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Advances in bipolar disorder: selected sessions from the 2011 International Conference on Bipolar Disorder

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Recently, the 9th International Conference on Bipolar Disorder (ICBD) took place in Pittsburgh, PA, June 9–11, 2011. The conference focused on a number of important issues concerning the diagnosis of bipolar disorders across the life span, advances in neuroscience, treatment strategies for bipolar disorders, early intervention, and medical comorbidity. Several of these topics were discussed in four plenary sessions. This meeting report describes the major points of each of these sessions and included (1) strategies for moving biology forward; (2) bipolar disorder and the forthcoming new DSM-5 nomenclature; (3) management of bipolar disorders—both theory and intervention, with an emphasis on the medical comorbidities; and, (4) a review of several key task force reports commissioned by the International Society for Bipolar Disorder (ISBD).

Keywords: bipolar disorders; medical comorbidity; neuroscience; diagnosis

Session on strategies for moving biology forward

Overview

The aim of the session "Strategies for Moving Biology Forward," chaired by Marion Leboyer (Universite Paris XII), was to investigate new disease mechanisms such as immune–inflammatory markers and oxidative stress, while describing the utility of tools such as transcriptomics and multiomic profiling. Genomics has already pointed to diverse molecular pathways that confer risk to bipolar disorder, though not to the anticipated extent. Etienne Sibille described how he is developing methods to integrate results and potentially synergize the analysis of the Genome-wide Association Study (GWA) studies and transcriptomic studies. Coregulated RNA transcripts have been shown to identify coherent gene modules with shared functions, consequently, it has been hypothesized that the coregulated gene modules that are enriched in genes associated with GWA results may identify relevant biological pathways to explore the underlying mechanisms of bipolar disorder. Robert Yolken and Faith Dickerson have shown that acute mania was associated with evidence of immune activation by: (1) elevated levels of cytokines, such as TNF-α; (2) inflammatory macromolecules, such as C-reactive protein (CRP); (3) antibodies to infectious agents, such as retroviruses; (4) antibodies to food antigens, such as gliadin; and (5) antibodies to brain proteins, such as the NR-2 peptide of the NMDA receptor. In many cases, the

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levels of these biomarkers are elevated during acute mania and are decreased six months later. Ongoing research should lead to the identification of a biological "signature" of mania, offering potential tools both for diagnosis of acute mania and for prediction of illness course, and hope for new therapies. Medications directed at the modulation of the immune response may form the basis of a new therapeutic armamentarium for the prevention and treatment of this disorder. Trevor Young presented work in the field of mitochondrial dysfunction and energy metabolism in bipolar disorder. Data clearly show that oxidative damage is present in the postsynaptic membranes and also found in the periphery. Indeed, several studies report increased oxidative stress in serum and plasma of bipolar patients. From a therapeutic perspective, this pathway may be of great importance as several mood stabilizers have antioxidant properties. The conclusion of this session is that studying genetic, immunoinflammation, and mitochondrial dysfunction will be very helpful to better understand the pathophysiology of bipolar disorder.

Genome-wide association studies

Etienne Sibille (University of Pittsburgh) opened this session and described a series of fascinating studies. Ranscriptome (the set of all expressed genes in a tissue sample) and genome-wide association (GWA) studies have separately provided clues to mechanisms of neuropsychiatric disorders, although not to the anticipated extent. Transcriptome studies mostly focus on changes in gene expression in disease states (*altered expression*), but also provide unique opportunities for assessing the less-investigated changes in the coordinated function of multiple genes (*altered coexpression*). Moreover, results from these large-scale investigations of changes in gene function are poised to interact with GWA studies of structural changes in genes and regulatory regions (DNA variant). Methods for integrating these approaches are now being developed.

Gene arrays allow for the unbiased quantification of expression (mRNA transcript levels) for 10,000 to 20,000 genes simultaneously (see Fig. 1A). Since gene transcript levels represent the integrated output of many regulatory pathways, the study of all expressed genes provides an indirect snapshot of cellular function under diverse conditions. For instance, using postmortem brain samples, this "reverse engineering" approach has implicated mitochondrial dysfunction and immune/inflammation-related changes in bipolar subjects.[1–3] However, current studies are still very few, were performed in heterogeneous cohorts, and utilized early and rudimentary versions of gene arrays. Moreover, gene array studies are subjects to similar limitations as GWA studies, in that large number of genes are tested ($n = 20$–$40{,}000$) in few subjects ($n = 10$–100). Typically, results identify 1–10% of genes affected in the illness, are characterized by very high rates of false discovery, and often do not properly account for numerous clinical (e.g., drug exposure, subtypes, duration), demographic (age, sex, race), technical parameters (RNA integrity, brain pH, postmortem interval for brain collection), or other potential cosegregating unknown cohort specificities. Conditions of postmortem brain collection also preclude the reliable identification of acute state-dependent gene changes, but are appropriate for investigating stable long-term disease-related homeostatic adaptations.[4]

Transcriptomics

A notable derivative and less investigated aspect of transcriptome studies is the development of gene coexpression studies. Here, two genes are defined as *coexpressed* in a dataset if their patterns of expression are correlated across samples (see Fig. 1B). Coexpression has been shown to reflect shared function between these genes, and may arise through multiple biological pathways, including cellular coexpression and common regulatory pathways (e.g., hormone signaling, transcription factors).[5,6] Hence, coexpression links have been used to build gene networks, and to identify communities, or modules, of genes with shared functions (see Fig. 1B).[7,8] Notably, by incorporating multiple interactions among large number of genes, the study of gene coexpression networks provides one solution to tackle the complexity of biological changes occurring in complex polygenic disorders.[5] Indeed, the information content of a large-scale gene network could be compared to the operation of a symphonic orchestra of many hundreds of instruments, where the intrinsic balance (coexpression) between instruments (genes) provide harmonious (homeostatic) function.[9] Efforts from our research team has demonstrated that brain gene coexpression networks assemble into small-world and scale-free networks,[10] an efficient

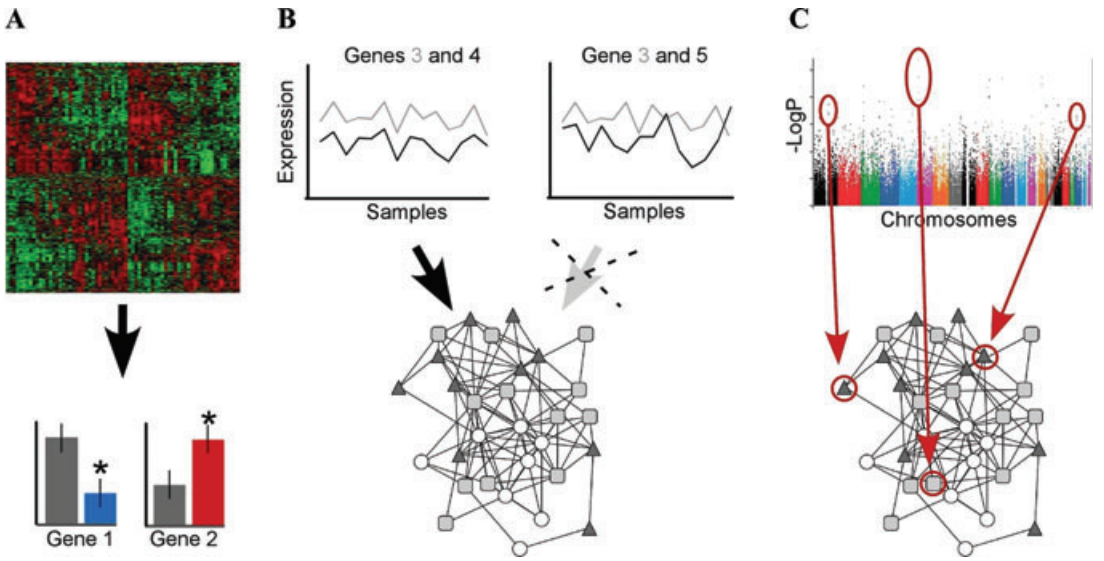

Figure 1. (A) Altered gene expression. Large-scale gene arrays simultaneously investigate expression levels of thousands of genes (top) and seek changes in gene transcript levels between conditions (bottom). (B) Gene coexpression. (top) Genes 3 and 4 display correlated patterns of expression across samples (X axis) between two conditions (gray and black lines). This relationship is quantified by Pearson correlation and provides a link in the gene coexpression network (bottom). Genes 3 and 5 are not coexpressed and do not contribute to the network. Nodes (genes) of different colors and shapes are associated with different cellular functions.[5,119] (C) Synergizing GWA and transcriptome studies. Genes associated with candidate DNA variants, as identified by GWA Manhattan plots (top), are overlaid onto gene coexpression networks (bottom). Gene coexpression networks that are enriched in GWA-associated genes are hypothesized to represent candidate biological systems for disease mechanisms.

network topology that is often observed in biological systems, but also in communication and social networks.[9] Interestingly, our initial study suggests that the structure of brain gene coexpression networks is largely resilient to changes occurring in neuropsychiatric disorders (major depression, bipolar depression, and schizophrenia), and instead points to a peripheral network localization of differentially-expressed genes.[10] This is in striking contrast to cancer- and other systemic illness-related networks, where affected genes tend to display a "disease/lethality–network centrality" relationship.[11] This contrast may relate to the difficulty in identifying silver-bullet types of drugs in neuropsychiatry, since affected genes may attend to control biological gene networks from the periphery, rather than through central gene hubs.[10]

Based on the assumptions that (1) hits on different components of a biological pathway may lead to the same disease phenotype, even in the absence of common changes across subjects, and (2) that DNA genetic polymorphisms and gene mRNA transcript levels represent independent and complementary measures of gene structure and function, we have hypothesized that modules of coexpressed genes, which are enriched in genes associated with GWA-identified polymorphisms, may represent candidate biological pathways for recruitment in mechanisms of disease (see Fig. 1C). To address this question, our approach has been to identify conserved and robust gene modules based on multiple and extensive transcriptome studies in the human brain and to overlay onto those modules, genes that are located nearby DNA polymorphisms associated with neuropsychiatric disorders, as identified by GWA studies. Current efforts are addressing the difficulties in combining heterogeneous studies and the statistical and analytical challenges that emerge from integrating multiple large-scale approaches (transcriptome, coexpression network, and GWA).

