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### **Illness and autonomy: Neurobiology, behavior, and treatment of bipolar mania**

Bipolar disorder (BD) is a complex, devastating and chronic psychiatric disease, the prognosis of which remains poor. As many as one out of five of those suffering with the illness will lose their lives to suicide (Depression and Bipolar Support Alliance, 2012). Etiologically speaking, the disease is known to have a substantial genetic basis, with a heritability rate of 70-80% (Kendler, 1983). That being said, it is not well understood how environmental factors contribute to the onset of the disorder, nor are we certain about its underlying neurobiological mechanisms. Moreover, despite the availability of highly effective pharmacological treatment, many continue to suffer from symptoms and engage in the dangerous behaviors associated with the illness. This is likely due, in part, to formidable problems with medication adherence in the bipolar community. In fact, up to 64% of patients will exhibit poor medication compliance during the course of their illness (Colom, et al., 2000), a trend that must clearly be addressed. But one may question whether patients with BD are culpable for their actions, including that of complying with medication. If genetics is such a critical factor in the development of BD, and the illness itself entails certain behaviors (including dangerous and impulsive ones), can it really be said that patients are responsible for how they act? Put differently, to what degree are such behaviors determined and involuntary, and to what degree are they performed under free will? We may begin to answer such questions by investigating that which constitutes the disease on the neurobiological, psychological, and behavioral levels; in doing so it will be clearer whether free will is a feature of the illness. Moreover, and most importantly, as we enhance our

understanding of mechanisms related to BD, we will make strides towards improving the prognosis of its sufferers.

BD is a disease characterized by intense “highs” and “lows” that cycle throughout the course of illness. The primary diagnostic marker is that of mania (the “high”), which is identified by several criteria: an abnormally elevated, expansive, or irritable mood; inflated self-esteem or grandiosity; a decreased need for sleep; excessive talking; racing thoughts; distractibility; an increase in goal-directed social, work-related, or sexual behavior; and excessive involvement in pleasurable activities that have potentially painful consequences (such as buying sprees, sexual promiscuity, and impulsivity). The symptoms must last for at least one week and cause clinically significant distress or impairment in social or occupational domains (Ettinger, 2011). Patients with BD also typically experience depressive episodes (the “low”), though depression is not necessary for diagnosis. Moreover, one with BD may also experience a mixed episode, which occurs when criteria are met for both manic and major depressive episodes. Although it is commonly thought that BD involves a consistent and predictable cycling between mania and depression, most fall closer to one or the other end of the spectrum. That is, most tend to experience either more manic episodes than depressive ones, or vice versa. Moreover, most spend a substantial amount of time in a state of euthymia, or an absence of symptoms, between episodes.

Relative to other psychiatric disorders, BD is not well understood neurobiologically. That being said, we do have some clues. Research has suggested that the disease may involve features such as enlarged ventricles (Dewan, et al., 1988; Schlegel & Krtezschar, 1987; Strakowski, et al., 1993; Swayze, Andreasen, Alliger, Ehrhardt, & Yuh, 1990), increased expression of the mRNA transcripts for both the NR2D subtype of the glutamate *N*-methyl-D-aspartate (NMDA)

receptor and the  $\alpha$ -amino-5-methyl-4-isoxazolepropionic (AMPA) receptor (Meador-Woodruff, Hogg, & Smith, 2001), altered levels of cAMP and protein kinase A (PKA) (Manji & Lenox, 2000), increased levels of protein kinase C (PKC) (Friedman, Hoau, Levinson, Connell, & Singh, 1993), increased levels of dopamine (DA) (Berk, Dodd, & Kauer-Sant'anna, 2007), alterations in serotonin, acetylcholine, and norepinephrine (Gershon & Yuwiler, 1960), and decreased levels of brain-derived neurotrophic factor (BDNF) (Machado-Vieira, et al., 2007). However, while these findings are certainly of import, most are only preliminary and have not yet been extensively replicated. Further research will be necessary to achieve a more definitive theory of the fundamental neurobiology of BD.

