Artykuł poglądowy/Review article

Metabolic dysfunction within the anterior limbic network in bipolar disorder: a model for studying new treatments

Dysfunkcje metaboliczne w przedniej części układu limbicznego w chorobie afektywnej dwubiegunowej: model badania nowych sposobów leczenia

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Abstract

Bipolar disorder is a dynamic psychiatric condition that, early in its course, progresses to a recurrent and lifelong illness. Although a number of treatment options now exist, identifying effective medications for a specific bipolar individual requires trial-and-error in the absence of useful treatment response predictors. However, new imaging research suggests that bipolar disorder may result from hypermetabolism within specific brain regions constituting the anterior limbic network. This model of bipolar disorder may provide targets for monitoring treatment response and ultimately holds the promise of developing predictors of treatment response. This article provides a focused review of evidence supporting this neurophysiologic model of bipolar disorder and highlights how this model may lead to studies of medication effects and treatment response.

Key words: bipolar disorder, functional magnetic resonance imaging (fMRI), magnetic resonance spectroscopy (MRS), anterior limbic network

Streszczenie

Choroba afektywna dwubiegunowa ma dynamiczny przebieg, a jej progresja w postaci nawrotów choroby może następować w ciągu całego życia. Istnieją liczne sposoby leczenia tej choroby, a mimo to znalezienie skutecznego lekarstwa dla poszczególnych osób z chorobą dwubiegunową wymaga postępowania metodą prób i błędów, ponieważ nie mamy użytecznych sposobów wczesnego przewidywania wyników leczenia. Nowe badania obrazowe wskazują, że choroba afektywna dwubiegunowa może być związana z hipermetabolizmem w określonych regionach mózgu, takich jak przednia część układu limbicznego. Taki model neurofizjologiczny choroby afektywnej dwubiegunowej może ułatwić monitorowanie wyników leczenia za pomocą różnych metod i być może także identyfikację czynników predykcyjnych odpowiedzi na leczenie. W niniejszym artykule dokonano przeglądu dowodów na funkcjonowanie powyższego modelu neurofizjologicznego choroby afektywnej dwubiegunowej i wskazano na jego przydatność w ocenie efektów stosowania różnych leków i odpowiedzi na leczenie.

Słowa kluczowe: choroba afektywna dwubiegunowa, czynnościowy rezonans magnetyczny (fMRI), spektroskopia rezonansu magnetycznego, przednia część układu limbicznego

Bipolar disorder is a common psychiatric illness, with a lifetime population prevalence of 1-3%, that typically begins in late adolescence or early adulthood and is associated with significant morbidity and mortality (Goodwin & Jamison 1990). It is the sixth leading cause of disability worldwide in developed nations (Murray & Lopez 1998). In addition to these considerable consequences for individuals, bipolar disorder has significant societal and economic impact; for example, in the United States, the direct and indirect costs of bipolar disorder are estimated to be in the range of billions of dollars. Bipolar disorder is defined by the occurrence of mania (type I) or hypomania (type II), and the course of illness is characterized by recurring affective episodes, including manic, depressed and mixed states, interspersed with periods of euthymia. The symptomatic course of bipolar disorder is dynamic, with relatively

frequent changes in the cognitive, affective, psychotic, and behavioral expressions of the illness. Additionally, the early course of bipolar disorder is progressive. For example, in his classic text *Manic-Depressive Insanity*, Kraepelin (1921) observed that, "The shortening of the intervals, at first rapid then slower, with the number of the repetitions <of attacks> is clearly seen" (Figure 1). More recently, Roy-Byrne and colleagues (1985) used life-chart methods to identify cycle lengths in 95 bipolar patients recruited at the National Institute of Mental Health in the United States. Their findings were similar to those of Kraepelin (Figure 1). As Angst and Sellaro (2000) stated in their comprehensive review of the last century's research, "So far, then, it would seem to have been established that the course of bipolar disorder is recurrent and progressive." Specifically, the interval between affective recurrences tends to rapidly shorten between the first few (i.e., 3-5) episodes, followed by a relative flattening of changes in cycle length subsequently (Goodwin & Jamison 1990). Together, these findings suggest that the early course of bipolar disorder is characterized by cycle progression during which the underlying neurophysiology of this long-term, dynamic and recurrent illness is established.