In summary, the potential of transcriptome studies for unbiased novel discovery and for investigating basic pathological changes beyond the usual suspects is vast, but not yet realized in neuropsychiatry. Early results from transcriptome studies of altered gene expression in bipolar disorders and other major mental illnesses are promising, but results need to be replicated across multiple

cohorts and research groups. More studies are needed using updated genetic information and technological platforms. Shared access to the raw data is also necessary, as the next generation of transcriptome studies will need to apply novel statistical methods for within-study parameter integration and for across-study meta-analyses, including permutation-based methods and accurate control of false discovery. Currently, the study of gene coexpression networks in neuropsychiatric disorders is still in its infancy, but the field will benefit from applying network methodologies developed for investigating other complex biological systems, including development, cancer, and brain functional activity. Finally, concepts and methods for integrating functional (transcriptome) and structural (DNA polymorphism GWA) studies of the molecular bases of complex neuropsychiatric disorders need to be developed to harness the potential of systematic large-scale molecular and genetic investigations of the brain.

Immune–inflammatory markers

Robert Yolken (Johns Hopkins University) and Faith Dickerson (Sheppard Pratt Health System) then described some of their new work. Mania is an abnormal mood state, and the defining characteristic of bipolar disorder in which the etiology is unknown. Immunological abnormalities have been identified which may contribute to the pathophysiology of mania as well as to bipolar disorder more broadly.[12–16] Such factors may help explain the marked fluctuations in mood symptoms, which are the hallmark of the disorder.

In a previous study, they examined the level of CRP, a nonspecific marker of inflammation in individuals with bipolar disorder.[17] CRP is a pentameric protein that is generated in the liver and secreted in the blood. The measurement of CRP in the blood provides a reliable marker of chronic inflammation caused by infectious and other inflammatory agents. We measured the level of CRP in $N = 122$ outpatients with bipolar disorder and $N = 165$ control individuals and evaluated the symptom severity of the bipolar disorder patients. Within the bipolar disorder sample, CRP was significantly associated with the Young Mania Rating Scale (YMRS)[18] score and in a multivariate analysis, CRP was the only independent predictor of YMRS score. The CRP levels of the $n = 41$ individuals with YMRS > 6 were significantly greater than the levels of the $n = 81$ individuals with YMRS $\leq$, 6. The CRP levels of the group with YMRS > 6 were also significantly greater than the levels of the control group while the CRP levels of the group with YMRS ≤ 6 did not differ from that of controls.

Based on the results of this cross sectional study, they undertook a longitudinal study of individuals hospitalized for symptoms of acute mania. Our aim was to measure inflammatory markers in acute mania and to determine changes over time in these markers and also to determine the correlation of markers with clinical outcome, whether or not persons were rehospitalized for a new illness episode in the six-month follow-up period. From blood samples we measured inflammatory markers including antibodies to intestinal antigens, antibodies to neuroreceptors, antibodies to endogenous retroviruses, and cytokines. The sample of $N = 60$ participants had a mean age of 35.4 (SD $= 12.9$) years and was 30% male and 67% Caucasian. The diagnoses of study participants were divided among bipolar disorder, most recent episode manic (55%), most recent episode mixed (34%), and schizoaffective disorder, current manic episode (11%). The mean YMRS score at the time of evaluation during the hospital stay was 18.7 (SD $= 8.6$) and the Positive and Negative Syndrome Scale total score[19] was 75.2 (SD $= 11.7$). For most study participants, blood samples were measured at three time points: the day of hospital admission from archived samples from the medical admission work-up ($n = 44$); the day of evaluation for the current study, on average 3–5 days following hospital admission ($n = 60$); and at a planned six month follow-up ($n = 39$).

Results of the longitudinal study show that patients hospitalized with mania had increased levels of immune markers that were lower six months later. Some of the markers appear to be mania specific. Some of the markers were associated with clinical outcome, whether or not patients were rehospitalized for a new illness episode during the follow-up period.

The results of these studies are consistent with a body of literature suggesting that acute episodes of mania are associated with evidence of immune activation. The pathways, which are suggested to be involved, are shown in Figure 2. The literature indicates an association between mania and elevated levels of cytokines including interferon γ,

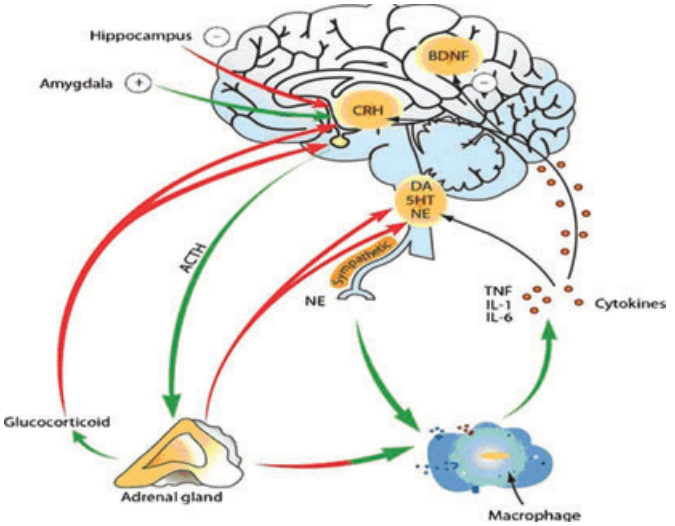

Figure 2. **Molecular processes are affected by stress and depression. From Ref. 120, with permission from John Wiley and Sons.**

interleukin 2 (IL-2), IL-6, TNF-α;[20] cell-mediated immunity, including the composition of lymphocytes and T cell receptors;[21] complement such as immune complexes and C1q,[16] and lipid levels such as cholesterol.[22] Studies indicate that many of these abnormalities normalize following resolution of acute mania and differ from patterns found in bipolar depression. Our data support the study of interventions addressed at lowering levels of markers of immune activation as a possible treatment for mania. This research may lead to improvements in the diagnosis and treatment of bipolar disorder.

Trevor Young (University of Toronto) presented the final report in this session in which he reviewed the evidence for mitochondrial dysfunction and oxidative stress in this illness. Earlier findings of maternal inheritance in bipolar disorder suggested the importance of mitochondria[23] and the field moved forward quickly with the finding of increased mitochondrial DNA deletions in postmortem brain.[24] It was then quite intriguing that several microarray studies on independent samples of brain tissue found remarkable decreases in mRNAs for components of the electron transport change,[25] which is one of the core functions of the electron transport chain. Their lab has followed up on these data and found compelling evidence of mitochondrial dysfunction in bipolar disorder. They reported decreased levels of one of the components of complex I of the electron transport chain and also the activity of this complex in prefrontal cortex obtained postmortem from patients with bipolar disorder.[26] There was also increased protein carbonylation and 3-nitrotyrosine levels in the same samples. There was a significant inverse correlation between complex I activity and the oxidative metabolites in the same brain region. They next measured the brain's antioxidant system in the same samples and found that in bipolar disorder, as in schizophrenia and major depression, that the mean levels of glutathione were depleted in all diagnostic groups suggesting an impact of chronic psychiatric illness on this system.[27] Interestingly, the same findings appear to be present in another postmortem brain sample from subjects with bipolar disorder and the differences are particularly evident in the synaptosomal fractions (Andreazza *et al.*, unpublished data), which suggests that oxidative damage might be present in postsynaptic membranes and could affect function at this level which would be consistent with traditional sites of pathophysiology in mood disorders.

What is particular fascinating and might be relevant to move the field forward is that many of these findings are also found in blood samples from patients with bipolar disorder. Indeed, Konradi *et al.*[2] found that the expression of a number of electron transport chain mRNAs was altered in lymphocytes from patients with bipolar disorder. More recently, mitochondrial clustering has been demonstrated in lymphocytes and fibroblasts from patients with bipolar disorder.[28] There have been a number

of findings of increased oxidative stress in serum and plasma markers and a meta-analysis has shown that several of these findings are evident across studies.[29] These data have been particularly important in the work of one of the International Society of Bipolar Disorders (ISBD) committees on the study of biomarkers (see below). Finally, this pathway might also be relevant for treatment of bipolar disorder since several mood stabilizers, lithium, and valproate, have antioxidant properties,[30] and at least several studies suggest that the antioxidant, *N*–acetylcysteine, may have some mood stabilizing properties.[31] The conclusion of this presentation is that, indeed, continued study of mitochondrial dysfunction may be very helpful to gain a more fulsome understanding of the pathophysiology of bipolar disorder.

Session on diagnosis

Overview

The session on diagnosis was chaired by Carlos Zarate (National Institute of Mental Health). The concept of bipolar disorder, initially known as manic-depressive insanity, has gone through considerable revision since it was first proposed.[32] Bipolar disorder consists of two major components, depression and hypo/mania, which vary greatly in severity, duration, and course. In addition, these components may present simultaneously or separately in time. Over the years, the boundaries of depression, mania, and bipolar disorder continue to shift. In recent years, attention has been given to the concept of bipolar spectrum disorders.[33] The DSM was introduced in part to clarify the ambiguities in psychiatric diagnosis. However, even with the advent of the DSM, there remains considerable uncertainty on diagnostic concepts of bipolar disorder.