As we have known for centuries, mania can be remarkably destructive. Many of those suffering with BD have ruined relationships, lost jobs, engaged dangerously in substance abuse, and been incarcerated for actions performed during a manic episode. To mitigate symptoms, a mood-stabilizer, anti-convulsant, or anti-psychotic are typically prescribed; impressively, these medications are reported to have an 80% success rate in BD (National Advisory Mental Health Council, 1993). The mood stabilizer lithium—a light alkali metal—is considered to be the gold-standard of treatment for BD; it has been shown to possess anti-manic, anti-depressant, and anti-suicidality properties (Ettinger, 2011). In the present review, I will focus on studies related to the manic phase of BD specifically, as it pertains more closely to our central question. That is, by exploring the neurobiology of mania—the phase during which dangerous and impulsive activity most often occurs—we may gain insight into whether there is liability in such detrimental behaviors.

There are numerous hypotheses about what factors underlie the pathophysiology of manic states. One such hypothesis stipulates that dysfunction of the  $\text{Na}^+, \text{K}^+$ -ATPase  $\alpha 3$  (NKA)

sodium pump may play a role. For example, one study (Kirshenbaum, et al., 2011) found that the heterozygous *Myshkin* (Atp1a3Myk/+; Myk/+) mice with a missense in the neuron-specific NKA  $\alpha 3$  isoform demonstrated mood-related abnormalities mimicking manic behavior in humans with BD. Within a novel environment, for example, humans with mania will explore new objects more frequently, travel longer distances (hyperambulation), and show a chaotic path of exploration relative to healthy individuals (Young, Minassian, Paulus, Geyer, & Perry, 2007). In the present study, compared with wild-type mice (WT), *Myshkin* mice exhibited hyperambulation, increased walking speed, and decreased freezing. Moreover, the locomotor activity overall was significantly more chaotic than the WT. Another chief feature of mania in humans is a decreased need for sleep while still maintaining a high level of energy. Accordingly, *Myshkin* mice had significantly more wake time and consequently less non-REM and REM sleep than WT; moreover, the endogenous circadian period of the *Myshkin* mice was extended due to increased activity. Similarly to the impulsivity exhibited in humans with mania, the *Myshkin* mice displayed a greater preference for the open arms in the elevated plus maze (EPM) test, indicating a preference for risky behavior. *Myshkin* also exhibited hyperhedonic behavior as assessed by increased consumption of sucrose in the sucrose preference test (SPT) and displayed higher levels of drive and motivation assessed through increased activity in the forced-swim task (FST). Clearly, the behavioral profile of the *Myshkin* mice is remarkably similar to that of human manic behavior. Moreover, it was shown that the manic-phenotype was rescued through administration of lithium as well as through the transgenic restoration of functional NKA  $\alpha 3$ , suggesting its importance in the regulation of mania-like behavior.

Additionally implicated in bipolar mania is the action of protein kinase C (PKC). One notable study (Friedman, et al., 1993) investigated the activity of PKC and PKC translocation in

response to serotonin in manic participants. Prior studies show that lithium inhibits PKC-activated 5-HT (serotonin) release, most likely through inhibiting stimulation-induced PKC translocation from the cytosolic fraction to the membranous fraction of the brain tissue (Wang & Friedman, 1989). In order to evaluate this potential mechanism in the manic brain, PKC levels were examined both before and after treatment with lithium. Blood samples were collected from 12 patients in a current manic episode for measurement of platelet PKC. The patients were then treated with lithium dosages ranging from 900-2100mg per day; blood samples were again collected on days seven and 14 of lithium treatment. Finally, various levels of serotonin were added in vitro in order to measure PKC in ratios of activity in membrane/cytosol. It was found that bipolar manic patients had high platelet PKC activity and increased serotonin-induced PKC translocation. Furthermore, both were significantly attenuated by lithium. These results provide evidence that alterations in platelet PKC play a role in bipolar mania. Moreover, the authors suggest that activation of 5-HT<sub>2</sub> receptors may be responsible for the sensitivity of platelets to PKC translocation.

