Prevention of Pediatric Bipolar Disorder

Integration of Neurobiological and Psychosocial Processes

KIKI CHANG, MEGHAN HOWE, KIM GALLELLI, AND DAVID MIKLOWITZ

Pediatric Bipolar Disorders Program, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, California, USA

ABSTRACT: Bipolar disorder (BD) is a prevalent condition in the United States that typically begins before the age of 18 years and is being increasingly recognized in children and adolescents. Despite great efforts in discovering more effective treatments for BD, it remains a difficult-to-treat condition with high morbidity and mortality. Therefore, it appears prudent to focus energies into developing interventions designed to *prevent* individuals from ever fully developing BD. Such interventions early in the development of the illness might prevent inappropriate interventions that may worsen or hasten development of BD, delay the onset of first manic episode, and/or prevent development of full BD. Studies of populations at high-risk for BD development have indicated that children with strong family histories of BD, who are themselves experiencing symptoms of attention-deficit/hyperactive disorder (ADHD) and/or depression or have early mood dysregulation, may be experiencing prodromal states of BD. Understanding the neurobiological and genetic underpinnings that create risk for BD development would help with more accurate identification of this prodromal population, which could then lead to suitable preventative interventions. Such interventions could be pharmacologic or psychosocial in nature. Reductions in stress and increases in coping abilities through psychosocial interventions could decrease the chance of a future manic episode. Similarly, psychotropic medications may decrease negative sequelae of stress and have potential for neuroprotective and neurogenic effects that may contribute to prevention of fully expressed BD. Further research into the biologic and environmental mechanisms of BD development as well as controlled early intervention studies are needed to ameliorate this significant public health problem.

Address for correspondence: Kiki D. Chang, M.D., Stanford University School of Medicine, Division of Child and Adolescent Psychiatry, 401 Quarry Road, Stanford, CA 94305-5540. Voice: 650-725-0956; fax: 650-723-5531.
e-mail: kchang88@stanford.edu

Ann. N.Y. Acad. Sci. 1094: 235–247 (2006).
doi: 10.1196/annals.1376.026

KEYWORDS: **bipolar disorders; children; prevention; neurobiology; genetics**

INTRODUCTION

Bipolar disorder (BD) affects up to 4% of the U.S. population[1] and leads to costs of more than $45 billion per year.[2] A total of 25–50% of individuals with BD attempt suicide at least once, and 8.6–18.9% die by suicide.[3] Suicidal risk appears highest in childhood-onset BD,[4] with nearly one-third of children and adolescents with BD already having had a suicide attempt.[5] Between 15% and 28% of bipolar adults experience illness onset before the age of 13 years, and between 50% and 66% before the age of 19 years.[6–8] The exact prevalence in children is unknown, but estimates range from 420,000–2,072,000 among U.S. children alone.[9] Onset of BD in childhood or adolescence confers a more severe, adverse, and continuously cycling course of illness than adult-onset, typically with more mixed episodes, psychosis, and comorbid disorders.[10] The complexity of early-onset BD, especially given high rates of comorbidity with attention-deficit/hyperactive disorder (ADHD), conduct disorder, anxiety disorders, and substance abuse, usually makes these patients more treatment-refractory than adults with BD.[8,11,12] Thus, pediatric-onset BD patients are often severely derailed in social, academic, and emotional development.

In the last decade, much research has gone into discovering effective pharmaco- and psychotherapies to treat BD in children and adults. However, despite these efforts, BD remains difficult to treat. Furthermore, morbidity and mortality have not appreciably improved over the last 20 years,[13,14] which likely reflects the chronic disabling nature of the disorder and the fact that other than lithium, medications used to treat this disorder have all originally been developed to treat other conditions. Therefore, it appears prudent to focus energies into developing interventions designed to *prevent* individuals from ever fully developing BD. Such interventions early in the development of the illness might prevent inappropriate interventions that may worsen or hasten development of BD, delay the onset of first manic episode, and/or prevent development of full BD.

IDENTIFICATION OF PRODROMAL PEDIATRIC BD

Before intervention studies can take place, methods for detecting a suitable high-risk population must be determined. It is clear that a family history of BD elevates risk for BD.[15] As twin and family studies report a 59-87% heritability of BD, first-degree relatives of probands with BD are at very high risk of BD themselves.[16] Therefore, these relatives are a good starting point for identifying children and adolescents at high-risk for BD development.