The DSM is now going into its 5th edition, and the bipolar disorder subworkgroup in collaboration with the full Mood Disorder Workgroup for the DSM-5 has come up with proposed revisions addressing some of these diagnostic ambiguities. It is important to note that when there is a proposed revision that this is done by following a series of revision principles and utilizing generally accepted validators of a diagnostic entity. The principles of revision used in the workgroup were to optimize clinical utility, to make recommendations guided by research evidence, to maintain continuity with previous editions, and to set the stage for future developments in our understanding of the brain. For there to be a change in the criteria it is also necessary to elucidate the reason for change and present evidence in support of change. Jules Angst summarized work and research on evidence-based efforts to redefine bipolar disorders, Ellen Frank discussed revisions to the concept of mixed episodes in DSM-5, and Trisha Suppes covered criteria of hypomanic episodes.

The report by Angst uses a new specifier (increased energy/activity levels) to understand the associations among major depressive disorder, bipolar I, and bipolar II disorders. When using this specifier in the BRIDGE study (bipolar disorders: improving diagnosis, guidance, and education), what was found was that a significant number of individuals in a major depressive episode diagnosed with major depressive disorder in reality had a bipolar disorder diagnosis. When using the specifier criteria, the authors found that the distinction between BP-I versus BP-II disorders was much sharper. BP-I disorders had higher suicide attempt rates, whereas individuals with BP-II disorders had a greater association with anxiety disorders. Also, both bipolar I and II disorders, when compared with MDD, had higher rates of association with social phobia, substance use disorders, obsessive-compulsive disorder, suicide attempts, and attention disorder hyperactivity disorder. BP-II disorder compared to MDD had significantly more generalized anxiety disorder and panic.

Mixed episode, initially described as mixed states of manic-depressive insanity, has received many revisions since originally conceptualized.[32] Early on, it was evident that some patients with acute mania or hypomania simultaneously experience prominent depressive symptoms. Clinicians tried to capture this ambiguity that surrounds this condition by developing diagnostic criteria. A number of diagnostic criteria have been proposed over the years.[33] DSM-IV criteria specified that in order to meet criteria for a mixed episode that an individual was required to simultaneously fulfill criteria for both a manic and major depressive episode nearly every day for a period of at least one week. This was viewed as too broad and is often not seen. Instead clinicians were more likely to encounter individuals with a simultaneous admixture of depressive and manic symptoms that did not meet DSM-IV criteria for a mixed episode. Such clinical presentations were also

associated with many of features of this more stringent form (i.e., more likely to be associated with suicidality, longer duration of illness, concomitant alcohol or sedative-hypnotic abuse, poorer outcome, and less adequately responsive to lithium). Thus, identifying the mixed state presentations across the spectrum would likely have major clinical implications. The paper by Frank *et al.*[59] proposes that mixed states be identified by *specifiers* that can be applied to episodes of either depression or mania/hypomania and that can be applied to individuals with a lifetime diagnosis of either major depressive disorder or bipolar disorder. It is believed that the use of specifiers would lead to earlier diagnosis and treatment.

Another challenge in the classification of bipolar disorder is how to define a hypomanic episode. The paper by Trisha Suppes and colleagues[34] addresses this important issue. Currently in DSM-IV-TR, the prototypical symptom of hypomania is elevated mood (and/or irritable mood). The DSM-5 bipolar subgroup proposes to take out one of the criterion B symptoms, "increase in goal-directed activity," and to place it with "elevated mood" in criterion A. Thus, the change in criterion A would be a distinct period of abnormally and persistently elevated, expansive, or irritable mood AND change in activity/energy levels, which should also be abnormally and persistently increased. This suggested change would lead to increase specificity without loss of sensitivity. The other issue addressed in the paper by Suppes is the number and duration of hypomanic/manic symptoms necessary to meet criteria for a hypomanic episode. Clinicians are often unsure how to proceed when diagnosing a hypomanic episode. This is not surprising as diagnosis of hypomanic episode is the most unreliable using DSM-IV criteria. There has been an abundance of studies looking at whether hypomanic symptoms should be present for two, three, four, or more days in order for the diagnosis to be made. The workgroup proposes to keep the four-day requirement, which would increase specificity with reasonable sensitivity.

The proposed DSM-IV changes are an important step to resolve some of the ongoing diagnostic ambiguities of bipolar disorder. Clearly, the proposed changes are in need of testing, which will occur under the field trials. The DSM-5 committee is open for comment and considering changes in diagnostic criteria for bipolar disorder in light of these proposals (www.dsm5.org).

Mood disorder workgroup reports

Jules Angst presented first. Conventionally, mood disorders are classified into depression, mania, and bipolar disorders. While these distinctions are very useful for international communication and treatment decisions, nature is more complex. The two components, depression and mania, vary greatly in severity and course, as do the subgroups of bipolar disorders (BP-I, BP-II, Md (mania with minor depressive disorders)).[35] As Cassano *et al.*[36] demonstrated in regard to patients with recurrent major depression, there is a linear increase in the number of manic symptoms as a function of depressive symptoms over the patient's lifetime. Bipolar disorders often manifest first as depression; we know for a fact that their diagnosis may often be delayed by up to ten years[37] and that depression in patients with bipolar or subthreshold bipolar disorder is less responsive to antidepressants.[38,39]

Depression has long dominated the field in terms of prevalence, treatment and, especially, in the estimates of global burden of disease. But if we assume a spectrum from depression via bipolar disorders to mania, it is important to investigate how many subjects suffering from major depressive disorders also manifest sub-threshold hypomania. In recent years, reanalysis of two large epidemiological studies (Early Developmental Stages of Psychopathology (EDSP) study in Munich, Germany and the National Comorbidity Study-R in the United States) found that as many as 40% of patients with DSM-IV major depressive disorder (MDD) met criteria for sub-threshold bipolarity; the latter was strongly predictive for BP-I disorder ten years later.[40,41]

The structured interviews (DIS) applied in those studies did not assess sub-threshold hypomania in any detail. This gap has been filled by the BRIDGE study, which made detailed assessments allowing an operational definition. The study comprised 5,635 patients with DSM-IV major depressive episodes (MDE) recruited in North Africa, Europe, and the Near and the Far East.[42] The study validated a new "specifier" (S) definition for hypomania/mania.[43] This adds increased activity/energy to DSM-IV criterion A (elated or irritable mood) and eliminates all the DSM exclusion criteria (e.g., hypomania under antidepressants) because they rule out patients

who have a clinical profile of bipolarity. The other criteria for BP-I-S are identical to those of DSM-IV. BP-II-S, on the other hand, differs from DSM-IV BP-II by requiring a hypomanic episode duration of only one day or longer (instead of the 4+ days in DSM-IV) and the lack of any exclusion criteria. The validity of short hypomanic episodes of one and 2–3 days was demonstrated by the BRIDGE study.[42]

The consequences of redefinition by the specifier criterion are very considerable: not only does it identify many more patients with affective disorders as having bipolar disorders, it also distinguishes more clearly between the new bipolar subgroups and the remaining MDD in terms of validators and other clinical characteristics (comorbidity, nonresponse to antidepressants). The current DSM-IV criteria diagnosed 4,732 (84%) of the 5,635 patients with a MDE as having MDD, but the specifier criteria diagnosed only 2,988 (53%) (MDD-S). Forty-seven percent were diagnosed as suffering from bipolar disorders. The specifier concept turned out to be more valid than the DSM-IV classification, as illustrated by the frequent presence of a family history of mania, a progressively more recurrent course, more full remission between episodes, and other clinical characteristics for bipolar disorders.[42]

DSM-IV diagnosed 12.1% of the 5,635 MDE patients as having BP-I and 2.3% as having BP-II; specifier criteria diagnosed 23.9% as having BP-I-S and 23.1% as having BP-II-S. The distinction between BP-I versus BP-II disorders was much sharper when specifier diagnoses were applied. BP-I-S disorders were associated with higher suicide attempt rates, and BP-II-S disorders to a greater extent with anxiety disorders (generalized anxiety disorder (GAD), panic disorder (PD), and obsessive-compulsive disorder (OCD)). In comparison with MDD-S both BP-I-S and BP-II-S disorders differed in their higher rates of association with social phobia, OCD, binge eating, suicide attempts, substance use disorders, ADHD, and borderline personality disorder. Whereas, compared to MDD-S, BP-II-S disorder was significantly more associated with GAD and PD, there was no difference at all between BP-I-S disorder and MDD-S in this respect. The strong comorbidity of BP-II-S disorders with anxiety states is clearly of great clinical interest. Figure 3 illustrates the enormous differences between the varying concepts in the diagnosis of bipolar disorders. The DSM-IV definition gave the lowest rates; these doubled with the omission of the exclusion criteria and tripled with application of the specifier criteria. Self-assessment using the Hypomania Checklist 32-R2 as a screening instrument yielded the highest rates. It is of particular interest that the clinicians' initial diagnosis identified almost twice as many patients as bipolar compared to the DSM-IV criteria.

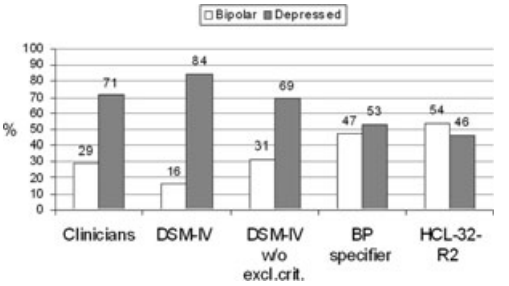

Figure 3. Diagnosis of bipolar versus depressive disorder by varying definitions in the Bridge Study of 5,635 patients with MDE.

In conclusion, the specifier definition of hypomania identifies with good validity many more patients with MDE as having bipolar I and bipolar II disorders and thus allows a much earlier diagnosis and hopefully a better treatment. The findings need replication by other studies. The DSM-5 committee is considering changes in diagnostic criteria for bipolar disorder in light of these findings (www.dsm5.org). Changes may allow a better characterization of major depression as either unipolar or bipolar and give consideration to dimensional issues.[44] This is particularly relevant to the definition of mixed states. While the results of the Bridge study and the application of the bipolarity specifier should not necessarily change the overall proportion of subjects from the general population who suffer from affective disorders, it may have an impact on the proportion of these affective patients who are recognized as belonging to the bipolar spectrum, as opposed to the unipolar spectrum. The impact of such change on treatment and outcomes should be monitored over the next decade.