Brain-derived neurotrophic factor (BDNF), a growth factor associated with neuronal plasticity, neurogenesis, and cellular resilience (Duman & Monteggia, 2006), also seems to be critically involved. It has been shown that BDNF might be a risk gene locus for BD (Neves-Pereira, et al., 2002; Sklar, et al., 2002) and that decreased levels of serum BDNF are associated with severity of symptoms in other psychiatric disorders (Karege, et al., 2002; Tooyoka, et al., 2002). One study (Machado-Vieira, et al., 2007) investigated the levels of BDNF specifically in subjects experiencing mania. 30 drug-naïve bipolar patients in a manic episode were recruited for the study. Each participant received a score higher than 25 on the Young Mania Rating Scale (YMRS); subjects who were rapid-cycling, in a mixed episode, or with comorbidities were

excluded. For each subject, blood was drawn and levels of plasma BDNF were quantified. A significant decrease in BDNF plasma levels relative to controls and a significant negative correlation between BDNF levels and severity of manic symptoms were found. These findings follow suit with other studies regarding the role of BDNF in mood disorder-related neurobiological processes (Karege, et al., 2002; Shimizu, et al., 2003). Furthermore, the authors speculate that decreased levels of BDNF in mania may alter a common-signaling pathways involved in plasticity, energy levels, and mood modulation. Overall, BDNF appears to be a promising target of future research for BD and mechanisms of mania.

Reduced functioning of the dopamine transporter (DAT) has been associated with BD through genetic linkage studies (Greenwood, et al., 2001; Greenwood, Schork, Eskin, & Kelsoe, 2006), decreased DAT levels in depressed BD patients (Amsterdam & Newberg, 2007), and reduced DAT expression (Horschitz, Hummerich, Lau, Rietschel, & Schloss, 2005). A related study (Young, vanEnkhuizen, Winstanley, & Geyer, 2011) examined the role of DAT with specific regards to mania. The authors compared the performance of DAT knockdown (KD) mice versus WT mice in the Iowa Gambling Task (IGT). The IGT has been shown to be able to quantify the impulsive and detrimental gambling trait of patients with BD (Clark, Iversen, & Goodwin, 2001; Kim, Grant, Eckert, Faris, & Hartman, 2006). During the IGT the subject is asked to repeatedly choose from four decks of cards from which they may be rewarded (gain) or punished (loss). Across a series of 100 trials, healthy controls usually choose from the two decks that do not provide the most reward, but provide the least punishment. BD mania patients typically take longer to choose from the “safe” decks. The IGT was adapted for use in animal research and employed in the present study to evaluate whether the DAT KD would induce the risky behaviors associated with mania in humans. Moreover, mice were evaluated in the

Behavioral Pattern Monitor (BPM), a paradigm involving the monitoring of activity levels (diversive exploration), investigatory behavior (specific exploration), and patterns of movement. In the BPM, acutely manic humans exhibit abnormal exploration patterns involving increased activity levels, increased specific exploration and abnormal movement patterns (Perry, et al., 2009). As predicted, it was found that the DAT KD mice exhibited significantly riskier behavior than controls—as assessed by preference for disadvantageous choices and a longer latency to transition to the “safe” choice. Moreover, the DAT KD mice demonstrated a similar exploratory profile as exhibited by patients with BD mania. Thus, the present results support a role for decreased DAT levels in BD during manic episodes, contributing to the erratic exploratory patterns and risky behaviors characteristic of such episodes. Furthermore, it corroborates the DAT KD as a reliable mouse model of mania—something that will be significant for the progression of mania-related research in the future.

Additionally, it will be important to consider structural alterations in the manic brain. It has been shown that BD patients exhibit enlarged ventricles, although there have not been entirely consistent findings on this matter (Strakowski, Adler, & DelBello, 2002; Strakowski, DelBello, Adler, Cecil, & Sax, 2000). One study (Strakowski, DelBello, et al., 2002) investigated the possibility that this inconsistency is due to differences in the illness duration—or the number of manic episodes experienced—of the clinical subjects. The authors hypothesized that multiple-episode patients would show larger ventricles than first-episode patients. Magnetic resonance imaging (MRI) was employed to compare lateral and third ventricular volumes in these two groups, as well as periventricular structures such as the thalamus, the hippocampus, and the striatum. All recruited patients were in a current manic or mixed episode and scored at least 15 on the YMRS. 18 belonged to the “first-episode group”, meaning they had no prior manic

episodes, no prior psychiatric hospitalizations, and no prior treatment with mood stabilizers or anti-psychotics. 17 patients met the criteria for the “multiple-episode group”, meaning they had two or more prior manic episodes, one or more prior psychiatric hospitalizations, and prior treatment with mood stabilizers or anti-psychotics. As predicted, it was found that multiple-episode patients exhibited significantly larger ventricles than first-episode patients. Additionally, it was found that number of manic episodes was positively correlated with ventricular volume, suggesting that the illness progressively induces these neuroanatomical changes. Striatal volumes were larger in both first-episode and multiple-episode subjects, indicating that striatal alterations are not progressive but may be a good neuroanatomical predictor of BD.