With repeated exacerbations, bipolar patients appear to develop more severe affective episodes (Nolen et al. 2004) and cognitive impairments (Martinez-Aran et al. 2004; Lebowitz et al. 2001). Additionally, functional recovery lags symptom resolution by many months (Keck et al. 1998; Strakowski et al. 1998; Tohen et al. 2000, 2003a), so with decreasing well intervals, patients accumulate functional disabilities over time (MacQueen et al. 2000; Meeks et al. 1999; Tsai et al. 2001). Moreover, studies suggest that treatment response in bipolar disorder, particularly to lithium, decreases with increasing number of affective episodes (Swann et al. 1999). The accumulation of affective episodes becomes the strongest predictor of future episodes in bipolar patients, even after adjusting for individual differences in vulnerabilities for recurrences (Kessing et al. 2004). The risk associated with accumulating affective episodes is so widely recognized that minimizing or eliminating mood episodes is considered the central treatment goal for improving long-term outcome in bipolar patients (Keck et al. 2004; Sachs & Rush 2003; Strakowski et al. 2003).

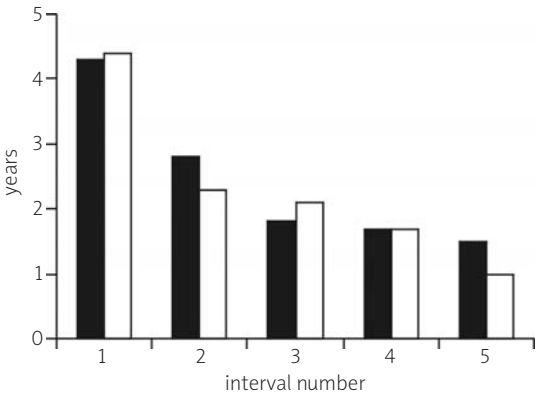

Fig. 1. Chart illustrating decreasing length of intervals between successive affective episodes (dark bar=Kraepelin 1921;[1] light bar=Roy-Byrne et al 1985[2])

Medications that are currently available for the treatment of bipolar disorder clearly improve symptoms (Strakowski et al 2001). Although these medications are effective, large clinical trials suggest that only approximately half of any patient group will exhibit an acute treatment response to any given medication. For example, Bowden et al. (2004) reported a 48% and 49% acute response to divalproex and lithium, respectively, in a 3-week acute mania trial. The lithium response in this study was typical of other controlled lithium trials for mania (Keck et al. 2000a). Recent acute mania trials with the atypical antipsychotics have reported similar response rates, despite differences in trial design and methodology (Bowden et al. 2005; Hirschfeld et al. 2004; Keck et al. 2003a,b; Tohen et al. 1999). The acute antidepressant response of lithium, in the range of 40%, appears to be less than its antimanic response (Zornberg & Pope 1993). Response rates of other medications used for bipolar depression (e.g., olanzapine, lamotrigine) are not appreciably different (Tohen et al 2003b; Calabrese et al. 1999). Combining medications improves response rates, but typically only by about 10-15 percentage points and at the cost of more adverse events (Müller-Oerlinghausen et al. 2000; Sachs et al. 2002, 2004; Tohen et al 2002; Yatham et al. 2004). Furthermore, maintenance studies report high rates of affective episode recurrences even in the presence of good medication adherence (Bowden et al. 2003; Keck et al 2000b; Tohen 2003c,2006). Although a number of clinical predictors of drug response (e.g., specific symptoms) have been hypothesized, these predictors are unreliable in individual patients and are confounded by being subjective and unstable, essentially by the very nature of bipolar disorder. Moreover, most patients experience at least mild symptoms between

episodes, so that in the absence of specific indicators of illness progression, it is unclear when these symptoms warrant aggressive treatment, which may require tolerating side effects despite only mild symptoms. Consequently, the early treatment course of bipolar disorder consists of repeated empirical medication trials hoping to identify a tolerable pharmacotherapy regimen that minimizes affective recurrences. This trial-and-error often takes months or even years and virtually guarantees that many, if not most, bipolar patients experience multiple affective episodes prior to achieving long-term mood stability, ensuring the course progression noted earlier (Sachs & Rush 2003; Strakowski et al. 2001, 2003).

