onset bipolar disorder may exceed that of adult-onset bipolar disorder. In other words, it is possible that genetics play a greater role in early-onset (vs. adult-onset) bipolar disorder.

Twin Studies

While family studies provide some evidence of the heritability of bipolar disorder, it is important to acknowledge that these findings could be related to a shared environment and not to shared genes. Thus, twin studies have been an important research methodology. Because twins share both a common environment and all (in the case of identical twins) or half (in the case of fraternal twins) of their genes, comparison of these sibling groups can help to determine the relative contribution of genetics and environment. Among adults Tsuang and Faraone's (1990) review suggested 60 % of bipolar disorder variance to be accounted for by genetic factors. However, more recent research has suggested an even more powerful role for genetics in the adult-onset of this disorder (with at least two studies reporting over 85 % of the bipolar disorder variance to be due to genetics; Althoff et al., 2005).

Twin studies of early-onset bipolar disorder are limited. However, Boomsma and colleagues (2006) have suggested that the heritability of early-onset bipolar disorder (as defined by Child Behavior Checklist profiles) increases with age (from 63 % at age 7 to 75 % at age 12). At the same time, this research suggested the environment to become less important as the child ages (or alternatively more important during the formative years of early-onset bipolar disorder).

Molecular Genetic Studies

While family and twin studies (as well as a limited number of adoption studies) have provided powerful evidence that bipolar disorder has a genetic component, they do not identify the specific genes implicated in the development of this disorder. Thus, researchers have employed molecular genetic studies, which have included linkage studies and candidate gene searches.

Linkage studies examine the genetic material of families that include individuals with bipolar disorder. Within these families, DNA sequences (or markers) along different chromosomes are examined for slight differences (or polymorphisms). Researchers then try to find differences that are consistently found among family members who have bipolar disorder, but not among those without the disorder. By determining how close the polymorphism, unique to the bipolar disorder family members are to a specific gene (done via statistical methods), the polymorphism can be “linked” to that gene. Hayden and Nurnberger’s (2006) review suggested the best evidence for such linkages are areas on chromosomes 2p, 4p, 4q, 6q, 8q, 11p, 12q, 13q, 16p, 16q, 18p, 18q, 21a, 22q, and Xq. Study of early-onset bipolar disorder is limited and what research exists is not consistent with the findings of adult-onset research. For example, Faraone and colleagues (2004) found the age of onset of mania to be linked to chromosomes 12p, 14q, and 15q. From this finding Faraone and colleagues concluded “that individuals with an early onset of bipolar disorder are biologically different from those with a typical onset age and clinical presentation” (p. 628).

Candidate gene studies begin with the assumption that certain specific genes are likely to be associated with bipolar disorder. These prior assumptions are typically based upon clinical and empirical evidence (including linkage studies) that a specific gene is associated with the development of specific bipolar symptoms. Hayden and Nurnberger’s (2006) review suggested a role for a number of different candidate genes including those listed in Table 2.1. Overall, findings from genetic and behavioral genetic research suggest that bipolar disorders are caused by many different genes working together. Identifying each one of the genes requires very careful investigations. Still, information about each separate gene contributes only a narrow window of insight into genetic mechanisms behind bipolar disorder.

Table 2.1 Specific genes thought to be associated with bipolar disorder

Gene ^a	Abbreviation ^a	Chromosome location ^a	Function
Catechol- <i>O</i> -methyltransferase	COMT	22q11.21-23	Breaks-down catecholamines and may modify the course of BPD, by increasing predisposition to rapid cycling ^b
Solute carrier family 6 (neurotransmitter, dopamine), member 3	SLC6A3 (AKA DAT)	5p13.3	Removes dopamine from synaptic cleft ^c
5-hydroxytryptamine (serotonin) receptor 4	HTR4	5q32	Modulates the release of various neurotransmitters ^a
Dopamine D4 receptor	DRD4	11p15.5	Mutations in this gene have been associated with various behavioral phenotypes ^a
Dopamine receptor D2	DRD2	11q23	Encodes the D2 subtype of the dopamine receptor, inhibits adenylyl cyclase activity ^a
5-hydroxytryptamine (serotonin) receptor 2A	HTR2A	13q14	A receptor for serotonin ^a
Solute carrier family 6 (neurotransmitter transporter, serotonin), member 4	SLC6A4	17q11.1-12	Encodes a membrane protein that transports serotonin from synaptic spaces into presynaptic neurons. Terminates the action of serotonin and recycles it in a sodium-dependent manner. A repeat length polymorphism in the promoter of this gene has been shown to affect the rate of serotonin uptake and may play a role in depression-susceptibility in people experiencing emotional trauma ^a
D-amino acid oxidase activator/G30 complex	DAOA or G72/G30	13q33	Polymorphisms in this gene have been implicated in susceptibility to schizophrenia and bipolar affective disorder, possibly due to decreased levels of D-serine and decreased NMDA receptor functioning ^a
Disrupted-in-schizophrenia 1	DISC1	1q42.1	This gene is disrupted in a translocation which segregates with schizophrenia and related psychiatric disorders in a large Scottish family ^a
Purinergic receptor P2X, ligand-gated ion channel 7	P2RX7	12q24	An ATP receptor ^a