High-Risk Studies

Children of parents with BD (bipolar offspring) are a logical population in which to implement preventative interventions. A meta-analysis of studies conducted before 1997 found that offspring of parents with BD were at 2.7 times higher risk for development of any psychiatric disorder and 4 times higher risk for developing a mood disorder than children of parents without psychiatric illness.[17] Recent studies have found that 50–60% of such offspring have some type of psychiatric disorder,[18–20] especially mood, anxiety, and disruptive behavior disorders.[18–21] Rates of BD spectrum disorders in these offspring range from 14–50%, and rates of major depressive disorder (MDD) range from 7 to 43%.[22]

Putative Prodromal BD

Symptom complexes predating the first manic episode can be identified from studies of high-risk samples. The high rate of MDD in bipolar offspring raises the distinct possibility that those children are experiencing an initial bipolar depression, and will experience a manic episode in the near future. In fact, the most reliable symptom complex predating mania has been depression. In a cohort of 642 adults with BD onset before the age of 18 years, approximately 60% reported depression as their initial mood episode.[8] Prospective studies have found high rates (20–30%) of switching to mania in children who initially presented with prepubertal MDD.[23,24] The rate of conversion to BD in depressed children who are offspring of bipolar parents is even greater. In a 5-year prospective study of 129 children of bipolar parents, 12 of the 13 offspring who developed BD had an antecedent depressive episode.[25]

ADHD in bipolar offspring also may be a harbinger of later BD development.[8,18,22,26–28] In recent cross-sectional studies, approximately 27% of bipolar offspring have met criteria for ADHD or significant behavioral or attention problems.[22] This finding, combined with the high comorbidity of ADHD and BD in childhood,[29] family studies,[29,30] and retrospective histories of ADHD predating BD onset,[18,31] supports that ADHD in certain children with strong family histories of BD is a first sign of developing BD.

Given the above epidemiological and phenomenological data, it appears that children with ADHD and/or depression who have strong family histories of BD are at high risk for BD development. The few longitudinal studies published also have supported this hypothesis.[21,32,33] However, it is also likely that not all these children will develop full BD, and that some may never progress to this point. Therefore, diagnostic tools other than symptom complexes and family history would be helpful in diagnosing BD before mania onset. The most logical tools to pursue currently are neurobiological and genetic markers of the disorder.

NEUROBIOLOGICAL MARKERS

Despite this profile of BD prodromes in children, it is far from certain at what rates these children will develop full BD. Furthermore, by the time children present with such symptomatology, it may be relatively late in illness development for ideal intervention as a preventative measure. Therefore, other diagnostic tools, such as biological markers, would be helpful in identifying children at highest risk for BD. Neurobiological markers are a logical choice, but currently there are no neurobiological findings that are pathognomonic of BD. Identification of the brain characteristics most highly associated with BD development, along with the genetic factors that affect their development, could lead to early identification of those at highest risk for BD development and a better understanding of the pathophysiology of BD.

Neuroimaging studies in adults and children with BD have implicated numerous regions of the brain in the pathophysiology of BD, namely regions serving prefrontal-limbic circuitry.[34] Prefrontal areas include dorsolateral prefrontal cortex (DLPFC), medial prefrontal cortex (including anterior cingulate cortex), and ventrolateral (or orbitofrontal) cortex.[35] Subcortical areas include hippocampus, caudate, putamen, thalamus, and amygdala. The amygdala is particularly interesting due to its role in mood and emotion, and consistent findings of decreased amygdalar volume in children with BD.[36–39] However, this finding is not specific to BD[40] and currently cannot be used diagnostically. Nonetheless, prefrontal amygdalar circuits are good candidates for further study in this regard. Other potential tools for marker discovery include magnetic resonance spectroscopy (MRS),[41] fMRI,[42–44] and diffusion tensor imaging (DTI).[45]

GENETIC MARKERS

Genetic markers may also serve to help determine risk for BD as well as age at onset (AAO). It is becoming increasingly clear that BD is a polygenic disorder, with many genetic polymorphisms creating small risk for BD individually, presenting together to generate increased risk for BD.[46,47] These polymorphisms could be used to help quantify risk for BD development.

For example, two potential BD gene candidates code for the serotonin transporter (5-HTT) and for brain-derived neurotrophic growth factor (BDNF). Polymorphisms of these genes have been associated with depression and BD (including early-onset and rapid-cycling varieties).[48–53] However, because these polymorphisms are relatively common in the population, they likely have gross overarching effects on the brain (such as general changes in serotonergic transmission, or varied availability of BDNF), thus creating only small risk for BD by themselves. However, by a summation of various at-risk genes, it is possible that a certain level of quantification for genetic risk of BD can be achieved.