From these considerations, it is clear that identifying reliable predictors of treatment response could dramatically improve medication assignment, eliminate ineffective drug trials, and decrease the number of affective episodes early in the progressive course of bipolar disorder. An important step toward identifying treatment response predictors is to first define a viable model of the progressive neurophysiology of bipolar disorder to provide potential targets for both treatment development and treatment response monitoring. In this paper, then, we provide a focused review of neuroimaging studies in bipolar disorder in order to achieve this first step. This paper extends previous review articles by us and others (Strakowski et al. 2005a; Stork & Renshaw 2005).

The functional neuroanatomy of bipolar disorder: the anterior limbic dysfunction model

Unlike many psychiatric conditions, in which patients progress to a relatively stable end-state (e.g., the negative syndrome in schizophrenia), bipolar disorder remains a constantly fluctuating illness throughout its course. Consequently, the dynamic expression of bipolar disorder suggests that its neurophysiology involves dysfunction of brain networks that maintain emotional homeostasis. In particular, human emotional behavior appears to be modulated by ventral prefrontal cortical and subcortical brain regions that share common phylogenetic and cytoarchitectural features and form circuits that we term the 'anterior limbic network' (Mega et al. 1997; Ongür & Price 2000). The anterior limbic network (Figure 2) consists of medial orbitofrontal (Brodmann area, BA, 11) and ventrolateral prefrontal areas (BA 10, 47) that exhibit extensive reciprocal projections to basal and accessory basal amygdala, para-hippocampal gyrus (BA 36), rostral (agranular) insula, and subgenual (BA 25) and rostral anterior (BA 24, 32) cingulate (Mega et al. 1997; Ongür & Price 2000; Strakowski et al. 2005a). Through these connections, these prefrontal areas receive extensively processed multisensory and visceral information that is integrated to produce emotional and behavioral responses. Specifically, projections from the anterior limbic network to the hypothalamus produce visceromotor outputs that create bodily sensations (i.e., "feelings") (Mega et al. 1997; Ongür & Price 2000; Strakowski et al. 2005a). The prefrontal areas of this network form feedback loops with ventromedial striatum and thalamus to modulate effector mechanisms for psychomotor responses, i.e., to generate behavioral responses to emotional stimuli. Reciprocal connections with dorsal prefrontal areas contribute to the cognitive expression of mood. With these extensive connections and outputs, prefrontal areas of the anterior limbic network appear to constantly monitor internal and external sensory information in order to iteratively modulate emotional and social behavior and, ultimately, maintain emotional homeostasis (Ongür & Price 2000; Nauta 1971). Consequently, we and others have suggested that the dynamic symptoms of bipolar disorder arise from dysfunction within this network (Bearden et al. 2001; Blumberg et al. 2003a; Ketter et al. 2001; Phillips et al. 2003; Strakowski 2002; Strakowski et al. 2002a; Strakowski et al. 2005a).

Both positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) studies have reported over-activation in portions of the anterior limbic network in patients with bipolar disorder, even during periods of euthymia. For example, we used fMRI to study euthymic bipolar and healthy comparison subjects matched by age, sex, and ethnicity while they performed a simple attentional task (Strakowski et al. 2004). These patients had been identified from a long-term outcome study (Strakowski et al. 2005b, in press) because they had self-discontinued medications (against medical advice), yet had maintained euthymia for at least one month prior to and one month after the scan. Bipolar subjects demonstrated increased activation in left amygdala, ventrolateral prefrontal cortex (VLPFC), insula, and hypothalamus, all regions of the anterior limbic network. Yet, despite the increased emotional network activation, the