(continued)

Table 2.1 (continued)

Gene ^a	Abbreviation ^a	Chromosome location ^a	Function
Monoamine oxidase A	MAOA	Xp11.3	Encodes monoamine oxidase A, an enzyme that degrades amine neurotransmitters, such as dopamine, norepinephrine, and serotonin ^a
Brain-derived neurotrophic factor	BDNF	11p13-15	The protein encoded by this gene is a member of the nerve growth factor family. It is induced by cortical neurons, and is necessary for survival of striatal neurons in the brain. This gene may play a role in the in the biology of mood disorders ^a

^aEntrez Gene (<http://www.ncbi.nlm.nih.gov/sites/entrez?Db=gene>)

^bLachman et al. (1996)

^cGreenwood et al. (2001)

Environment

While bipolar disorder appears to have a strong genetic component (McGuffin et al., 2003), it is likely that the environment plays a role (NIMH, 2008) and may interact with genes to cause this disorder (Serretti & Mandelli, 2008). There is emerging evidence that psychosocial stressors may contribute to the onset (and recurrence) of bipolar disorder (Leahy, 2007). For example, in their literature review, Alloy and colleagues (2005) report:

Overall, studies of life events have found that bipolar individuals experience increased stressful events prior to the first onset and recurrences of mood episodes. Moreover, most studies have found that negative life events precede the manic/hypomanic as well as the depressive episodes of bipolar individuals. (p. 1048)

Post and Leverich (2006) have suggested that psychosocial stress plays an important role in the onset (as well as the course) of bipolar disorder. In other words, childhood adversity may be a risk factor that increases the chances of early onset bipolar disorder.

Jones and Bentall's (2008) review of the literature examining the children of bipolar parents reveals that there has been limited study of the relationship between early onset bipolar disorder and negative life events. However, they conclude that given the evidence obtained from the study of adult bipolar disorder suggesting that different events influence manic and depressed episodes and that life events have

consistently been associated with the first onset of this disorder, these environmental variables warrant additional study. The Jones and Bentall review also observed that the family functioning as a risk factor for early onset bipolar disorder has been the subject of limited empirical investigations. Again, however, they conclude that the evidence obtained from the study of adult bipolar disorder suggests that critical comments, hostility, or emotional over-involvement among relatives has been associated with risk of relapse among adults with bipolar disorder; these environmental variables also warrant additional study.

Most recently, the role of stressful life events has been studied among youth already diagnosed with bipolar disorder. Romero and colleagues (2009), in a study of over 400 children and adolescents with bipolar disorder, reported that 20 % had experienced physical and/or sexual abuse. While not associated with an early onset of the disorder, when compared to individuals without bipolar disorder, the presence of child abuse was reported to be associated with a longer duration of bipolar disorder.

Neurobiology

When linking bipolar disorder to brain functioning, contemporary research examines possible abnormalities in (a) brain structure or neuroanatomy (various regions of the brain, such as fronto-limbic regions), and (b) brain chemical agents that regulate its activity (e.g., neurotransmitters) or neurochemistry (e.g., Sublette, Oquendo, & Mann, 2006).

The building blocks of our nervous system are a highly specialized group of cells. Identified as “neurons,” these cells are connected to one another via branches. In between any two connected neurons is a small space—a synapse. Neurons emit neurotransmitters as a chemical message via the synapse so that the next neuron receives the signal by accepting the neurotransmitter. The message is then transmitted in this way from one neuron to the next until it reaches its destination in the brain or any other region of the body. The route of the neurotransmitter in this message delivery is called a neuropathway. There are many different neuropathways that the brain is “wired” with and that we use to function. For example, when we logically solve a problem, it is mainly the neuropathways located in the frontal lobes that are activated. Emitting neurotransmitters into the synapse is the only way in which neurons relay signals. If the neuropathway and/or neurotransmitter release is altered in some way it will effect brain functioning. Many of the functions that are central to bipolar disorder, such as mood regulation and impulse control, are dependent on neuropathways and governed by various neurotransmitters (Lacerda et al., 2004). In fact, many of the symptoms of bipolar disorder have been found to be related to dysfunction of brain circuitry and neurobiological abnormalities (e.g., Chang, Adleman, Wagner, Barnea-Goraly, & Garrett, 2006; Gogtay et al., 2007).