Nonetheless, it is the proteins coded by the genes, which then influence brain functioning, that are relevant to understanding how risk leads to disorder. Thus, it is useful to study the effect of genes on brain structure and function, both in "healthy" individuals as well as those with BD.[54] For example, subjects with compared to those without the short allele of the 5-HTT gene have been found to have increased amygdalar and orbitofrontal activation when watching fearful faces or aversive pictures.[55,56] This finding is interesting in light of the amygdalar abnormalities found in BD, including amygdalar overactivity,[44,57,58] and the association of the short allele with BD.[51]

Finally, AAO genes could also be used to determine risk for early-onset BD specifically. While there has been some progress in this direction,[59] more research is needed. One promising area of research remaining is the possibility of trinucleotide repeat expansion in AAO regions of the chromosome, leading to anticipation of the disorder.[60] Discovery of such phenomena would again help elucidate the degree of urgency needed for intervention in at-risk youth.

EARLY INTERVENTION/NEUROPROTECTION

First applied to seizure disorders, the theory of kindling in affective disorder holds that the combination of psychosocial stress and genetic vulnerability gradually leads to a full mood episode, after which it becomes progressively "easier" to trigger subsequent episodes, until they become spontaneous.[61] Interventions early in the course of kindling may reverse the illness course. For example, rats given repeated subseizure level electrical stimulation to their amygdalae will eventually develop seizures, leading to a spontaneous seizure disorder. However, if the same rat is administered valproate prior to the onset of electrical stimulation, no seizure disorder develops.[62] Thus, if similar interventions are performed early enough in bipolar illness development, it is possible that the full expression of BD could be completely averted.

Medications

Thus, medications have the potential to prevent BD due to antikindling effects. Another mechanism by which they might act is to stimulate healthy neurogenesis. For example, it is becoming clearer that areas in the prefrontal cortex, as well as other limbic areas, suffer neurodegeneration with prolonged bipolar illness.[63–66] Stress from repeated mood episodes has been postulated to be causal to this process.[67,68] leading to less prefrontal mood regulation and greater cycling and treatment resistance.[43] Thus, an intervention that prevents this process or restores healthy neuronal circuits in these regions could have a combined effect on preserving prefrontal function and neuronal integrity and thus prevent or delay future mood episodes.

Mood stabilizers, and to some degree antipsychotics, which are used to treat BD, have been found to have neuroprotective and neurogenic properties. Antikindling (seizure prophylaxis) properties have been described in animals with valproate[69–71] and lamotrigine.[72] Other animal studies have indicated that both valproate and lithium increase brain bcl2 (a neuroprotective protein), and activate protein kinases, which lead to increased neural dendritic growth.[73,74] In humans, lithium may increase gray matter volume,[75] and exposure to lithium or valproate may prevent decreased gray matter volumes in anterior cingulate[76] or amygdala.[36] Both lamotrigine and olanzapine have been reported to lead to increases in prefrontal N-acetylaspartate, a marker of neuronal density and viability.[77,78]

Because of these properties, mood stabilizers and antipsychotics may prove to be effective medications in early intervention/prevention schemas. In one[79] but not another[80] study, valproate was found effective in treating acute mood symptoms in children with subsyndromal BD, considered a group at high risk for BD development. Quetiapine was also effective in treating mood symptoms in a similar population, with some evidence of prefrontal N-acetyl aspartate (NAA) increase as well.[81] However, no longitudinal studies have been conducted to investigate *prevention* of the occurrence of full mania with these types of agents. Clearly, while difficult to conduct, this type of study is paramount for discovering valid options for BD prevention.

Psychotherapy

Psychosocial stressors such as dysfunctional family environments, stressful life events, and ineffective coping strategies interact with genetic predispositions to induce the full expression of BD.[82] The mechanisms by which environmental threats affect the course of BD may involve psychological vulnerability factors (e.g., negative cognitive styles[83,95] or activation of brain circuitry involved in emotional self-regulation.[43] Specific psychotherapeutic interventions targeted at psychosocial risk factors in high-risk individuals may help prevent or delay the onset of BD.

Although requiring more time and effort than psychopharmacology, psychotherapy can be a precise, targeted intervention with sustained effects even after it is completed. Furthermore, whereas treatment with medication may be accompanied by deleterious side effects and cannot specifically treat psychosocial stressors, psychotherapy is a safe modality that can address specific stressors and correct behaviors that lead to mood episodes, such as irregular sleep patterns or medication nonadherence.