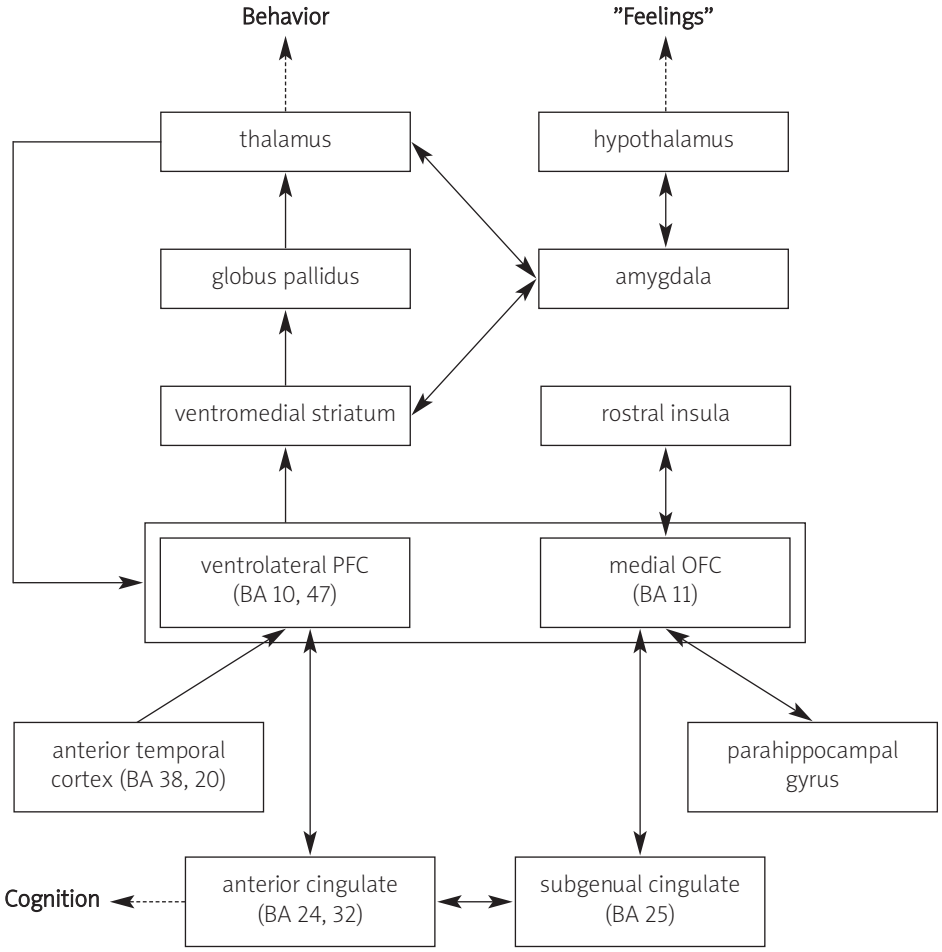

Fig. 2. Graphical representation of the anterior limbic network. PFC=prefrontal cortex; OFC=orbitofrontal cortex; BA=Brodmann Area(s)

bipolar and healthy subjects performed the task similarly. Notably, the bipolar subjects also exhibited increased activation in posterior attentional regions, which are associated with increasing task difficulty. We suggested that increased activation in posterior attentional brain regions in the patients compensated for interference from excessive anterior limbic activation, allowing the patients to perform the task normally. However, we also posit that because euthymic bipolar subjects are already compensating for overactive emotional networks, this compensation fails with more difficult tasks or under stress, leading to cognitive and mood symptoms (i.e., affective episodes). Notably, several other recent studies have observed abnormalities in regional brain activation in bipolar compared with healthy subjects, consistent with our findings (e.g., Adler 2004a; Blumberg et al. 2003a,b; Brambilla et al. 2005; Chang et al. 2004; Lawrence et al. 2004; Strakowski et al. 2004, 2005c; Yurgelun-Todd & Ross 2006). Together, these studies suggest a functional neuroanatomic model for bipolar disorder, consistent with over-activation of the anterior limbic network illustrated in Figure 2.