Ellen Frank (University of Pittsburgh) was the second presenter in this session. In order to meet criteria for a mixed episode in the DSM-IV, an individual was required to *simultaneously* fulfill the criteria for both a manic episode and for a major depressive episode (except for the duration criterion of two weeks) nearly every day during a

period of at least one week. In reviewing these criteria, the Mood Disorders Workgroup of the DSM-5 Task Force concluded that while this definition of Mixed Episode had a satisfying symmetry, it was rather like a unicorn: beautiful to imagine, but rarely, if ever, seen in reality. Yet, the mixed episode diagnosis was actually recorded with substantial frequency and patients were very often referred to as being "mixed" in discussions among clinicians. Furthermore, we identified a number of negative consequences of the DSM-IV definition. These include (1) general confusion and lack of clarity about a patients actual clinical state; (2) underestimation of suicide risk, inasmuch as even softer definitions of mixed states are associated with increased risk of suicide; (3) potentially inappropriate treatment selection, given the poor response to lithium among patients in a mixed state; and, finally, (4) a failure to identify those with a lifetime diagnosis of unipolar disorder who are at increased risk of progression to bipolar disorder. We, therefore, set as our goal a redefinition of Mixed Episode that would better conform to clinical reality and that would allow for the recognition of mixed states even among individuals with a lifetime diagnosis of unipolar disorder.

The workgroup is currently proposing mixed states be identified by *specifiers* that can be applied to episodes of either depression or mania/hypomania and that can be applied to individuals with a lifetime diagnosis of either unipolar or bipolar disorder.

The proposal for the *with depressive features* specifier requires that full criteria are met for either a manic episode or a hypomanic episode and that at least three of the following nine depressive symptoms are present nearly every day during the episode: subjective depression, worry, self-reproach, or guilt, negative self-evaluation, hopelessness, suicidal ideation or behavior, anhedonia, fatigue, and psychomotor retardation.

The proposal for the *with hypomanic features* specifier requires that full criteria are met for a MDE and that at least three of the following seven manic/hypomanic symptoms are present nearly every day during the episode: elevated mood, decreased *need* for sleep (i.e., sleeps little, but reports feeling rested), increased goal-directed activity, increased energy/visible hyperactivity (as distinct from agitation), grandiosity, accelerated speech, and racing thoughts.

The literature on mixed states suggested that a number of the generally accepted validators of a diagnostic entity apply to the softer definitions proposed by the workgroup. These validators include familial aggregation of both predominantly manic and predominantly depressive mixed states, prior psychiatric history variables, concurrent psychiatric symptoms not included in the definition, diagnostic stability over time, increased likelihood of progression from a unipolar to a bipolar diagnosis among those with mixed depressive episodes and treatment outcome.

Features of psychiatric history that are consistently observed among those experiencing mixed states, such as those defined by the proposed mixed specifiers, include early onset of illness, a history of multiple previous episodes, suicidal behavior, comorbid diagnoses of anxiety and alcohol or substance abuse, and brain trauma. Interestingly, all of these are also features that tend to distinguish individuals with a lifetime history of bipolar disorder from those with a lifetime history of unipolar depression.

Two major concerns of the workgroup in developing the mixed specifier criteria were to select the most appropriate symptoms and to decide on the number of symptoms that should be required. In selecting the specific symptoms to be included, the workgroup focused on selecting those symptoms that were clearly distinct from those of the predominant episode polarity. This was done entirely based on face validity, as no literature was available to guide us. In deciding on the number of symptoms that should be required, we looked to previous studies of validators and to information about the likelihood of change in diagnosis. In a longitudinal follow-up study lasting almost 30 years, Fiedorowicz *et al.*[45] found a highly significant difference in the risk of conversion from unipolar to bipolar disorder among depressed individuals who presented with two vesus three or more manic/hypomanic symptoms.

The concept of Bipolar Disorder, Not Otherwise Specified (NOS) as it appeared in DSM-IV, and likely to be referred to as Bipolar Disorder, Not Elsewhere Classified (NEC) in DSM-5, will be reserved for presentations of bipolar disorder that are subsyndromal by virtue of an insufficient number of symptoms to meet the criteria for episodes of depression and/or mania or hypomania, or an insufficient episode

duration to meet those criteria and there is no requirement that these subsyndromal presentations be concurrent. By contrast, to meet the criteria for one of the proposed mixed specifiers, an individual would be required to present in a fully syndromal episode of depression or mania or hypomania that is simultaneous for at least one week with at least 3 of the designated symptoms of the opposite pole.

Recognizing the considerable prognostic importance of mixed states, the DSM-5 workgroup on mood disorders has proposed a new definition of such states that we believe is more consistent with clinical reality, is likely to be used more appropriately and correctly than the mixed episode diagnosis in DSM-IV, should lead to earlier recognition of those depressed individuals likely to develop bipolar disorder and, perhaps most importantly, may help in the recognition of those at risk for suicidal behavior.

Trisha Suppes (Stanford University) finished this session with a third report. A debate often faced by psychiatrists working in mood disorders is what combination of symptoms is required to make a diagnosis of bipolar disorder, particularly which symptoms and for what duration. DSM-IV-TR offers guidance by distinguishing the criteria for number of hypomanic symptoms and concurrent days of hypomania and mania in bipolar disorder; however, there has been increasing recognition of both the presence and importance of subsyndromal hypomanic symptoms for patients experiencing distress.

The Mood Disorders Workgroup for the DSM-5 is making the recommendation for the addition of "activity or energy" to criterion A for hypomanic and manic episodes. The proposal for the updated criterion is as follows: a distinct period of abnormally and persistently elevated, expansive, or irritable mood and *abnormally and persistently increased activity or energy*. Symptom lists (criterion B) would be essentially not changed. The addition of requiring increased activity/energy to criterion A will make explicit the requirement that this hallmark symptom of bipolar I disorder be present in order to make the diagnosis. Addition of this feature is supported by a number of studies suggesting that activity or energy is at least as important as mood; moreover, some studies argue that activity and energy are more important than mood.[46–55]

The Mood Disorders Workgroup for DSM-5 is also making the recommendation to maintain the criterion A for an episode of hypomania at four days. The proposal is as follows: a distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased activity or energy, *lasting at least four days and present most of the day*, nearly every day, that is clearly different from the usual nondepressed mood.

The evidence is fairly compelling that maintaining at least a four day requirement retains the specificity of the diagnosis with reasonable sensitivity. The review of the evidence suggests that decreasing the duration requirement would significantly increase the prevalence of bipolar II disorder. This could, in turn, decrease specificity of the diagnosis and add to the periodic skepticism regarding the integrity and validity of bipolar II as a separate diagnostic category. This recommendation is based on a review of available empirical data potentially supporting a change in the criteria, discussed in detail below. Under consideration was whether there was justification to change the criterion for a hypomanic episode to two days, shortening the required period of symptoms from four days. Some researchers have suggested that the duration requirement be eliminated. For example, Angst and colleagues,[47] as well as others, have suggested that the duration requirement should be discarded and the focus moved to changes in activity plus clinically significant symptoms. In one single-site observational study, characteristics of patients reporting two versus four day hypomania were similar.[56]

The recent BRIDGE study, is one of the few studies in which duration of hypomania is a specific focus. In this large globally ascertained sample of more than 5,500 patients currently experiencing a MDE, an evaluation was made of various cut points for duration between 1, 2–3, and 4–6 days of hypomania relative to a number of external validators.[42] The external validators considered included: first degree relatives with a mood disorder; early adult onset; recurrent mood episodes; mood lability; seasonality; and history of suicide attempts. There was a clear linear relationship between each of the external validators evaluated and the duration of the hypomanic symptoms. For example, the percent of the population reporting family history of mood disorders increased as number of days of hypomania increased. The difference between requiring 2–3 versus 4–6 in these validators was notable, in many cases improving by 20% or more.

In further support of maintaining duration criteria at four days, Bauer and colleagues[57] found that, in a sample of 203 bipolar patients, if the hypomania duration criterion was reduced from four days to two days, the percent of hypomanic days would increase twofold from 4% to 8% for each patient; the number of patients with a hypomanic episode would double (in this sample from 44 to 96); and the number of hypomanic episodes for all patients would increase about threefold (from 129 to 404 in this sample).

In sum, these data, particularly the increase in strength and number of external validators when a hypomania episode was defined by a minimum of four days,[42] and the likely marked increase in prevalence for bipolar II disorder that would occur if the entry criteria for hypomania were changed,[57] were taken by the Mood Disorder Workgroup committee to support maintaining the hypomania episode requirement at four days.

Finally, the Mood Disorders Workgroup for the DSM-5 proposes to revise Bipolar Disorder NOS to allow subcategories to be coded and to be specific in definition. This is an important change from DSM-IV-RS where NOS was defined by "examples include." This proposed change will allow the capture of the well-recognized phenomena of patients experiencing hypomanic symptoms with notable change from usual behavior that are fewer than four days in duration or of a lower symptom count than is required to meet criteria for a full hypomanic episode. It is important to note that in contrast to the Mixed Features Specifier proposed,[58] where symptoms occur simultaneously, symptoms for Bipolar NOS, by definition, occur at separate times. Specific proposed definitions include:

- Codable subcategories within Bipolar NOS that would classify characteristic symptoms of hypo/mania or depression that are present *during separate time periods* and cause distress or dysfunction, but are not of sufficient duration and/or intensity to meet criteria for a specific bipolar diagnosis.
- Subsyndromal hypomania, short duration: patients who experience lifetime episodes of depression that meet full criteria for MDE AND experience hypomanic periods of sufficient number of criterion symptoms, but of insufficient duration ($\geq$ 2 and $<$ 4 consecutive days).
- Subsyndromal hypomania, insufficient symptoms: patients who experience lifetime episodes of depression that meet full criteria for MDE AND experience hypomanic periods of sufficient duration, but of insufficient number of criterion symptoms ($\geq$2, 3 consecutive days if mood is only irritable).
- Other Bipolar NOS: this includes atypical presentations of bipolar symptoms not considered above that cause significant distress or psychosocial dysfunction.
- In summary, in this session, DSM-5 Mood Disorder Workgroup proposals were reviewed, including the addition of activity or energy to the mood item in criterion A; that the duration criterion for hypomanic episodes remain at four days; and that specific, codable Bipolar NOS categories for subthreshold mood symptoms be added. More information about proposed changes in DSM-5 can be found at www.dsm5.org.