Specific psychotherapeutic interventions for high-risk individuals should ameliorate psychosocial vulnerability factors and enhance the at-risk person's coping ability to prevent or delay the onset of BD. Recent research has suggested that family environments characterized by high expressed emotion (EE)

attitudes[84] or low maternal warmth[85] are associated with poorer outcomes of pediatric BD over 2–4 year follow-ups. In a sample of children of mothers with BD, maternal negativity contributed to risk for offspring BD development through its association with impaired frontal lobe functioning as measured by the Wisconsin Card Sorting Task.[86] Thus, maternal relationships in the context of family environment is one area to target for BD prevention.

Other strategies for reducing the likelihood of developing full BD can be inferred from data supporting the efficacy of psychosocial interventions for the prevention of relapse of mood episodes in patients already with BD.[84] It is currently recommended that patients with BD receive both medication and adjunct psychotherapy.[87,88] Thus, although extensive advances have been made in the pharmacological treatment of BD, it has become apparent that medication alone is not enough for the management of this chronic, recurrent illness. Medication noncompliance, lack of ability to recognize symptom exacerbation, and the inability to cope with stressors that precipitate illness episodes are problematic for many individuals with BD and are often related to illness relapse.[89,90]

Thus, potential psychotherapeutic interventions geared toward prevention of worsening to full BD could be based on current techniques geared toward prevention of mood episode relapse in patients already with full BD. Family focused therapy (FFT) has been found effective for adolescents with BD,[91] and would be a good candidate for modification for a high-risk population. Other promising candidates would be cognitive behavioral therapy (CBT)-type therapies[92] or more behaviorally oriented therapies for younger children,[93] both found useful in pediatric BD. Due to the highly familial nature of the disorder, a unique factor of these therapies could be the treatment of family members with BD-spectrum disorders, thus decreasing EE and stress in the family and theoretically decreasing BD risk in the at-risk family member(s). Such controlled studies in at-risk populations are clearly warranted.

CONCLUSIONS

It is the hope that a combination of brain and genetic markers, symptom complexes, and family history can lead to more accurate diagnoses of prodromal BD. Then early intervention could occur in a population at clear, perhaps even quantifiable, risk for BD development. Promising areas for further exploration of brain markers for this purpose include prefrontal-limbic areas, especially the amygdala. However, more understanding about how alterations in the relevant circuitry lead to bipolar symptoms would likely reveal markers more specific to BD than morphometric or neurochemical abnormalities by themselves. Furthermore, the neurobiological underpinnings of circadian rhythm disruption, fairly specific to BD, are vastly understudied. The search for AAO genes as well as additional genes that are linked to BD will help the

early identification/prevention cause. Early-onset cohorts particularly should be studied to generate these candidate genes for prevention purposes.[94]

Intervention studies should not wait until these markers are definitively established, as the burden of BD is too great.[9] The neuroprotective and neurogenic properties of psychotropic medications are exciting: in the future the grim sentence of lifelong medications for patients with BD may be lifted if intervention with these agents, along with appropriate psychotherapies, is instituted early enough in the disorder evolution to halt the kindling process. A short, corrective course of these medications at the "right" time could also prevent prolonged exposure to them later in life. Controlled, long-term intervention studies in high-risk populations should therefore include biological and genetic assessment to more precisely match intervention with underlying neurobiology and genetic predisposition and to study effects of these interventions on brain function. Implementing psychotherapeutic and psychopharmacologic interventions that are placed upon such a neurobiological and genetic framework would be a powerful step toward the eventual eradication of this disorder.

REFERENCES

1. KESSLER, R.C. *et al*. 2005. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch. Gen. Psychiatry **62:** 593–602.
2. KLEINMAN, L. *et al*. 2003. Costs of bipolar disorder. Pharmacoeconomics **21:** 601–622.
3. CHEN, Y.W. & S.C. DILSAVER. 1996. Lifetime rates of suicide attempts among subjects with bipolar and unipolar disorders relative to subjects with other Axis I disorders. Biol. Psychiatry **39:** 896–899.
4. CARTER, T.D. *et al*. 2003. Early age at onset as a risk factor for poor outcome of bipolar disorder. J. Psychiatr. Res. **37:** 297–303.
5. GOLDSTEIN, T.R. *et al*. 2005. History of suicide attempts in pediatric bipolar disorder: factors associated with increased risk. Bipolar Disord. **7:** 525–535.
6. LEVERICH, G.S. *et al*. 2003. Factors associated with suicide attempts in 648 patients with bipolar disorder in the Stanley Foundation Bipolar Network. J. Clin. Psychiatry **64:** 506–515.
7. LEVERICH, G.S. *et al*. 2002. Early physical and sexual abuse associated with an adverse course of bipolar illness. Biol. Psychiatry **51:** 288–297.
8. PERLIS, R.H. *et al*. 2004. Long-term implications of early onset in bipolar disorder: data from the first 1000 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). Biol. Psychiatry **55:** 875–881.
9. POST, R.M. & R.A. KOWATCH. 2006. The health care crisis of childhood-onset bipolar illness: some recommendations for its amelioration. J. Clin. Psychiatry **67:** 115–125.
10. GELLER, B. *et al*. 2002. Two-year prospective follow-up of children with a prepubertal and early adolescent bipolar disorder phenotype. Am. J. Psychiatry **159:** 927–933.