Anterior limbic metabolic dysfunction in bipolar disorder

Several lines of evidence suggest that abnormalities in energy-dependent cellular processes (e.g., Kato & Kato 2000; Modica-Napolitano & Renshaw 2004; Stork & Renshaw 2005) may underlie dysfunction observed in the anterior limbic network (Strakowski et al. 2004) and, ultimately, the expression of bipolar disorder. For example, Dager et al. (2004) used ^{1}H (proton)-MRS to compare medication-free, predominantly depressed bipolar and healthy subjects. They found elevated gray matter lactate and Glx levels in the bipolar patients,

particularly in cingulate and insula (i.e., cortical areas of the anterior limbic network, Figure 2). Lactate is typically not visible with ^{1}H-MRS; its presence suggests a shift in energy redox state from oxidative phosphorylation toward less efficient glycolysis. Since glycolysis tends to predominate in highly activated states, this finding in bipolar patients might reflect hypermetabolism in brain areas that modulate mood, including the anterior limbic network (Stork & Renshaw 2005). Elevated Glx resonance also supports this conclusion. Although the ^{1}H-MRS Glx resonance includes glutamate, glutamine, and small amounts of GABA, in prefrontal cortical areas Glx is predominantly the excitatory neurotransmitter glutamate, particularly with higher magnetic fields (Pouwels & Frahm 1998; Ross 1991). Several other investigators have identified elevated Glx concentrations using ^{1}H-MRS in bipolar disorder during affective episodes (Castillo et al 2000; Cecil et al. 2002; Dager et al. 2004; Michael et al. 2003), although not during euthymia (Chang et al. 2003; Winsberg et al. 2000). Therefore, affective episodes may be associated with elevated levels of glutamate, and consequently, glutamatergic excitotoxicity, which might be reflected in functional and structural changes in the brain as well as in markers of neuronal health (e.g., neuronal density). Levels of N-acetyl aspartate (NAA) provide one measure of neuronal density, and ^{1}H-MRS studies have identified decreased prefrontal NAA concentrations in bipolar compared to healthy subjects (Cecil et al. 2002; Chang et al. 2003; Winsberg et al. 2000). Recent work suggests that NAA plays an integral role in the energetics of neuronal mitochondria (Stork & Renshaw 2005). Therefore, metabolic inefficiencies in bipolar disorder might also contribute to decreased NAA levels, particularly as patients accumulate affective episodes (i.e., experience repeated excitotoxicity). Indeed, studies have found that NAA concentrations are inversely proportional to illness duration (Change et al. 2003; Winsberg et al. 2000). Moreover, these putative metabolic abnormalities would be expected to disrupt other high energy processes, such as neuronal phospholipid (membrane) metabolism (Stork & Renshaw 2005). Several studies have reported elevations of ^{1}H-MRS choline (Cho) levels in bipolar disorder, particularly in the striatum (again, a component of the anterior limbic network) (reviewed in Stork & Renshaw 2005). The Cho peak comprises predominantly membrane-based choline compounds such as phosphocholine and glycerophosphocholine. Additionally, *myo*-inositol (mI) levels are also elevated in bipolar disorder; mI is an important precursor to the membrane phospholipid phophatidylinositol. These Cho and mI elevations support suggestions of accelerated membrane turnover and breakdown consistent with a hypermetabolic state in bipolar disorder (Stork & Renshaw 2005). Moreover, mI is a substrate for the phosphoinositide second-messenger system, so that abnormalities in the mI peak observed with MRS may also reflect abnormalities in cellular communication, again potentially as a result of disrupted cellular metabolism.

Supporting these ^{1}H-MRS findings, phosphorus (^{31}P)-MRS studies of bipolar disorder also report abnormalities in bioenergetic processes. ^{31}P-MRS provides a means to assess brain energetics (i.e., α-, β- and γ-ATP, creatine phosphate, PCr) and high-energy membrane metabolism [i.e., phosphomonoesters (PME) and phosphodiesters (PDE)]. For example, PCr is a high-energy phosphate that is formed from ATP and creatine. When ATP is consumed, PCr transfers its phosphate to ADP to replenish ATP stores, essentially buffering the concentration of ATP. PCr concentrations decrease in response to increased energy demand, reflecting this role. ^{31}P-MRS studies found lower prefrontal PCr levels in bipolar patients during affective episodes than in healthy subjects (Kato et al. 1994, 1998; Murashita et al. 2000). These observations are consistent with the presence of hypermetabolic processes in bipolar patients during mood episodes. Moreover, studies reported that the PME resonance in euthymic bipolar patients is lower than in healthy subjects (Yildiz et al. 2001). The ^{31}P-MRS PME resonance consists of phospholipid membrane components, namely phosphocholine, phosphoethanolamine, phosphoserine, and sugar phosphates including inositol-1-monophosphate. Therefore, low PME levels in bipolar disorder suggest excessive membrane turnover, consistent with the previously noted Cho findings. Additionally, the presence of this PME abnormality during euthymia suggests it may be a trait, rather than state, marker.

