Multiple levels of impaired neural plasticity and cellular resilience in bipolar disorder: Developing treatments using an integrated translational approach

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Abstract
Objectives. This paper reviews the neurobiology of bipolar disorder (BD), particularly findings associated with impaired cellular resilience and plasticity. Methods. PubMed/Medline articles and book chapters published over the last 20 years were identified using the following keyword combinations: BD, calcium, cytokines, endoplasmic reticulum (ER), genetics, glucocorticoids, glutamate, imaging, ketamine, lithium, mania, mitochondria, neuroplasticity, neuroprotection, neurotrophic, oxidative stress, plasticity, resilience, and valproate. Results. BD is associated with impaired cellular resilience and synaptic dysfunction at multiple levels, associated with impaired cellular resilience and plasticity. These findings were partially prevented or even reversed with the use of mood stabilizers, but longitudinal studies associated with clinical outcome remain scarce. Conclusions. Evidence consistently suggests that BD involves impaired neural plasticity and cellular resilience at multiple levels. This includes the genetic and intra- and intercellular signalling levels, their impact on brain structure and function, as well as the final translation into behaviour/cognitive changes. Future studies are expected to adopt integrated translational approaches using a variety of methods (e.g., microarray approaches, neuroimaging, genetics, electrophysiology, and the new generation of –omics techniques). These studies will likely focus on more precise diagnoses and a personalized medicine paradigm in order to develop better treatments for those who need them most.

Key words: Bipolar disorder, depression, treatment, neurobiology, brain

Introduction
Bipolar disorder (BD) is a severe, multifactorial, and chronic mental illness, with a prevalence of approximately 4.4% in the United States (Merikangas et al. 2007). BD likely results from interactions between genetic vulnerability and environmental stressors that cause widespread dysfunction across a wide range of biological systems. Impaired cellular resilience and neuroplasticity pathways across biological systems at multiple levels have been implicated in the pathophysiology of BD (Figure 1).

Since the initial use of lithium to treat BD more than half a century ago, no other treatment has been developed specifically for this disorder; indeed, all other current therapeutics had different primary indications before being tested in BD. In addition, the rate of treatment resistance remains high, underscoring the need to develop new, improved therapeutics for BD. Interestingly, in both clinical and preclinical models, chronic treatment with mood stabilizers, especially lithium, reversed or minimized different compromised components associated with impaired cellular resilience and plasticity (Machado-Vieira et al. 2009; Quiroz et al 2010; Soeiro-de-Souza et al. 2012), but very few longitudinal studies have provided insight regarding the
Genetic factors

Genetic factors play a major role in the aetiology of BD (Craddock and Sklar 2009) but, to date, studies have not clearly implicated specific genes. Instead, currently available data reinforce the polygenic basis of BD, with significant state-related abnormalities in gene expression. Nevertheless, some findings regarding genes that display state-related changes in expression in BD were not replicated across studies (Munkholm et al. 2012).

The first data suggesting a role for genetic factors in BD came from twin studies showing a higher concordance rate for monozygotic than dizygotic twins (reviewed in Goodwin and Jamison (2007)). Linkage studies subsequently identified a variety of chromosomal regions that may harbor susceptibility loci for BD (Nurnberger and Foroud 2000). Later, genome-wide association studies (GWAS) similarly identified a number of loci showing a strong association with BD in 2008, Baum and colleagues identified the first gene for BD that went beyond the genome-wide significance threshold of $P < 5 \times 10^{-8}$ in a GWAS: diacylglycerol kinase eta (DGKH) (Baum et al. 2008), a gene that activates protein kinase C (PKC). This finding was subsequently confirmed in another study (Weber et al. 2011).

Methods

PubMed/Medline articles and book chapters published over the last 20 years were identified using the following keyword combinations: BD, calcium, cytokines, endoplasmic reticulum, genetics, glucocorticoids, glutamate, imaging, ketamine, lithium, mania, mitochondria, neuroplasticity, neuroprotection, neurotrophic, oxidative stress, plasticity, resilience, and valproate.
In addition to DGKH, diverse risk genes for BD that directly or indirectly interact with second-messenger systems and circadian rhythms have been identified. Some of the genetic findings have been independently replicated, while others have not (Table I). Other polymorphisms within the alpha 1C subunit of the L-type voltage-gated calcium channel (CACNA1C), Ankrin 3, and Neurocan have also been associated with BD (Gichon et al. 2011). These genes have been implicated in ionic channel transport, cellular structure and growth, and neurotransmitter metabolism, all of which have been associated with mood and cognitive changes in diverse models. Interestingly, several of the genes encoded in these chromosomal regions are consistent with the notion that subtle differences in neural development and/or neuromplasticity may underlie mood disorders (Scott et al. 2009). Recently, the Psychiatric GWAS Consortium Bipolar Disorder group performed a combined analysis of 7481 individuals with BD and 9250 controls (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011). The combined analysis of the discovery and replication sample confirmed genome-wide significant evidence of association for CACNA1C (Psychiatric GWAS Consortium Bipolar Disorder Working Group 2011). However, a recent meta-analysis of 487 GWAS in BD found that no candidate gene was associated with BD risk after correction for multiple testing (Seifuddin et al. 2012). These findings emphasize the need for alternative approaches when evaluating the potential genetic basis of BD.