11. BIEDERMAN, J. *et al*. 2003. Current concepts in the validity, diagnosis and treatment of paediatric bipolar disorder. Int. J. Neuropsychopharmacol. **6:** 293–300.
12. BIEDERMAN, J. *et al*. 2003. Can a subtype of conduct disorder linked to bipolar disorder be identified? Integration of findings from the Massachusetts General Hospital Pediatric Psychopharmacology Research Program. Biol. Psychiatry **53:** 952–960.
13. ANGST, J. *et al*. 2005. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch. Suicide Res. **9:** 279–300.
14. KASPER, S.F. 2004. Living with bipolar disorder. Expert Rev. Neurother. **4:** S9–S15.
15. FARAONE, S.V. & M.T. TSUANG. 2003. Heterogeneity and the genetics of bipolar disorder. Am. J. Med. Genet. C Semin. Med. Genet. **123:** 1–9.
16. SMOLLER, J.W. & C.T. FINN. 2003. Family, twin, and adoption studies of bipolar disorder. Am. J. Med. Genet. C Semin. Med. Genet. **123:** 48–58.
17. LAPALME, M., S. HODGINS & C. LAROCHE. 1997. Children of parents with bipolar disorder: a metaanalysis of risk for mental disorders. Can. J. Psychiatry **42:** 623–631.
18. CHANG, K.D., H. STEINER & T.A. KETTER. 2000. Psychiatric phenomenology of child and adolescent bipolar offspring. J. Am. Acad. Child Adolesc. Psychiatry **39:** 453–460.
19. CHANG, K. *et al*. 2003. Bipolar offspring: a window into bipolar disorder evolution. Biol. Psychiatry **53:** 945–951.
20. WALS, M. *et al*. 2001. Prevalence of psychopathology in children of a bipolar parent. J. Am. Acad. Child Adolesc. Psychiatry **40:** 1094–1102.
21. CARLSON, G.A. & S. WEINTRAUB. 1993. Childhood behavior problems and bipolar disorder—relationship or coincidence? J. Affect. Disord. **28:** 143–153.
22. CHANG, K.D. & H. STEINER. 2003. Offspring studies in child and early adolescent bipolar disorder. *In* Bipolar Disorder in Childhood and Early Adolescence. B. Geller & M. DelBello, Eds.: 107–129. The Guilford Press. New York.
23. GELLER, B., L.W. FOX & K.A. CLARK. 1994. Rate and predictors of prepubertal bipolarity during follow-up of 6- to 12-year-old depressed children [see comments]. J. Am. Acad. Child Adolesc. Psychiatry **33:** 461–468.
24. GELLER, B. *et al*. 2001. Adult psychosocial outcome of prepubertal major depressive disorder. J. Am. Acad. Child Adolesc. Psychiatry **40:** 673–677.
25. HILLEGERS, M.H. *et al*. 2005. Five-year prospective outcome of psychopathology in the adolescent offspring of bipolar parents. Bipolar Disord. **7:** 344–350.
26. EGELAND, J.A. *et al*. 2000. Prodromal symptoms before onset of manic-depressive disorder suggested by first hospital admission histories. J. Am. Acad. Child Adolesc. Psychiatry **39:** 1245–1252.
27. FERGUS, E.L. *et al*. 2003. Is there progression from irritability/dyscontrol to major depressive and manic symptoms? A retrospective community survey of parents of bipolar children. J. Affect. Disord. **77:** 71–78.
28. LISH, J.D. *et al*. 1994. The National Depressive and Manic-depressive Association (DMDA) survey of bipolar members. J. Affect. Disord. **31:** 281–294.
29. FARAONE, S.V. *et al*. 1997. Is comorbidity with ADHD a marker for juvenile-onset mania? J. Am. Acad. Child Adolesc. Psychiatry **36:** 1046–1055.
30. FARAONE, S.V. *et al*. 1997. Attention-deficit hyperactivity disorder with bipolar disorder: a familial subtype? J. Am. Acad. Child Adolesc. Psychiatry **36:** 1378–1387; discussion 1387–1390.