Session on medical comorbidity

Overview

In the comorbidity session chaired by Fouzia Laghrissi-Thode (F. Hoffmann-La Roche Ltd.), an emphasis was placed on the considerable medical comorbidity present in bipolar disorder. The burden of cardiometabolic conditions in bipolar disorder is vast and has an impact on levels of morbidity and mortality, and a reduced life expectancy of 10 to 25 years. In this session, there was the following: a review of treatment disparities; recommendations for integrative care; the examination of risk factors and how to address them; and, finally, the current state of intervention in an integrated care model. Several presentations addressed these important issues.

Cardiometabolic conditions

Benjamin Goldstein (University of Toronto) discussed the burden of cardiometabolic conditions in bipolar disorder. Cardiometabolic conditions, such as obesity, diabetes, and cardiovascular disease, are a common source of morbidity and mortality in bipolar disorder. Excessive cardiovascular disease (CVD) is the leading cause of death in bipolar disorder, contributing to 10- to 25-year shorter life expectancy. Despite the fact that CVD is the leading cause of death in the general population, standardized mortality ratios are fully doubled in bipolar

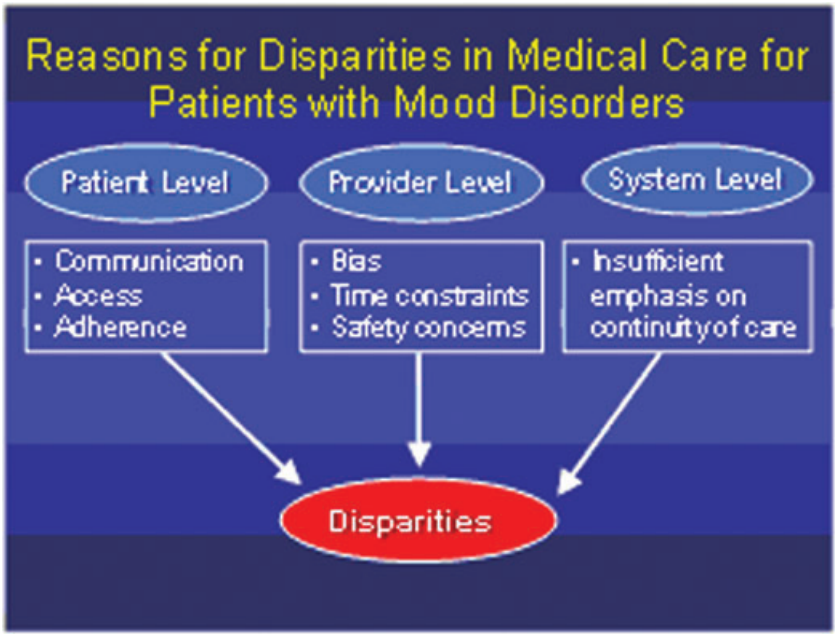

Figure 4. Reasons for disparities in medical care for patients with mood disorders, at the patient level, provider level, and system level. Adapted from Frayne *et al.*[121]

disorder, in large part because CVD in these patients occurs exceedingly early in life. Recent findings from the United States general population suggest that CVD patients with bipolar disorder are 14 years younger than CVD patients without mood disorders. Indeed, evidence of increased cardiovascular risk among youth with bipolar disorder is accumulating. The question of whether cardiometabolic conditions in bipolar disorder are due to the strain of having the illness (e.g., mood symptoms and their functional sequelae), suboptimal lifestyle (e.g., sleep disruption, smoking, nutrition, physical activity), or shared biological causes (e.g., inflammatory mediators, hypothalamic–pituitary–adrenal disturbance, CACNA1C genotype) remains insufficiently answered. Nonetheless, in addition to concerns about medical outcomes, cardiometabolic conditions are associated with a more pernicious course of bipolar disorder.[59]

Disparities exist in the medical treatment of patients with severe mental illness, and this has been observed in rigorous studies from a number of countries including Canada, Denmark, Sweden, and the United States. For example, despite being nearly three times as likely to die of CVD, patients with bipolar disorder or schizophrenia are no more likely to access related hospital resources. Those who do access treatment are at greatly increased risk of cardiovascular death within five years, and yet are almost half as likely to receive invasive cardiovascular treatment as patients without these psychiatric illnesses. Other findings demonstrate extensive delays in treatment from the first point of contact through cardiac catheterization, and disparities in prescriptions for preventive cardiometabolic medications postdischarge have been documented. Potential reasons for these disparities have been highlighted by others (see Fig. 4). Cardiometabolic monitoring of second-generation antipsychotics is problematic. Despite publication of joint guidelines by the American Diabetes Association and American Psychiatric Association, adherence with suggested monitoring at baseline and after 12 weeks of treatment remains dismal, with the vast majority of patients not receiving monitoring. Among youth, adherence with monitoring guidelines occurs in only 5% to 15% of patients.

Strategies that may prevent or delay the accumulation of medical burden in bipolar disorder include regular medical monitoring, behavioral interventions focusing on obesity prevention, and use of medications that minimize the propensity for

weight gain and metabolic disturbance. Treatment models for integrating greater emphasis on medical comorbidity in the treatment of patients with severe mental illness have recently been elaborated and published in landmark studies. Integrating nurse care managers into mental health clinics was shown to increase compliance with preventive services and evidence-based cardiometabolic services and to improve Framingham scores. Similarly, integrating supervised nurses into the provision of primary care for patients with depression and diabetes or cardiovascular disease led to more fine-tuned adjustments of insulin, antihypertensives, and antidepressants. Importantly, reductions in glycosylated hemoglobin and systolic blood pressure, and improvements in quality of life and treatment satisfaction, were also observed. Preliminary findings suggest that similar modifications can benefit the overall health of patients with bipolar disorder specifically. Although these manualized interventions are not widely available, they share several core elements that can be readily integrated into treatment. These include: psychoeducation about the link between psychiatric and cardiometabolic illness, liaison with other healthcare providers about specific patients and about monitoring and risk factor management in general, encouraging self-management, and supporting patient self-efficacy and effective engagement of healthcare providers.

In summary, medical comorbidity is salient to the care of all patients with bipolar disorder, irrespective of age or type of treatment. Familiarity with the magnitude of this risk and with preventive and intervention strategies may improve outcomes for patients with bipolar disorder.

Sleep and circadian rhythms

In the second talk in the session, Allison Harvey (University of California at Berkeley) then presented an important overview of the role of sleep and circadian rhythms in bipolar disorder. Bipolar disorder is a severe and chronic psychiatric illness associated with significant interepisode impairment, high rates of medical morbidity, and premature mortality. Three lines of evidence highlight the strong coupling between sleep and circadian disturbances with mood episodes, inadequate recovery, and relapse risk in bipolar disorder: (1) sleep and circadian disturbance is a core symptom of bipolar disorder; (2) experimental studies suggest that sleep deprivation can trigger manic relapse; and (3) there is evidence that sleep deprivation can adversely affect emotion regulation the following day.[60] Relatively recently, it has become clear that bipolar disorder is also associated with greater medical morbidity and premature mortality.[61] Multiple complex factors are likely to contribute to the association between bipolar disorder and health problems, medication side effects perhaps being the most prominent. The question we ask and seek to begin to answer here is: Are the sleep and circadian problems that are core features of bipolar disorder one important but understudied contributor to the known association between health problems and bipolar disorder? Below we seek to show the plausibility of this hypothesis by highlighting that problems relating to a selection of health conditions and health behaviors have been linked to both sleep problems and bipolar disorder. If sleep problems are contributors to the health problems experienced by bipolar patients, the public health implications are potentially startling because sleep and circadian problems are *modifiable*. Harvey summarized the following areas:

Several longitudinal studies have identified short sleep duration, long sleep duration, and insomnia as predictors of CVD morbidity and mortality.[62] Sleep disturbance has also been associated with the increased prevalence of traditional CVD risk factors, including obesity, hypertension, and diabetes mellitus[3].

There is a 1.5–2.5 fold increase in risk for CVD-related mortality for individuals with bipolar disorder compared to the general population, making CVD the leading cause of death in bipolar disorder.[63] Moreover, traditional CVD risk factors, such as hypertension, obesity, and diabetes mellitus, occur with greater frequency in bipolar patients than the general population.[64]

The results of a meta-analysis involving 30 studies (12 in children, 18 in adults) and 634,511 participants are compelling. There was a 60–80% increase in the odds of being a short sleeper among both adults and children who were obese. Moreover, adults sleeping five hours or fewer versus more than five hours had significantly greater odds of being obese and an increase of one hour per night of sleep was associated with a decrease of 0.35 body mass index (BMI).[65] Fagiolini *et al.*[66] reported that 68% of patients with bipolar disorder were overweight,

with 32% meeting criteria for obesity (less than 20% of controls met criteria for obesity). These individuals suffered a range of poorer outcomes including shorter time to recurrence of an episode, particularly of depression, and had a greater number of previous episodes of depression and mania.[66] Similarly, McElroy *et al.*[67] reported that 58% of bipolar patients were overweight and 21% were obese. The associated adverse outcomes included arthritis, hypertension, and diabetes mellitus.