A further study (Rubinsztein, et al., 2001) investigated decision-making dysfunction, a prominent feature of BD, and its neural correlates during mania. The authors recruited manic subjects, scoring an average of 25 on the YMRS, as well as subjects with unipolar depression as affective controls. Subjects participated in a probability-based decision-making task involving the choice between small, probable rewards (conservative choice) and large, improbable rewards (risky choice) (Rogers, et al., 1999). PET was performed during the task to examine neural activity. No significant handicap was found in either patients or control subjects for the choice of the most likely outcome. That being said, while depressed and control subjects exhibited response latency during more difficult tasks, manic patients showed no difference in response time. This suggests that manic patients were impulsively responding to the task. Additionally, PET data demonstrated an increase in task-related activation in the dorsal anterior cingulate region and decreased activation in the superior frontal gyrus in manic patients, indicating a foundational change in the neural circuitry involved in decision-making during mania.



Collectively, these findings contribute to a richer picture of the illness in neurobiological and neuroanatomical terms. But how do these dysfunctional processes impact the functional outcome of the patients on the behavioral level? Impulsivity is one member of the BD profile that ought to be taken the most seriously; it has been consistently linked to an increased risk of suicidal behavior (Maser, et al., 2002; Simon, et al., 2001; Swann, et al., 2005), substance abuse (Moeller, et al., 2002), and other conduct issues (Swann, Lijffijt, Lane, Steinberg, & Moeller, 2009). Moreover, though impulsivity is often associated with manic episodes, it has also been shown to be elevated even during periods of euthymia (Peluso, et al., 2007). One study (Jimenez, et al., 2012) evaluated the relationship between trait impulsivity in BD and overall functional impairment. 138 euthymic patients with BD were recruited and completed the Hamilton Depression Rating Scale (HDRS) and the YMRS to evaluate the presence of depressive or manic features. In addition, subjects completed the Functioning Assessment Short Test (FAST) and the Barratt Impulsiveness Scale (BIS-11). The FAST is a reliable scale designed to assess functional outcome that evaluates six domains of functioning: autonomy, occupational functioning, financial issues, interpersonal relationships, and leisure time. The BIS-11 questionnaire assesses trait impulsivity. It was found that FAST total score was significantly associated with BIS-11 overall score and each subscale. Overall functioning was significantly related to age, depressive symptoms, number of total mood episodes, and previous hospitalizations. Autonomy was associated with depressive symptoms, impulsivity, and number of past hospitalizations. Occupational functioning was associated with manic and depressive symptoms, impulsivity, total number of mood episodes, and previous hospitalizations. Cognitive functioning was associated with age, depressive symptoms, number of previous hospitalizations, illness duration, impulsivity, and total number of mood episodes. Finally, financial issues were associated with

depressive symptoms, number of previous hospitalizations, impulsivity, and suicidal ideation. These results importantly elucidate the specific factors, including impulsivity and poor cognitive functioning, that are associated with overall functional impairment in BD.

Perhaps the most important reason to conduct research on BD is to determine how its high rate of suicide may be attenuated. In fact, suicidal risk may be greater in BD than any other psychiatric disorder (Tondo, Isacson, & Baldessarini, 2003). One such study (Gonzalez-Pinto, et al., 2006) investigated how suicidality may be treated in BD as well as what risk factors are associated with it. It has been shown that lithium therapy is associated with decreased rates of suicide and suicide attempts and that discontinuation of lithium is associated with sharp increases of suicidal risk (Rucci, Frank, & Kostelnik, 2002; Tondo, Hennen, & Baldessarini, 2001). Accordingly, the authors evaluated the impact of lithium treatment and adherence on suicidal risk. 72 BD patients were treated clinically with lithium carbonate and their adherence and behavioral patterns monitored for a period of ten years. It was found that non-adherent subjects were much more likely to be unmarried, male, to have co-morbid substance abuse, to have more manic episodes, and to have more prior hospitalizations. The factors associated with suicidal behavior included poor adherence to lithium, a history of suicidal behavior, more hospitalizations, family history of mood disorder, and young age. Thus, the present study demonstrates that lithium adherence significantly impacts suicidal behavior. Moreover, it demonstrates various risk factors associated with such behavior; mania, for example, seems to increase the rate of non-adherence (Copeland, Zeber, & Salloum, 2008). The early recognition of such risk factors may considerably aid in the prevention of suicide in BD patients.