31. SACHS, G.S. *et al*. 2000. Comorbidity of attention deficit hyperactivity disorder with early- and late-onset bipolar disorder. Am. J. Psychiatry **157:** 466–468.
32. EGELAND, J.A. *et al*. 2003. Prospective study of prodromal features for bipolarity in well Amish children. J. Am. Acad. Child Adolesc. Psychiatry **42:** 786–796.
33. HODGINS, S. *et al*. 2002. Children of parents with bipolar disorder: a population at high risk for major affective disorders. *In* Child and Adolescent Psychiatric Clinics of North America, Vol. 11. G.A. Carlson & J.H. Kashani, Eds.: 533–554. W.B. Saunders Co. Philadelphia, PA.
34. STRAKOWSKI, S.M. *et al*. 2000. Neuroimaging in bipolar disorder. Bipolar Disord. **2:** 148–164.
35. STRAKOWSKI, S.M., M.P. DELBELLO & C.M. ADLER. 2005. The functional neuroanatomy of bipolar disorder: a review of neuroimaging findings. Mol. Psychiatry **10:** 105–116.
36. CHANG, K. *et al*. 2005. Reduced amygdalar gray matter volume in familial pediatric bipolar disorder. J. Am. Acad. Child Adolesc. Psychiatry **44:** 565–573.
37. DELBELLO, M.P. *et al*. 2004. Magnetic resonance imaging analysis of amygdala and other subcortical brain regions in adolescents with bipolar disorder. Bipolar Disord. **6:** 43–52.
38. DICKSTEIN, D.P. *et al*. 2005. Frontotemporal alterations in pediatric bipolar disorder: results of a voxel-based morphometry study. Arch. Gen. Psychiatry **62:** 734–741.
39. CHEN, B.K. *et al*. 2004. Cross-sectional study of abnormal amygdala development in adolescents and young adults with bipolar disorder. Biol. Psychiatry **56:** 399–405.
40. DELBELLO, M. & K. CHANG. 2005. Bipolar disorder in children and adolescents—are we approaching the final frontier? Bipolar Disord. **7:** 479–482.
41. ADLEMAN, N.E., N. BARNEA-GORALY & K.D. CHANG. 2004. Review of magnetic resonance imaging and spectroscopy studies in children with bipolar disorder. Expert Rev. Neurother. **4:** 69–77.
42. BLUMBERG, H.P. *et al*. 2003. Frontostriatal abnormalities in adolescents with bipolar disorder: preliminary observations from functional MRI. Am. J. Psychiatry **160:** 1345–1347.
43. CHANG, K. *et al*. 2004. Anomalous prefrontal-subcortical activation in familial pediatric bipolar disorder: a functional magnetic resonance imaging investigation. Arch. Gen. Psychiatry **61:** 781–792.
44. RICH, B.A. *et al*. 2006. Limbic hyperactivation during processing of neutral facial expressions in children with bipolar disorder. Proc. Natl. Acad. Sci. USA **103:** 8900–8905.
45. ADLER, C.M. *et al*. 2006. Evidence of white matter pathology in bipolar disorder adolescents experiencing their first episode of mania: a diffusion tensor imaging study. Am. J. Psychiatry **163:** 322–324.
46. SCHULZE, T.G. & F.J. MCMAHON. 2003. Genetic linkage and association studies in bipolar affective disorder: a time for optimism. Am. J. Med. Genet. C Semin Med. Genet. **123:** 36–47.
47. TSUANG, M.T., L. TAYLOR & S.V. FARAONE. 2004. An overview of the genetics of psychotic mood disorders. J. Psychiatr. Res. **38:** 3–15.
48. CASPI, A. *et al*. 2003. Influence of life stress on depression: moderation by a polymorphism in the 5-HTT gene. Science **301:** 386–389.
49. GELLER, B. *et al*. 2004. Linkage disequilibrium of the brain-derived neurotrophic factor Val66Met polymorphism in children with a prepubertal and early adolescent bipolar disorder phenotype. Am. J. Psychiatry **161:** 1698–1700.