In their extensive review, Stork and Renshaw (2005) concluded that the current MRS findings support a hypothesis of mitochondrial dysfunction in bipolar disorder characterized by impaired oxidative phosphorylation (and/or regional hypermetabolism) with a resultant shift toward glycolytic energy production (increased lactate and glutamate), a decrease in total energy

production and/or substrate availability (decreased PCr and NAA) and altered phospholipid metabolism (elevated Cho and decreased PME). The excellent Stork and Renshaw (2005) review provides additional details on these associations for the interested reader.

The suggestion of regional hypermetabolism is consistent with the previously reviewed study of unmedicated, euthymic bipolar patients, which found increased fMRI activation in prefrontal and other regions of the anterior limbic network (Strakowski et al. 2004); i.e., these functional brain abnormalities may reflect the hypothesized metabolic dysfunction. Moreover, findings in euthymic patients suggest that hypermetabolic networks are a trait of bipolar disorder, putting patients at risk for mood instability and the development of affective episodes. We propose that it is early in the course of illness that these neurophysiological features are established, and that they are reflected in brain functional (fMRI) and neurochemical (MRS) measures.

A model for bipolar disease progression

From the previous considerations, we hypothesize that, in bipolar disorder, inherent inefficiencies in neural metabolism within anterior limbic brain regions lead to regional hypermetabolism and excessive glutamate production during affective episodes. Recurrent glutamatergic excitotoxicity then produces neural tissue injury reflected by changes in regional brain function and structure. These changes then contribute to the initial progression of the course of illness. Recent neuroimaging work supports these suggestions. For example, using MRI we examined the morphometry of the cerebellar vermis in first- and multiple-episode manic bipolar patients and healthy subjects (DelBello et al. 1999; Mills et al. 2005). The vermis is heavily connected within the anterior limbic network. Vermal volumes of first-episode patients were similar to healthy subjects, whereas multiple-episode patients exhibited significantly smaller volumes than both other groups. The decrease in vermal size was associated with the number of prior affective episodes. In another study, we compared lateral ventricular volumes in first- and multiple-episode manic bipolar and healthy subjects (Strakowski et al. 2002b). The distribution of lateral ventricular volumes of first-episode patients was essentially the same as healthy subjects, whereas multiple-episode patients exhibited significant ventricular enlargement relative to both other groups. Ventricular volume was associated with the number of previous manic episodes. This association suggested that progressive ventriculomegaly occurred with recurrent affective episodes. This progression in ventricular volume could not be explained by volume loss in periventricular gray matter structures (e.g., striatum). Instead, the finding suggested loss of periventricular white matter. Periventricular white matter includes pathways connecting components of the anterior limbic network (Strakowski et al. 2005a; Adler et al. 2004b). Coupled with the vermal findings, these results suggest that structural brain changes occur with recurrent affective episodes in brain regions associated with mood, consistent with the initial progression of bipolar illness. These structural changes appear to be reflected in brain dysfunction as well (Strakowski et al. 2005a).

Drug effects on anterior limbic metabolic dysfunction in bipolar disorder

Using MRS, lithium has been demonstrated to alter energy and membrane metabolism (Yildiz et al. 2001). Lithium inhibits inositol monophosphatase, leading to increases in inositol-1-monophosphate (reflected in the ^{31}P-MRS PME resonance) and decreased inositol, which can be assessed with ^{1}H-MRS. Moore et al. (1999) observed a decrease in the prefrontal *myo*-inositol ^{1}H-MRS resonance 5-7 days after initiating lithium treatment that persisted through at least 3 weeks. Symptom improvement did not temporally correlate with changes in *myo*-inositol levels. This finding might indicate that *myo*-inositol changes are unrelated to treatment response; alternatively, these changes may be an early marker of a cascade of events leading to normalized cellular metabolism and clinical improvement. Consistent with the latter suggestion, Davanzo et al. (2004) reported decreases in *myo*-inositol levels in bipolar adolescents treated with lithium, but only in treatment responders. Additionally, Patel et al. (in press) also found that lithium-induced decreases in mI early in the course of treatment were associated with treatment response in bipolar depression. Lithium treatment has also been associated with reductions of glutamate (Glx) (Friedman et al. 2004) and increases in NAA levels (Moore et al. 2000a). Moore and colleagues suggested that lithium-induced increases in NAA levels may be due to direct neurotrophic effects that prevent or reverse the