Neuroimaging research is expected to provide insight into neurophysiological correlates or markers for pediatric bipolar disorder.

Brain Structure and Activity

Among the commonly used brain or neuroimaging techniques are Computerized Axial Tomography (CAT) and Magnetic Resonance Imaging (MRI). CAT is similar to digital photography where a series of X-rays or photos are taken to scan the brain and create a three-dimensional image. MRI produces a multitude of digital photos of the brain from different angles to yield a rather precise three-dimensional image of the brain. Research studies that employ CAT and MRI techniques have helped uncover structural changes that are present in the brain of individuals diagnosed with bipolar disorder. Across all age groups, lateral ventricle enlargement and increased rates of deep white matter hyperintensities have been associated with bipolar disorder (Kempton, Geddes, Ettinger, Williams, & Grasby, 2008).¹ Perhaps helping us to understand the different presentations of adult vs. early onset bipolar disorder, a recent meta-analysis found children and adolescents to have significantly smaller amygdalas (located in the medial temporal lobe and a part of the brain that regulates emotional valence) when compared to a control group (a difference that was not found when bipolar adults were compared to controls; Pfeifer, Welge, Strakowski, Adler, & Delbello, 2008).

Gogtay et al. (2007) conducted one of the few dynamic investigations of cortical brain development in early-onset bipolar disorder. Cortical growth was evaluated both before and after onset of first manic episode, allowing researchers to detect changes over time. The changes observed in individuals with bipolar disorder were significantly different from changes observed in individuals with childhood-onset schizophrenia. These findings are significant because it provides a clear basis for differentiating bipolar disorder from schizophrenia. Individuals with schizophrenia demonstrated an overall loss of grey matter volume. In individuals with an early-onset of bipolar disorder, cortical, or grey matter (the clay for neural pathways) growth was asymmetrical with greater mass concentration on the left side. However, these changes were seen only after the onset of first manic episode, not at the beginning of the study. This research provides insight into the deficits in motor inhibition (e.g., Leibenluft et al., 2007), spatial working memory, visual sequencing and scanning, abstract problem solving, and verbal fluency (e.g., Bearden et al., 2007) observed in individuals with bipolar disorder.

It is important to note that, while they help us to understand the possible etiology of bipolar disorder, at this point in time routine neuroimaging should not be used as

¹See Kempton (2008) for the meta-analysis database used in this study.

a diagnostic tool in cases of mood disorders. For example, Serene, Ashrari, Szeszko, and Kumra (2007) reviewed empirical investigations of brain development via neuroimaging and concluded that some of the reported abnormalities found in children diagnosed with mood disorders were also observed in healthy children. A majority of neuroimaging studies tend to be correlational in nature, include heterogeneous cases of bipolar disorder, and only take a snapshot of the individual's functioning. It is a burgeoning area of research and practice that holds great promise, but at present does not offer definitive answers.

Brain Chemistry

In addition to structural differences between relatively healthy and bipolar brains, neurochemical differences have been established. Research has identified several key neurotransmitters that seem to play an important role in bipolar disorder: dopamine (McTavish et al., 2001; Powell, Young, Ong, Caron, & Geyer, 2008; Silverstone, 1985; Yatham et al., 2002), GABA (Benes & Berretta, 2001; Cotter et al., 2002; Fatemi et al., 2005; Sakai et al., 2008), glutamate (Öngür et al., 2008), and norepinephrine and serotonin (Wiste, Arango, Ellis, Mann, & Underwood, 2008). When studying neurochemical functioning of the brain, researchers examine neurotransmitters' chemical variants, locations, and roles. Whether the presence, absence, or change in these chemicals is a cause or outcome of bipolar disorder remains to be determined, but the importance of neurochemicals in bipolar disease is indisputable. The relevancy of these findings to overall brain functioning in bipolar and normal individuals is not yet understood (e.g., Singh, Pfeifer, Barzman, Kowatch, & DelBello, 2007). Psychopharmacological treatment targets these chemical imbalances.

Concluding Comments

In summary, clinical research and practice on bipolar disorder in adults and children pinpoints the need to consider complex multidimensional nature of bipolar disorder. Current data are limited and mostly correlational in nature. At this point in time we can discuss possible triggers and co-occurring changes in bodily functioning, but not the exact *causes* of bipolar disorder. Establishing causal effects will require extensive longitudinal research. Available information suggests that the

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School

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