**Neuroimaging and neuropathology studies in BD: A synthesis**

Imaging studies conducted using magnetic resonance imaging or magnetic resonance spectroscopy (MRS) (Table II) have provided further insights into the neurobiological basis of BD, as have postmortem brain tissue studies (Table III). Due to space limitations, positron emission tomography and functional MRS studies are not reviewed.

**Imaging studies**

Recent studies have suggested the presence of neuroprogressive changes in BD; however, some limitations have also been noted (Schneider et al. 2012). For instance, most imaging studies have used a cross-sectional design, which is a limitation when one considers the fluctuating course and biological changes associated with BD. Thus, any conclusions drawn before conducting long-term prospective studies in adult or geriatric populations would be purely speculative. Reinforcing this notion, a recent meta-analysis of longitudinal neuroimaging studies in BD described stability over time in total brain volume in BD and healthy controls, as well as heterogeneous findings (increases and decreases) in all cortical and subcortical areas (Lim et al. 2013). Furthermore, mood state, illness duration, and pharmacological treatment were not homogeneous across studies.

One of the most replicated findings in BD is the presence of subcortical white matter hyperintensities in cross-sectional studies (Kato 2008a). However, this finding has also been found to occur in healthy individuals, those with other mental disorders, and as a consequence of aging (Debette and Markus 2010), thus raising issues of specificity. Nevertheless, white matter alterations may be more stable than other structural abnormalities, and may represent an early marker of disease risk (Schneider et al. 2012). In this context, diffusion tensor imaging (DTI) studies – which are capable of assessing microstructural abnormalities in myelinated tracts – have recently demonstrated deep white matter abnormalities in individuals with BD (Vederine et al. 2011; Torgerson

**Table I. Genetic findings in BD: Overview.**

Genetics: General aspects

- Elevated concordance rate in monozygotic twins
- Some evidence for overlap (common alleles) with schizophrenia
- Several risk alleles not replicated by different studies
- Most of the risk alleles present an unknown role in the pathophysiology of BD
- Not linked with specific phenotypes, no direct impact on therapeutics
- No relative risk for individual genes (polygenic basis)

Genetics: Potential risk genes

- *DGKH* (a diacylglycerol kinase involved in lithium’s sensitive inositol pathway)
- *CACNA1C* (a voltage-operated calcium channel that regulates calcium dynamics and synaptic plasticity)
- *ANK-3* (plays a key role in cell proliferation and activation)
- *NCAM*

Risk genes with obscure pathophysiological relevance:

*NDUFAB1, PALB2, DCTN5, MYO5B*

BD, bipolar disorder; DGKH, diacylglycerol kinase eta; CACNA1C, alpha 1C subunit of the L-type voltage-gated calcium channel; ANK-3, Ankrin 3; NCAM, neural adhesion cell molecule.
Other studies using DTI have further reported decreased fractional anisotropy changes, which have been associated with fiber integrity in BD (James et al. 2011; Vederine et al. 2011). These myelinated tracts connect regions involved in regulating emotions, and may involve changes in limbic connectivity and emotional processing in BD.

In addition, reduced subgenual prefrontal cortex (PFC) volume was observed in BD, and also linked to treatment response (Drevets et al. 1997; Hirayasu et al. 1999; Sharma et al. 2003). Meta-analyses of voxel-based morphometry describe grey matter reductions in anterior insula, inferior frontal cortex, and anterior cingulate cortex (ACC) in individuals with BD (Bora et al. 2010). Amygdala and hippocampal volume have been inconsistent across BD studies (Schneider et al. 2012), which may be due to varying patient exposure to mood stabilizers, especially lithium (Lyoo et al. 2006; Moore et al. 2009).