progressive loss of brain tissue suggested by the structural MRI studies previously discussed (Moore et al. 2000a,b). Alternatively, lithium may be correcting a hypermetabolic state, leading to restoration of NAA stores.

Less is known of the neurometabolic effects of other medications used in bipolar disorder. Silverstone et al. (2002) found that both lithium and divalproex normalized PME and *myo*-inositol resonances in euthymic bipolar patients; however, in contrast to lithium, divalproex did not increase NAA levels (Silverstone et al. 2003). Moreover, whereas lithium appears to decrease Glx levels, divalproex does not (Friedman et al. 2004). Recently we completed an ^{1}H-MRS study examining the effects of olanzapine as an acute treatment for mania in bipolar adolescents (DelBello et al 2006). Prefrontal NAA levels significantly increased in patients who achieved remission on olanzapine, but decreased in those who did not; these differential effects were not observed until after the seventh day of treatment. Additionally we found that higher baseline choline concentrations were associated with remission, suggesting that membrane metabolic abnormalities identified by MRS may be useful for predicting treatment response. However, unlike the lithium studies previously reviewed, olanzapine did not appear to have significant effects on *myo*-inositol concentrations. Although the data are clearly preliminary, these studies suggest that different medications used for treating bipolar disorder differentially alter high-energy brain processes. Moreover, many of the changes are associated with clinical improvement, and the neurophysiological ramifications of these changes could be assessed with neuroimaging. For example, using fMRI we recently found that medication treatment of euthymic bipolar patients was associated with increased activation in cognitive (dorsolateral prefrontal and anterior cingulate) brain regions while performing a Stroop task (Strakowski et al. 2005c). Since mood and cognitive networks appear to have reciprocal connections, mediated through the anterior cingulate (Mayberg et al. 1999; Yamasaki et al. 2002), this finding may reflect effects of medications to decrease anterior limbic hypermetabolism, thereby decreasing interference from overactive mood circuits and increasing activation in the corresponding cognitive networks. Consistent with this idea, Blumberg et al. (2005) found less amygdala over-activation in medicated bipolar patients compared with unmedicated patients.

Moving forward: the anterior limbic dysfunction model for treatment assessment

As noted previously, only half of a bipolar sample will respond to any specific drug monotherapy. Importantly, failure to respond to one medication does not predict failure to respond to another, so that it is not the same 50% of patients who respond to all treatments. This observation suggests heterogeneity in the underlying neurophysiology of bipolar disorder, which is further supported by the previously noted observations that treatment responders may have different neurochemical profiles than nonresponders (Davanzo et al. 2001; DelBello et al 2006). Nonetheless, because brain metabolism can be influenced through a number of pathways (e.g., lithium's effects on inositol monophosphatase or atypical antipsychotics' effects on neuromodulators such as serotonin or dopamine) different treatments may normalize metabolism or alter glutamatergic neurotransmission through different mechanisms, or may modulate symptoms through alternative pathways. Therefore, the effects of different treatments may be reflected in differential changes in brain metabolism or function. Once identified, these fMRI and MRS treatment response markers can be further developed through prospective targeted drug trials in order to identify treatment response predictors, allowing improved treatment assignment in patients early in the course of illness (and perhaps even prior to developing illness), potentially preventing disease progression.

In summary, then, recent studies suggest that hypermetabolism within the anterior limbic network may underlie the expression of bipolar disorder. This model of bipolar disorder provides specific targets to monitor treatment and clinical response as well as, over time, to develop treatment response predictors. Although research in this area is still quite preliminary, integrating specific neurophysiological models with treatment trials and imaging techniques may provide a means for rational drug development for bipolar disorder in the future.

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