Sleep deprivation is associated with hormonal responses that increase appetite, caloric intake, and influence the selection of foods.[68] When sleep deprived, individuals focus food selection on sugar, fat, and carbohydrates. In a comparison of 2,032 patients with bipolar disorder and controls, Kilbourne *et al.*[69] reported that patients with bipolar disorder were more likely to report poorer eating behaviors relative to individuals without a serious mental illness, including having fewer than two daily meals (OR = 1.32) and difficulty obtaining or cooking food (OR = 1.48).

Sleep quality is improved by exercise[70] and is an effective treatment for chronic insomnia[71] and reduces presleep anxiety.[72] Moreover, healthy participants have less tolerance for exercise after sleep deprivation.[73] Kilbourne *et al.*[69] reported that patients with bipolar disorder were more likely to report poor exercise habits relative to individuals without a serious mental illness, including infrequent walking (OR = 1.33) and infrequent strength exercises (OR = 1.28). Another study reported predominately sedentary routine daily activities in a sample of bipolar patients.[74]

We have reviewed evidence that sleep disturbance is associated with an increased CVD risk, more obesity, poorer diet, and less exercise. We have also reviewed evidence that sleep disturbance is pervasive in bipolar disorder and that bipolar disorder is associated with higher CVD risk, more obesity, poorer diet, and less exercise. Taken together, it is tempting to speculate that sleep disturbance may be an important contributor to the association between health problems and bipolar disorder. However, there is surprisingly little research that includes a measure of sleep and a measure of a health outcome in individuals with bipolar disorder. Accordingly, we recently probed the National Comorbidity Survey-Replication (NCS-R) to examine the prevalence of three self-reported cardiovascular risk factors (obesity, hypertension, and diabetes) across bipolar respondents with chronic insomnia symptoms, acute insomnia symptoms, and good sleep ($n = 176$). Insomnia symptoms included difficulty falling asleep, difficulty maintaining sleep, and early morning awakening. Rates of obesity and hypertension were greater in bipolar patients with chronic (41.8%; 28.8%) and acute (43.7%; 24.1%) insomnia symptoms compared to bipolar patients with good sleep (19.7%; 5.9%). Longer insomnia symptom duration increased odds of hypertension (OR = 2.2, 95% CI = 1.2–3.9) and a higher number of insomnia symptoms was associated with elevated rates of obesity (OR = 1.5, 95% CI = 1.0–2.1), hypertension (OR = 1.9, 95% CI = 1.1–3.6) and diabetes (OR = 4.7, 95% CI = 2.0–11.1). Although causal inferences are not possible given the cross-sectional design, these results add to the evidence that sleep disturbance may contribute to the association between health problems and bipolar disorder.[75]

With funding from NIMH, we have developed an eight session intervention for sleep and circadian problems in bipolar disorder, combining principles from motivational interviewing,[76] cognitive behavior therapy for insomnia,[77] interpersonal and social rhythms therapy (IPSRT),[78] and chronotherapy.[79] The hypothesis tested is that improving sleep and circadian problems will improve sleep, reduce mood symptom and risk of relapse, improve quality of life as well as health among individuals with bipolar disorder.

Unlocking the contributors to the increased risk for premature health-related morbidity and morbidity associated with bipolar disorder will be complex as there will be multiple factors. Herein, we present initial evidence, albeit all based on cross-sectional evidence, that the sleep and circadian problems that are prominent features of bipolar disorder may contribute to several adverse health outcomes and may contribute to an unhealthy lifestyle. Sleep and circadian problems are likely to be *modifiable* with relatively simple behavioral changes. Hence, if sleep/circadian problems do turn out to be important contributors to the health problems experienced by bipolar patients, there will be an important opportunity for major health improvement.

Adverse health-related behaviors

In the final report of this session, Michael Ostacher (Stanford University) reported on several other adverse risk factors and behaviors that increase the morbidity and mortality in bipolar disorders. Adverse health-related behaviors increase the risk of morbidity in bipolar disorder. High rates of obesity, smoking, drug and alcohol use, sleep cycle abnormalities, and inadequate treatment adherence conspire to worsen the course of bipolar disorder for many people. Perhaps more importantly, these may be responsible for elevated mortality rates compared to the general population, mediated through diabetes, lipid disorders, hypertension, and heart disease. Clinicians should be aware of the presence of these risks, and address and promote behavioral change and optimization of care. Smoking, alcohol, diet, and exercise, and barriers to such changes should be addressed from the perspective of ongoing treatment. Strategies for assessing these risks, monitoring motivation to change behavior, and intervening to promote change must be integrated into patient care.

It has become evident that a singular focus on mood symptoms in the study and treatment of bipolar disorder neglects what may be the most important outcome we could measure: health. People with severe mental illness in the United States may die 25 years earlier than their counterparts in the general population. While suicide certainly accounts for a disproportionate number of deaths in the first decade or two after the development of bipolar disorder, standardized mortality ratios for people with bipolar disorder continue to be double that of the general population. Nearly all of this increased mortality is due to medical causes. While there may be something inherent in bipolar disorder that increases risk for premature mortality (abnormalities in inflammatory factors, for instance), it is likely that the greatest proportion of increased risk is due to modifiable health behaviors, primarily smoking and obesity. If patients are to be well treated in the clinic, these behaviors must be addressed.

Patients with bipolar disorder are at increased risk for multiple problems—elevated BMI, smoking, diabetes, lipid disorders—that individually increase risk for cardiovascular events, but having multiple risk factors, according to the Framingham Heart Study, more than additively increases such risk. In public sector patients in Massachusetts, marked increased risk for death from cardiovascular disorder was apparent in severely mentally ill patients, including those with bipolar disorder, as early as age 25.

The association between obesity and poor mood and functional outcomes, including suicide attempts, in bipolar disorder is well known, as is its prevalence. In the Pittsburgh sample, upwards of 35% of subjects with bipolar disorder had BMIs in the obese range (>30). With obesity directly related to rates of diabetes and lipid disturbances, its high prevalence in bipolar disorder is especially concerning. Because patients with mental illnesses, including bipolar disorder, often receive less comprehensive medical care than those without mental illness, the consequences of these risks may be greater.

Smoking, too, is highly prevalent in bipolar disorder, with odds ratios for smoking in bipolar I and II disorders 3.5 and 3.2, respectively. Quit rates are lower in bipolar disorder and, aside from its association with suicidal behavior, has to be considered in understanding why mortality rates in bipolar disorder are so high. Smoking cessation is rarely studied in bipolar disorder, and patients, clinicians, and families may be fatalistic about the utility of interventions to help patients quit. Many psychiatric clinicians are unaware of or do not help patients utilize established smoking cessation resources, such as pharmacological interventions, smoking cessation programs, and quit lines.

It is time for psychiatric care to go beyond a focus on symptoms and functioning to include a focus on overall health outcomes and decreased mortality for our patients. Systematic identification processes for risk factors for mortality need to be part of everyday care, just as systematic diagnosis of psychiatric illnesses are. Educational efforts for providers that emphasize the detrimental effects of smoking, obesity, diabetes, lipid abnormalities, and other health risk behaviors on both mental and physical health, and strategies (such as motivational interviewing) need to become part of practice for all psychiatric caregivers, and needs to include careful weighing of the potentially detrimental health effects of many of our medications. The integration of interventions for smoking cessation, dietary change, and weight management, overall physical health behavior change into ongoing care needs to be a primary goal of our field. Our technologies for improving mood and functioning are limited and improving

only incrementally; now is the time to expect the view of psychiatric care to go beyond psychiatric symptoms and to expand to include overall health.

Session on reports from the International Society for Bipolar Disorder

Overview

The final session, coordinated by Michael Berk (University of Melbourne), discussed a series of reports from the International Society for Bipolar Disorders (ISBD). Bipolar disorder is a complex, common, and capricious disorder. Relative to its burden, which is between 1% and 5% of the global population, it is poorly researched and understood. Akin to what has been achieved in other major medical disorders, strategic international collaborations, networks, and partnerships are essential to leverage the resources and intellectual capital required to have an impact on these unmet needs. In this context, the series of special workgroups established by the ISBD attempts to address some of the core issues facing the field. The ISBD is the principal internationally recognized forum to foster ongoing international collaboration on education and research, with an objective to advance the treatment of all aspects of bipolar disorders, resulting in improvements in outcomes and quality of life for those with bipolar disorder and their significant others. In this context, the ISBD has chosen a number of areas for academic investment, including improving the quality and standardization of clinical trials, and fostering a better understanding and integration of the changes in cognition, neuroimaging, and biomarkers that are seen in the disorder.

The first issue pertains to the complexities and controversies regarding the design of clinical trials in bipolar disorders. The clinical trial evidence base is the cornerstone of clinical decision making, and the area is bedeviled by methodological inconsistency that bedevils quality care. Many trials fail because of poor design, and others contain critical biases. This workgroup, led by Tohen and colleagues will critically review the commonly utilized designs in clinical trials of bipolar disorder, as well as suggesting novel designs, including adaptive designs and mixed methods designs. A review of statistical techniques and cultural issues and challenges of implementing studies in emerging countries is part of the remit of this group. A major potential contribution to outcomes could derive from standardisation and optimisation of clinical trial design, and the adoption of innovative methodologies including statistical methods.

It is now appreciated that rather than simply being a disorder with highs and lows, with return to one's old self between episodes, bipolar disorder is associated with a cascade of progressive clinical features. Bipolar disorder follows a progressive trajectory; with an increased numbers of episodes and persistence of illness, there is an incrementally greater probability of recurrence, recurrence becomes triggered more easily, and there is a reduced likelihood of response to treatment. An active biological process of neuroprogression underpins this staged process, evidenced by novel evidence of both progressive neuroanatomical changes and cognitive decline. The biochemical foundations of this process appear to be mediated by changes in inflammatory cytokines, corticosteroids, neurotrophins and oxidative stress. The consequences of this noxious cascade include lipid peroxidation, protein carbonylation, DNA fragmentation and an increased vulnerability to apoptosis. This neural toxicity has overt functional consequences.