Furthermore, evidence suggests loss of grey matter volume and cell atrophy in the PFC, ACC, and subgenual areas (Kempton et al. 2008). These areas are directly involved in activating neuroplasticity and neurotrophic cascades. In line with these findings, MRS studies have described dysfunctional brain energy metabolism in BD. MRS studies have noted decreased phosphocreatine (Kato et al. 1994), intracellular pH (Kato et al. 1993), creatine (Port et al. 2008), and increased lactate (Dager et al. 2004) in BD. In addition, a recent systematic review and meta-analysis of MRS studies in BD noted that decreased N-acetylaspartate (NAA) levels in basal ganglia is one of the most consistent findings in BD, with altered parameters for creatine and choline, both of which are involved in energy metabolism (Kraguljac et al. 2012). MRS studies have also reported glutamatergic abnormalities in individuals with BD. For instance, both glutamate and Glx (glutamate + glutamine) levels were found to be higher in different limbic areas in individuals with BD during both the depressed and manic phases of the illness (Yüksel and Ongur 2010; Maddock and Buonocore 2012).

Interestingly, lithium treatment has been associated with increased NAA levels, supporting lithium’s mitochondrial-enhancing properties in addition to its known neurotrophic and neuroprotective effects (Quiroz et al. 2008). In addition, lithium increases grey matter volume in cerebral areas directly implicated in emotional processing and cognitive control (Kempton et al. 2008). The same meta-regression and meta-analysis analysing 98 structural studies in BD, bipolar disorder; PET, positron emission tomography; DTI, diffusion tensor imaging; fMRS, functional magnetic resonance spectroscopy; NAA, N-acetyl-aspartate; PFC, prefrontal cortex; ACC, anterior cingulate cortex.

Table II. Imaging findings in BD.

| Neuroimaging: General aspects | *Most of the data were not replicated in subsequent studies  
*Heterogeneous samples  
*Although BD is not a degenerative disorder, there is evidence for cell death  
*Promising areas: PET, DTI, fMRS.  
*Association with cognitive performance deficits |
| Neuroimaging: Main findings | *Subcortical white matter hyperintensities (potential biases)  
*Enlargement of lateral and third ventricles  
*Inconsistent data regarding amygdala and hippocampus  
*State-dependent increase in myo-inositol levels and decreased NAA in BD  
*Glutamate increase in BD  
*Lithium consistently increases grey matter volume and NAA levels  
*Functional relevance for PFC and ACC |

Table III. Synthesis of neuropathological findings in BD.

| Neuropathological: General aspects | *Support a role for neuronal and glial atrophy and death in individuals with BD  
*Limitations include heterogeneity of samples as regards premorbid status, medication, comorbidities  
*Few brain collections with limited number of samples lead to difficulties re: reliability of diagnostic criteria (especially as evaluated retrospectively) |
| Neuropathological: Main findings | *Changes in number, density, and size of neurons  
*Most prominent finding is altered number (decreased), density, and size (increased) of glial cells, especially oligodendrocytes  
*Changes in expression and levels of proteins involved in synaptic plasticity (e.g. GAP-43, synapsin family, SANP-25, etc.)  
*Proposed potential association with glutamate excitotoxicity and HPA deregulation |

BD, bipolar disorder; HPA, hypothalamic pituitary adrenal.
BD found that lithium consistently increased grey matter volume (Kempton et al. 2008). In a longitudinal study, Moore and colleagues found that patients with bipolar depression had a significant increase in total grey matter volume after four weeks of treatment with lithium and, furthermore, that this increase was associated with clinical improvement (Moore et al. 2009). Overall, the evidence suggests that mood stabilizers – particularly lithium – activate neuroplasticity and cellular growth, with the potential to reverse atrophic changes in neural structures and pathways in BD. However, further prospective studies are needed that focus on the association between biological and clinical outcomes.

Neuropathological studies

Most current evidence from postmortem studies suggests that apoptosis and oxidative stress play a key role in the pathophysiology of BD, leading to consistent cell shrinkage and decreased neuronal/glial cell number and altered mitochondrial proteins. Diverse studies have noted alterations in the ACC, PFC, and subcortical areas (Gigante et al. 2011; Andreatza et al. 2013). Decreased number, and/or size of neurons and glia, particularly oligodendrocytes, have been noted in the PFC, ACC, and amygdala (Gigante et al. 2011). These neuropathological findings may reflect the higher vulnerability of oligodendrocytes to insults (e.g., excess glutamate levels, stress, etc.) in the central nervous system, oligodendrocytes insulate long-range axons with myelin sheaths to form white matter tracts. Neuronal density and size were also found to be decreased in layers III, V, and VI in BD (Cotter et al. 2001; Rajkowska 2002). Changes in protein expression, which are highly implicated in the regulation of synaptic plasticity, have also been observed in the postmortem brains of individuals with BD; these include reduced levels of hippocampal GAP-43, netrins, and synapsin family proteins (Selemon and Rajkowska 2003; Gigante et al 2011). Methodological differences (e.g., premorbid status, medication use, lifestyle, comorbidities, misdiagnosis, etc.) have to be taken into account. Equally important is the fact that the brains studied in most published postmortem studies of BD (80%) were drawn from two US collections (the Stanley Foundation and the Harvard Brain Tissue Resource Center) (Deep-Soboslay et al. 2008). Overall, despite important initial findings, neuropathological studies in BD have not offered additional insights into the pathophysiology of this disorder. In contrast, results drawn from new advances in human neuroimaging in vivo seem to be more reliable and less subject to potential bias.