50. NEVES-PEREIRA, M. *et al*. 2002. The brain-derived neurotrophic factor gene confers susceptibility to bipolar disorder: evidence from a family-based association study. Am. J. Hum. Genet. **71:** 651–655.
51. LASKY-SU, J.A. *et al*. 2004. Meta-analysis of the association between two polymorphisms in the serotonin transporter gene and affective disorders. Am. J. Med. Genet. B. Neuropsychiatr. Genet. **133:** 110–115.
52. LOHOFF, F.W. *et al*. 2005. Confirmation of association between the Val66Met polymorphism in the brain-derived neurotrophic factor (BDNF) gene and bipolar I disorder. Am. J. Med. Genet. B Neuropsychiatr. Genet. **139:** 51–53.
53. GREEN, E.K. *et al*. 2006. Genetic variation of brain-derived neurotrophic factor (BDNF) in bipolar disorder: case-control study of over 3000 individuals from the UK. Br. J. Psychiatry **188:** 21–25.
54. HARIRI, A.R. & D.R. WEINBERGER. 2003. Functional neuroimaging of genetic variation in serotonergic neurotransmission. Genes Brain. Behav. **2:** 341–349.
55. HARIRI, A.R. *et al*. 2002. Serotonin transporter genetic variation and the response of the human amygdala. Science **297:** 400–403.
56. HEINZ, A. *et al*. 2005. Amygdala-prefrontal coupling depends on a genetic variation of the serotonin transporter. Nat. Neurosci. **8:** 20–21.
57. CHEN, C.H. *et al*. 2006. Explicit and implicit facial affect recognition in manic and depressed states of bipolar disorder: a functional magnetic resonance imaging study. Biol. Psychiatry **59:** 31–39.
58. YURGELUN-TODD, D.A. *et al*. 2000. fMRI during affect discrimination in bipolar affective disorder. Bipolar Disord. **2:** 237–248.
59. FARAONE, S.V. *et al*. 2004. Three potential susceptibility loci shown by a genome-wide scan for regions influencing the age at onset of mania. Am. J. Psychiatry **161:** 625–630.
60. O'DONOVAN, M., I. JONES & N. CRADDOCK. 2003. Anticipation and repeat expansion in bipolar disorder. Am. J. Med. Genet. C Semin. Med. Genet. **123:** 10–17.
61. POST, R.M. 1992. Transduction of psychosocial stress into the neurobiology of recurrent affective disorder. Am. J. Psychiatry **149:** 999–1010.
62. POST, R.M. 2002. Do the epilepsies, pain syndromes, and affective disorders share common kindling-like mechanisms? Epilepsy Res. **50:** 203–219.
63. MANJI, H.K. & R.S. DUMAN. 2001. Impairments of neuroplasticity and cellular resilience in severe mood disorders: implications for the development of novel therapeutics. Psychopharmacol. Bull. **35:** 5–49.
64. GALLELLI, K.A. *et al*. 2005. N-acetylaspartate levels in bipolar offspring with and at high-risk for bipolar disorder. Bipolar Disord. **7:** 589–597.
65. RAJKOWSKA, G., A. HALARIS & L.D. SELEMON. 2001. Reductions in neuronal and glial density characterize the dorsolateral prefrontal cortex in bipolar disorder. Biol. Psychiatry **49:** 741–752.
66. STRAKOWSKI, S.M. *et al*. 2002. Ventricular and periventricular structural volumes in first- versus multiple-episode bipolar disorder. Am. J. Psychiatry **159:** 1841–1847.
67. HASHIMOTO, K., E. SHIMIZU & M. IYO. 2004. Critical role of brain-derived neurotrophic factor in mood disorders. Brain Res. Brain Res. Rev. **45:** 104–114.
68. RAJKOWSKA, G. 2000. Postmortem studies in mood disorders indicate altered numbers of neurons and glial cells. Biol. Psychiatry **48:** 766–777.
69. LOSCHER, W. *et al*. 1989. Valproic acid in amygdala-kindled rats: alterations in anticonvulsant efficacy, adverse effects and drug and metabolite levels in various brain regions during chronic treatment. J. Pharmacol. Exp. Ther. **250:** 1067–1078.