The Neurocognition Task Force, led by Frangou and Yatham, aims to examine cognitive deficits in bipolar disorder as part of the process of neuroprogression in the disorder and to develop potential therapeutic strategies. Key goals are to standardize cognitive tests that are commonly used, ensure that they are validated in patients with bipolar disorder, and confirm that they target those domains that are most relevant to the disorder. In order to establish a common cognitive battery for bipolar disorder, the ISBD put together a working group tasked with reviewing the cognition literature to propose a preliminary neurocognitive battery for use in bipolar disorder. The ISBD-Battery for Neurocognitive Assessment (ISDB-BANC) was selected as an assemblage of recognized individual tests considered appropriate for bipolar disorder. It initiates the procedure for standardizing cognitive testing in bipolar disorder, which is a critical step to the use of comparable metrics across large-scale clinical studies. This provides the foundation for the next generation of cognitive remediation therapies. It is planned that the findings from the various task force will be integrated with the expectation that new strategies for assessment and treatment can be developed in the near future.

The ISBD Neuroimaging Task Force similarly had two primary goals, to assimilate neuroimaging research from leading bipolar disorder groups and to develop a conceptual agreement regarding the functional neuroanatomy of bipolar disorder. The task force aimed to examine the neural systems that modulate mood, as they are the probable neuroanatomical foundation of bipolar disorder. Affected brain areas include the amygdala, pituitary, hippocampus, and disruption of regional white matter connectivity. Neuroimaging data indicate changes in key components of both structural and functional networks in bipolar disorder, both structural and functional. An important clue to the pathophysiology of the disorder rests in follow-up studies of the onset phase of the disorder, adolescence. There are normal developmental changes in neuroanatomy in adolescence, which overlap with the pathological changes that occur in bipolar disorder as part of the process of neuroprogression. These data dovetail with the work of the neurocognition taks force, providing a neuroanatomic substrate for the changes in functional outcome and cognition.

These structural and functional changes are the outcome of a primary biochemical perturbation. The root of these changes remain opaque, however biomarkers are increasingly illuminating the possibilities. To this end, the Biomarkers working group of the ISBD was set up, and the report by Young and Kapczinski highlights the most promising avenues. Oxidative stress and systemic inflammation appear to be key pathways underpinning neuroprogression, and they operate in concert with reductions in neurotrophins such as BDNF. The task group aims to develop large scale collaborative research linkages to examine the role of these biomarkers as moderators of outcome and of risk. Collaborative linkages such as these have a habit of growing organically, providing a critical mass of expertise to assist in developing solutions to complex issues of substantial public health significance.

Clinical trials task force report

In the first presentation in this session, Mauricio Tohen (University of Texas) summarized the report from the Clinical Trials Task Force. This group has focused on the review of commonly utilized designs in the treatment of bipolar disorder. The most common clinical trial design for acute mania and bipolar depression is a short, two arm study, which in general, can yield differences between efficacious interventions and placebo. As investigators, clinicians and regulatory authorities may recognize that symptomatic treatment of manic and depressive episodes is a relatively small component of management of bipolar disorder and, therefore, other designs need to be considered.

In general, monotherapy, single point randomization, and blinding achieve major aims. One important advantage of these designs is that they are relatively inexpensive and not subject to many ambiguities of interpretation. Additionally, it is possible to include an established efficacious treatment to provide "assay sensitivity" and allow for secondary analyses of comparative efficacy and tolerability between a new and an established drug/regimen. Designs that employ current DSM criteria and a total score on a manic rating scale have inherent weaknesses and are thus limited. DSM criteria treat all symptoms as equal, when evidence does support that conclusion. Similarly, total scores are subject to rater inflation to qualify individuals, thereby reducing study power to detect differences; as well as overweighting of nonspecific symptoms that may advantage one drug over another. For example, sedation alone can reduce many manic symptom scores, but the aim of treatment is rarely principally sedation.

A major unmet need is that little recognition has been given to the reality that most bipolar I patients have few full manic or depressive episodes while in treatment. Rather, less severe, and generally shorter periods of manic or depressive recrudescence occur more often. Yet, almost no systematic experimental studies have been conducted on this group.

In terms of maintenance or prophylactic studies, adaptive designs could include alternative randomized actions when manic symptoms worsen. Other investigative actions would proceed without change. The analyses of results would include additional hypotheses around the exacerbations in manic or depressive symptomatology

Special populations for bipolar studies fall into two categories. First are characteristics that are unlikely to have major impact on interventions and their effectiveness. These include ethnic and racial identity, sex, and socioeconomic status. However, this does not dismiss as without benefit some studies; for example, several studies have provided some evidence for greater prevalence/severity of psychotic symptoms among African American patients.

Quality of life is of limited relevance to bipolar studies in the short run but of major importance in maintenance stuies. Studies have consistently reported that functional and quality of life benefits lag behind recovery from syndromal clinical states in bipolar disorder. However, adequate and psychometrically sound measures of QOL exist, and have yielded differences among interventions. A general weakness in these and other ancillary outcome measures is that lack of adequate rater training, and often use of raters who are uninvolved in the clinical care of subjects can result in loss of sensitivity of such measures. Many of the comments about QOL apply similarly to measures of functioning.

Only recently have studies persuasively shown the plasticity of clinically significant cognitive function in bipolar disorder cognitive assessment tests. Generally, these assessments required time and effort that was off-putting to patients and expensive as a component cost of trials. Cognitive tests exhibiting sensitivity to changes with acute treatments are now available; therefore, the practical barrier to their more focused use is no longer paramount (see below).

Perhaps the major difference in emerging countries is that costs of certain regimens and drugs are prohibitive for most patients. Therefore, studies that compare drugs that are available generically—and their cost per year ranges—warrant more attention. Emerging economies are also less likely to have funding from federal revenues, therefore most potential studies in such countries will be ones funded by the pharmaceutical industry.

Neurocognition task force report

In the second presentation, Sophie Frangou (Kings College London) summarized the report from the Neurocognition Task Force. Cognitive impairment is part of the extended phenotype of bipolar disorder and is associated with genetic risk,[80] clinical severity,[81–86] and psychosocial outcome.[87] Examination of cognitive deficits in bipolar disorder is therefore integral to our efforts to define the pathophysiology of the disorder and to develop appropriate therapeutic strategies. Ideally, this should involve cognitive tests, which are standardized and validated in patients with bipolar disorder, targeting those domains that are most relevant to the disorder. A successful example of this approach is the Consensus Cognitive Battery (MCCB) developed by the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) initiative.[88,89]

As a first step in establishing a common cognitive battery for bipolar disorder, the ISBD established a committee of experts who: (1) reviewed the literature to identify cognitive measures with high sensitivity for bipolar disorder and to identify gaps in current evidence; (2) evaluated the overlap with the MCCB and the usefulness of specific MCCB subtests for bipolar disorder; and (3) proposed a preliminary battery for use in bipolar disorder that also highlights areas where further research is required.

The literature review considered findings from meta-analyses of case-control studies of cognition in bipolar disorder[81–86] and from individual studies for specific cognitive domains with high relevance for bipolar disorder but with a limited evidence base. The evidence available is reasonably robust for some but not all cognitive domains of interest. Estimates of effect size are presented for those tests with sufficient information to allow meta-analytic treatment. Moderate to large impairments in bipolar disorder are present in tests of attention, processing speed, memory and learning, and in response inhibition and set-shifting. Remarkably, given the nature of the disorder, very few studies examined patients' performance in tests of emotional processing, social cognition, or decision making. This is, therefore, an area where further research is urgently required.

There is substantial empirical evidence suggesting that the MCCB subtests focused on the domains of attention and processing speed are suitable for bipolar disorder as these tests (or nearly identical versions) have already been demonstrated to show high sensitivity to the disorder. The MCCB subtests for the domains of working memory and visual learning/memory have not been as extensively studied in bipolar disorder, but available evidence suggests that they achieve a reasonable separation between bipolar disorder patients and controls, with effect sizes of 0.8 and 0.6–1, respectively.[90,91] Thus, it would appear reasonable at the present time to include these tests in a cognitive battery for bipolar disorder pending further confirmation by future studies. In the MCCB, verbal memory/learning is assessed with the Hopkins Verbal Learning Test (HVLT). This has not been a popular instrument in bipolar disorder because of concerns about its sensitivity. Indeed, case-control effect sizes for the HVLT in bipolar disorder range from 0.4–0.6;[90,91] these values are lower than

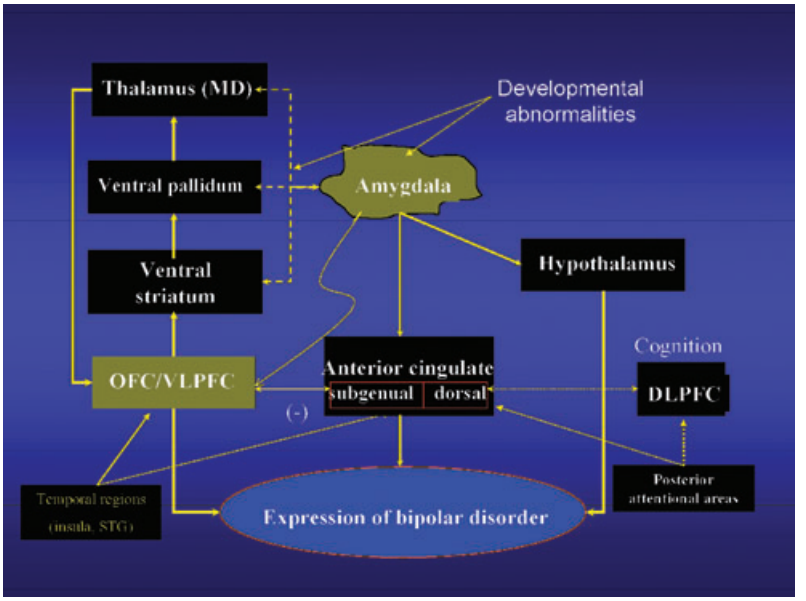

Figure 5. Schematic of abnormalities identified from neuroimaging within the ventromedial (OFC) and ventrolateral (VLPFC) emotional networks in bipolar disorder. Although the OFC and VLPFC are actually distinct circuits, they are combined here for simplicity. These networks modulate amygdala, which, in bipolar disorder, has functional and structural abnormalities, indicated by the uneven amygdala figure. Connections between amygdala and prefrontal cortex are abnormal as well, illustrated by the curving line. Prefrontal areas (OFC/VLPFC) are colored to indicate abnormalities in structure and function in these regions. Reciprocal connection between the emotional networks and cognitive (dorsal) brain systems, through the anterior cingulate, are indicated by the (−) on the arrow. Abbreviations: OFC, orbitofrontal cortex; VLPFC, ventrolateral prefrontal cortex; STG, superior temporal gyrus; DLPFC, dorsolateral prefrontal cortex.