Clearly, pharmacological treatment of BD is crucial for the alleviation of symptoms and the prevention of dangerous behaviors associated with the illness. As we have seen,

nonadherence is a critical factor in the performance of suicidal action. Additionally, unmedicated patients are more likely to engage in criminality and substance abuse; patients are at a significantly increased risk to commit a criminal offense when experiencing mania (Quanbeck, et al., 2004). In order to develop efficacious interventions for poorly adherent patients, it will be necessary to understand *why* such patients do not comply. One study (Sajatovic, et al., 2011) evaluated reasons for nonadherence among poorly adherent patients in a mixed-method (qualitative and quantitative) model. In doing so, the authors aimed not only to gain insight into the risk factors at play, but also how the patients perceived their illness and treatment circumstances. BD patients were evaluated using the Subjective Experience of Medication Interview Treatment Adherence Bipolar Disorder Version (SEMI TAT BD)—a qualitative measure. This interview explores patient factors, environmental/social factors, provider/system factors, health beliefs, and costs/burdens associated with treatment. Patients also completed the Attitude Toward Mood Stabilizers Questionnaire (AMSQ), the Drug Attitude Inventory (DAI), and the Rating of Medication Influences (ROMI). To address the issue quantitatively, subjects completed the HDRS, the YMRS, the Brief Psychiatric Rating Scale (BPRS), and the Clinical Global Impression for use in Bipolar Disorder. It was found using quantitative analysis that difficulties with medications routines, worry about medication side effects, and denial of illness severity were the most significant contributors to negative attitudes towards medications. Qualitatively, forgetting to take medications was strongly associated with nonadherence, as was the impact of side effects and the belief that medications were unnecessary. This study provides an important target for psychotherapeutic efforts designed to promote compliance.

Taken together, the above studies lend insight into the genetics, biology, and behavior of BD. Furthermore, it is important to consider the nature of such behaviors in relation to the person

that performs them. A patient with BD must contend with a number of variables that one with a healthy brain may avoid entirely. These begin before the patient is born, in his/her preassigned genetic pattern. With the onset of the disease, stable neurobiological processes are enacted that yield the symptoms experienced by the patients. In the case of BD, these processes will manifest as intense suffering on the one hand or grandiose euphoria on the other; in any case, the result is destructive and devastating. In addition to the patient's phenomenological experience, it is known that certain neurobiological mechanisms underlie behavioral impulsivity, substance abuse, criminality, and suicide. If this is the case, at what point does the patient as an autonomous agent come into play? Their circumstances were at least partly predetermined, remote from any decision on the part of the agent, by their genes. Can it not also be said that their behaviors are determined by the neurobiology that induces them? When, if ever, have they really *chosen* to do anything? Such questions become particularly pertinent with regards to medication adherence and criminality. Is it the agent or the underlying illness that is responsible for the "decision" to cease taking medication? Even less clear, is an agent culpable for a crime while experiencing a serious mood episode? Clearly, these are distinct circumstances to those incurred by a "healthy" criminal. It seems that the answer to these questions is an indeterminate one. A patient with BD is handicapped by no choice of her own. But it is less certain that genes and neurobiology *necessarily* entail the consequent behaviors. That is, though the illness may be overwhelming, it must be assumed that there is some point at which the agent may willfully intervene and inhibit certain destructive actions. Determining this point—the locus of culpability—is the challenging part. In any case, even if there is potential to inhibit the forceful dictates of the disease, it is important to be sympathetic to this serious difficulty socially and in criminal proceedings. A

crime committed by a victim of her severe mania ought to be considered for exemption and offered instead means of preventative treatment.