70. POST, R.M. & S.R. WEISS. 1996. A speculative model of affective illness cyclicity based on patterns of drug tolerance observed in amygdala-kindled seizures. Mol. Neurobiol. **13:** 33–60.
71. SILVER, J.M., C. SHIN & J.O. MCNAMARA. 1991. Antiepileptogenic effects of conventional anticonvulsants in the kindling model of epilespy. Ann. Neurol. **29:** 356–363.
72. STRATTON, S.C. *et al*. 2003. Effects of lamotrigine and levetiracetam on seizure development in a rat amygdala kindling model. Epilepsy Res. **53:** 95–106.
73. MANJI, H.K. & R.H. LENOX. 1999. Ziskind-Somerfeld Research Award. Protein kinase C signaling in the brain: molecular transduction of mood stabilization in the treatment of manic-depressive illness. Biol. Psychiatry **46:** 1328–1351.
74. MANJI, H.K., G.J. MOORE & G. CHEN. 2000. Clinical and preclinical evidence for the neurotrophic effects of mood stabilizers: implications for the pathophysiology and treatment of manic-depressive illness. Biol. Psychiatry **48:** 740–754.
75. MOORE, G.J. *et al*. 2000. Lithium-induced increase in human brain grey matter. Lancet **356:** 1241–1242.
76. DREVETS, W.C. *et al*. 1997. Subgenual prefrontal cortex abnormalities in mood disorders. Nature **386:** 824–827.
77. CHANG, K. *et al*. 2005. Prefrontal neurometabolite changes following lamotrigine treatment in adolescents with bipolar depression. 44th Annual Meeting of the American College of Neuropsychopharmacology, Dec 11–15, Waikoloa, HI, Poster.
78. DELBELLO, M.P. *et al*. 2006. Neurochemical effects of olanzapine in first-hospitalization manic adolescents: a proton magnetic resonance spectroscopy study. Neuropsychopharmacology **31:** 1264–1273.
79. CHANG, K.D. *et al*. 2003. Divalproex monotherapy in the treatment of bipolar offspring with mood and behavioral disorders and at least mild affective symptoms. J. Clin. Psychiatry **64:** 936–942.
80. FINDLING, R.L. *et al*. 2000. The rationale, design, and progress of two novel maintenance treatment studies in pediatric bipolarity. Acta. Neuropsychiatrica **12:** 136–138.
81. DELBELLO, M. 2006. Neuropharmacology of adolescents at risk for bipolar disorder. 5th Annual NIMH Pediatric Bipolar Disorder Conference. Chicago.
82. POST, R.M. *et al*. 2001. Developmental vulnerabilities to the onset and course of bipolar disorder. Dev. Psychopathol. **13:** 581–598.
83. ALLOY, L.B. *et al*. 1999. Depressogenic cognitive styles: predictive validity, information processing and personality characteristics, and developmental origins. Behav. Res. Ther. **37:** 503–531.
84. MIKLOWITZ, D. J. 2006. A review of evidence-based psychosocial interventions for bipolar disorder. J. Clin. Psychiatry **67**(Suppl. 11)**:** 28–33.
85. GELLER, B. *et al*. 2004. Four-year prospective outcome and natural history of mania in children with a prepubertal and early adolescent bipolar disorder phenotype. Arch. Gen. Psychiatry **61:** 459–467.
86. MEYER, S.E. *et al*. 2006. A prospective high-risk study of the association among maternal negativity, apparent frontal lobe dysfunction, and the development of bipolar disorder. Dev. Psychopathol. **18:** 573–589.
87. KELLER, M.B. 2004. Improving the course of illness and promoting continuation of treatment of bipolar disorder. J. Clin. Psychiatry **15**(Suppl. 65): 10–14.
88. KOWATCH, R.A. *et al*. 2005. Treatment guidelines for children and adolescents with bipolar disorder. J. Am. Acad. Child Adolesc. Psychiatry **44:** 213–235.

89. MIKLOWITZ, D.J. *et al*. 2000. Family-focused treatment of bipolar disorder: 1-year effects of a psychoeducational program in conjunction with pharmacotherapy. Biol. Psychiatry **48:** 582–592.
90. VIETA, E. & F. COLOM. 2004. Psychological interventions in bipolar disorder: from wishful thinking to an evidence-based approach. Acta. Psychiatr. Scand. Suppl. 34–38.
91. MIKLOWITZ, D.J. *et al*. 2004. Family-focused treatment for adolescents with bipolar disorder. J. Affect. Disord. **82**(Suppl. 1): S113–S128.
92. PAVULURI, M.N. *et al*. 2004. Child- and family-focused cognitive-behavioral therapy for pediatric bipolar disorder: development and preliminary results. J. Am. Acad. Child Adolesc. Psychiatry **43:** 528–537.
93. FRISTAD, M.A., S.M. GAVAZZI & B. MACKINAW-KOONS. 2003. Family psychoeducation: an adjunctive intervention for children with bipolar disorder. Biol. Psychiatry **53:** 1000–1008.
94. ALTHOFF, R.R. *et al*. 2005. Family, twin, adoption, and molecular genetic studies of juvenile bipolar disorder. Bipolar Disord. **7:** 598–609.
95. MIKLOWITZ, D.J. & S.L. JOHNSON. 2006. The psychopathology and treatment of bipolar disorder. Annual Review of Clinical Psychology **2:** 199–235.