the range typically reported in the meta-analytic studies summarizing data from more complex verbal list-learning measures, particularly the California Verbal Learning Test (CVLT). The CVLT may therefore be more appropriate for bipolar disorder patients, while the HVLT could be considered an acceptable substitute particularly in study designs that involve comparison with schizophrenia or repeated testing. The MCCB also targets reasoning and social cognition. Although both domains are relevant to bipolar disorder, the specific subtests have not been sufficiently studied or specifically implicated in bipolar disorder and are likely to lack assay sensitivity.[90] The greatest knowledge gap was identified in the assessment of the interaction between affective and nonaffective processes, where tasks of decision-making could prove particularly useful in bipolar disorder. Finally, after considering the validity and sensitivity of all the available tests discussed above, the committee also evaluated logistical aspects relating to brevity, ease of administration, reliability, repeatability, versatility and likely international utility.

The ISBD-Battery for Neurocognitive Assessment (ISDB-BANC) represents a collection of established individual tests deemed appropriate for use in bipolar disorder. It comprises eight core and two flexible subtests (choice between HVLT or CVLT) and, additionally, inclusion of the Wisconsin Card Sorting Test. The battery would be appropriate for applications where a broad screening of cognitive abilities is required, or where repeated assessments are necessary (e.g., treatment effects or clinical trials). Prospective studies in clinical populations will be required to support the psychometric properties of the ISBD-BANC and refine its constituent components. We consider the ISBD-BANC as the initial step in the process of standardizing cognitive testing in bipolar disorder.

Neuroimaging task force report

Steven Strakowski (University of Cincinnati) summarized the work of the Neuroimaging Task Force. The ISBD Neuroimaging Task Force met in Miami in December 2010 with two primary goals: (1) to review research from leading bipolar disorder

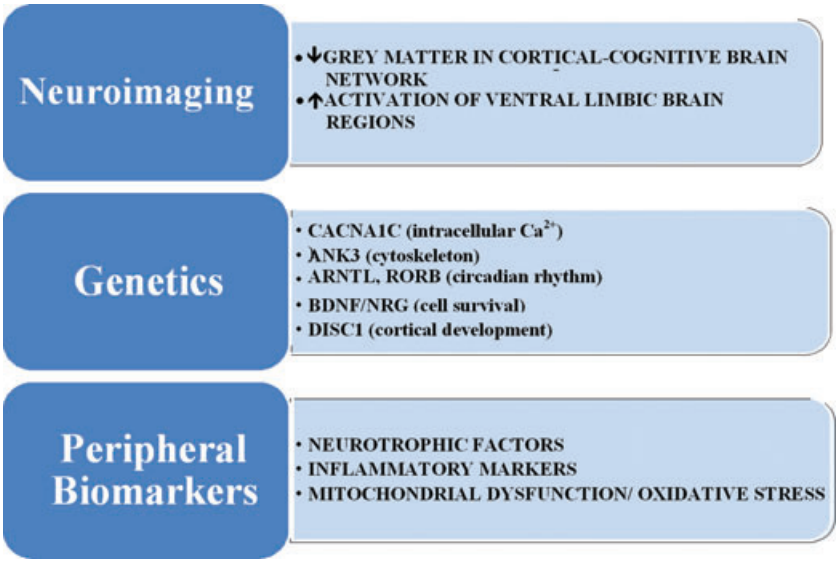

Figure 6. Potential candidates for biomarkers in bipolar disorder. Genetics studies have identified several potential candidate genes associated with increased risk for developing bipolar disorder, involving circadian rhythm, neuronal development, and calcium metabolism. Neuroimaging-based studies have consistently demonstrated loss of gray matter, and enlargement of striatum and amydgdala. In terms of peripheral biomarkers, repeated studies have found decreased levels of neurotrophic factors and increased proinflammatory cytokines and oxidative stress markers.

neuroimaging groups represented at the meeting; and (2) to develop consensus around a functional neuroanatomy for bipolar I disorder. The task force approached this subject working from the clinical assumption that bipolar disorder is a primary mood disorder; that is, that the systems most likely to underlie the condition involve those that modulate mood.

Although the specific control of emotional function in humans is not completely defined, two ventral prefrontal networks appear to modulate emotional behavior.[92–95] Both of these networks are similarly organized in that specific ventral prefrontal regions map to specific striatal then pallidal then thalamic brain areas to form iterative feedback loops that process information and modulate amygdala and other limbic brain areas. One network originates in the ventrolateral prefrontal cortex and is thought to modulate external emotional cues; the other originates in the ventromedial (orbitofrontal) cortex and is thought to modulate internal emotional stimuli.[92–95]These networks serve as a likely substrates for the functional neuroanatomy of bipolar disorder.

Neuroimaging studies suggest that abnormalities in key components of these networks occur in bipolar disorder. For example, Altshuler *et al.*[96] observed excessive amygdala activation in bipolar individuals during mania compared with healthy subjects while performing a facial affect matching task. Similar findings have been reported by others.[97–101] Abnormal amygdala activation has also been observed in bipolar disorder during other mood states.[102,103] Structural amygdala abnormalities are commonly reported in adults and adolescent bipolar subjects as well.[104,105]

A second common neuroimaging finding in bipolar disorder is abnormal ventral prefrontal activation. Several studies observed decreased activation in prefrontal cortex during mania,[90,106–108] which often occurs concurrently with amygdala overactivation.[109] Moreover, disrupted functional connectivity between amygdala and ventral prefrontal cortex has been observed during mania.[109] These findings suggest that loss of prefrontal modulation of amygdala activation may underlie the development of mood symptoms in bipolar disorder. Moreover, Strakowski *et al.* observed increased amygdala activation during euthymia that was associated with increased ventral prefrontal activation; the latter was interpreted to represent a compensatory mechanism in the ”well” state to manage limbic brain

overactivity. Several investigators have observed disruptions in the white matter connectivity between ventral prefrontal cortex and amygdala suggesting a structural basis for these functional observations.[110]

Bipolar disorder typically begins in adolescence. Recently, in a study of new-onset adolescent bipolar patients, during the year after the first manic episode, Bitter *et al.*[111] found that bipolar subjects did not exhibit amygdala growth that was seen in healthy adolescents (and adolescents with ADHD). However, at baseline, amygdala volumes among groups were the same, suggesting that amygdala developmental abnormalities occur as a result of illness progression, rather than as a cause of onset. In contrast, white matter abnormalities appear to precede the onset of bipolar illness as observed in studies of children at-risk for bipolar illness by virtue of having bipolar parents.[112]

Together, these data suggest a model of bipolar disorder (see Fig. 5) in which abnormalities within ventromedial and ventrolateral prefrontal networks lead to the expression of bipolar disorder. Disruptions in regional white matter connectivity may occur prior to illness onset, representing a potential vulnerability for developing bipolar illness. This model is illustrated in Figure 5 and provides a template to guide future investigations into the neurobiology of this important and common illness.

Biomarker committee report

Trevor Young (University of Toronto) summarized the report of the Biomarker group. The ISBD Biomarker Committee began meeting at the ICBD meeting in Pittsburgh in 2008, followed by gatherings at the ISBD meeting in San Paulo and several teleconferences. The Committee sought to have a comprehensive discussion of the area of biomarkers, which might help in the diagnosis and treatment of bipolar disorder. The group also took on a task to draft a positional paper which is under review at the journal *Bipolar Disorders*. The Committee met most recently at the ICBD meeting in Pittsburgh in June 2011.

It is clear that the etiology of bipolar disorder remains uncertain, however, there have been many recent advances in the area of genetics, pathophysiologic mechanisms, and brain imaging. The Committee reviewed the data and suggested that there were at least several biomarkers that could be identified from these three areas. The main potential candidates for biomarkers are shown in Figure 6. Neuroimaging studies have consistently shown loss of gray matter in cortical cognitive brain network[113] as well as alterations in the activation of relevant subfrontal, anterior temporal, and ventral prefrontal regions in response to an emotional stimulus in bipolar disorder.[114] Genetics has indicated several interesting potential candidate gene involvement ranging from circadian rhythms (ARNTL, RORB), to calcium metabolism (CACNA1C), cell survival, and cortical development (BDNF, DISC1).[97,115,116] With respect to peripheral biomarkers, three areas of particular interest include inflammation, mitochondrial dysfunction, and oxidative stress, and then finally changes in neurotrophic factors.[117,118]

Conclusions

Research in bipolar disorder has generated remarkable insights into the mechanisms associated with the disease risk, disease expression and treatment response. The insights highlight the complexity of bipolar disorder but also suggest that we may be close to successfully applying basic science findings in translational approaches to help us in our management of bipolar disorder. It is too early to know whether some of the most interesting targets identified will survive rigorous ongoing testing with adequate size samples and replication. To date. some of the biomarkers have already facilitated the development of new treatments, such as the work on using antioxidants in the treatment of symptoms of bipolar disorder. Techniques that strive to enhance brain health and to reduce the chance of cell loss have been a mainstay of bipolar disorder and are now supported by empirical work highlighting potential candidates that we may be able to measure in an ongoing fashion in patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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