One viable avenue to mitigate the dangerous behaviors performed during mood episodes is to psychotherapeutically treat the noncompliance that often precedes them. One study (Eker & Harkin, 2012) evaluated the effectiveness of a six-week psychoeducation program on medication compliance in patients with BD. 71 patients completed the Attitudes Towards Neuroleptic Treatment (ANT), the Medication Adherence Rating Scale (MARS) and the McEvoy treatment observation form to evaluate adherent behaviors. The psychoeducation program consisted of six sessions, each lasting 90-120 minutes. They were held once per week and contained 10-12 patients. The sessions involved the following sections: introduction; definition, reasons, and symptoms for bipolar affective disorder; treatments for bipolar disorder and importance of treatment adherence; medications used for bipolar affective disorder, their effects and side effects; detecting and controlling prodromal symptoms; and coping with stress, problem solving, and evaluation. It was found that medication adherence significantly increased after treatment; 40% of patients in the program were adherent before the program, while 86.7% were adherent after. Programs such as these should be increasingly encouraged or required in the psychiatric community in order to minimize the devastating effects of unmedicated illness.

BD is a severe and crippling mental illness, affecting 2.6 millions adults every year (Kessler, Chiu, Demler, & Walters, 2005). Though pharmacological treatment for the disease is quite effective, we are still in our infancy in terms of our understanding of its underlying neurobiological mechanisms. Nevertheless, a variety of hypotheses have emerged that provide a strong empirical framework upon which we may construct a clearer and more definitive theory of its neural substrates. The present review focused on mechanisms of mania, as it is most

commonly associated with the performance of impulsive and detrimental behaviors. For example, it has been proposed that dysfunction of the Na<sup>+</sup>,K<sup>+</sup>-ATPase  $\alpha$ 3 (NKA) sodium pump, altered levels of protein kinase C (PKC) and serotonin mediated PKC translocation, as well as decreased levels of brain-derived neurotrophic factor (BDNF) and dopamine transporter (DAT) underlie the manic episodes seen in BD patients. Moreover, it has been found that patients who have experienced more manic episodes exhibit larger ventricles, indicating a progressive neuroanatomical degeneration. PET imaging during a probability-based decision-making task demonstrated that manic patients have altered neurocircuitry and perform more impulsively while making decisions. One study found that factors such as trait impulsivity and cognitive impairment are associated with poor functional outcome in BD patients. Importantly, it was also found that lithium attenuates suicidal behavior and that poor medication adherence is associated with factors such as an increased number of manic episodes and prior hospitalizations. In order to further probe the question of nonadherence, one study found that BD patients were nonadherent most often due to denial of the severity of their illness and the belief that medications are unnecessary, among other things. Such beliefs ought to be targeted in psychotherapeutic treatment of medication noncompliance. In fact, it was found that a six-week psychoeducation program was significantly effective in mitigating the rate of nonadherence in BD patients. This seems to be a promising avenue to aid in the prevention of nonadherence and the consequent dangerous behaviors that are performed when patients are unmedicated. Ultimately, BD, specifically mania, is destructive to the patients themselves and potentially to those around them. Impulsive behavior resulting in criminality, substance abuse, and suicide occur most often during unmedicated episodes of mania. For this reason, understanding the patterns of mania from the neurobiological to behavioral levels is of the utmost importance; the present review has attempted to

underline some of these factors so that clinical research and preventative psychotherapeutic treatments may be advanced. Moreover, it is a critical question whether BD patients experience free will and autonomy or instead are the victims of a deterministic illness, the directives of which are inevitable. It seems that, to some extent, a patient's genetic circumstances and consequent neurobiological processes determines her behaviors. In other words, the patient must, by no choice of her own, be subject to the illness and all of its terms. That being said, it must be assumed that each patient is, for the most part, an autonomous agent that has the ability to interfere with the forceful dictates of the disease. An agent theoretically has the choice to comply with medication, though it may be far more effortful than it would be were he not ill. However, a patient experiencing severe mania may truly be outside of the realm of autonomy, and any consequent criminal or otherwise destructive behavior should be seriously considered for exemption. Ultimately, it ought to be appreciated that no one chooses to be ill, and that it requires enormous fortitude to resist what the illness compels one to do. Those of us with healthy brains should be cognizant of this fact and sympathize accordingly.

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