Neurotransmitters and second-messenger systems

Early studies proposed that BD resulted from abnormal levels of the intrasympathetic neurotransmitters norepinephrine, dopamine, acetylcholine, serotonin, and gamma-aminobutyric acid (GABA). The evidence was largely indirect, and stemmed from peripheral sources (plasma, serum, urine, etc.); thus, it was unclear how representative these peripheral measures were of central measures. In recent years, increasing attention has implicated altered glutamate as key to the pathophysiology and therapeutics of BD (reviewed in greater detail below). The implicated neurotransmitters in BD and their presumed alterations currently represent important therapeutic targets (summarized in Table IV).

With regard to second-messenger systems, both clinical and preclinical studies have identified a wide range of findings related to plasticity pathways involved in intracellular signalling.

One important second-messenger target involved in the neurobiology of BD is the ubiquitous PKC. PKC is a highly enriched protein widely distributed in the brain, where it helps regulate both pre- and post-synaptic aspects of neurotransmission. PKC activates many cellular processes, including transmembrane glucose transport, secretion, exocytosis, modulation of ion conductance, cell proliferation, and desensitization of extracellular receptors. PKC also facilitates neurotransmitter release and neuronal excitability plasticity (Zarate and Manji 2009). It is also a downstream biochemical target for the mood stabilizers lithium and valproate; indeed, some investigators have suggested that the action of mood stabilizers PKC may play a critical role in their clinical antimanic effects (Zarate et al. 2006a). In preclinical models, lithium and valproate were found to inhibit PKC function; in contrast, pro-manic psychostimulants activate PKC, suggesting that PKC modulation plays a critical role in the treatment of BD (Zarate and Manji 2009). In addition, serotonin-elicited platelet PKC translocation was increased in post-mortem studies of individuals with BD, as were PKC isozyme levels, activity, and translocation (Diaz-Granados and Zarate 2008). PKC also appears to be involved in regulating glutamate receptor functions (Szabo et al. 2009). Such preclinical findings are supported by clinical studies. In a 3-week, double-blind, placebo-controlled study evaluating 16 subjects with BD during a manic or mixed episode, the relatively selective PKC inhibitor tamoxifen significantly improved mania (response rate, 63%) compared to placebo (13%) as early as 5 days; this effect continued to be significant until study endpoint (Zarate et al. 2007). Several other studies
have similarly demonstrated that tamoxifen has beneficial effects in mania (Diazgranados and Zarate 2008). Selective PKC inhibitors are currently under evaluation in Phase I–III trials for different clinical conditions and may represent potential candidate drugs for future investigation in BD.

The glycogen synthase kinase 3β (GSK-3β) pathway may also be relevant to the pathophysiology of BD. GSK-3 is a serine/threonine kinase that regulates various cellular processes and directly modulates cell survival. GSK-3 is involved in a number of central functions implicated in the pathophysiology of BD, including synaptic plasticity, cellular structure and resilience, and the circadian cycle (Jope 2011). GSK-3 also regulates the turnover of neurotransmitters involved in the pathophysiology of BD, such as dopamine, glutamate, and serotonin (Beaulieu et al. 2009; Jope and Roh 2006). Increased expression of GSK-3β was also found to shorten the circadian period (Dokucu et al. 2005), an effect reversed by lithium treatment (Yin et al. 2006).

Peripheral administration of a GSK-3 inhibitor decreases amphetamine-induced hyperactivity in rats (Gould et al. 2004b). GSK-3 is potently inhibited by lithium, and is a downstream target for the action of other mood stabilizers (reviewed in Jope 2011). Interestingly, in human studies, a GSK-3 gene polymorphism was associated with earlier onset of BD (Benedetti et al. 2005); see Li and Jope (2010) for a review of other studies investigating genetic variations in GSK-3 in BD. However, as regards drug development, caution is required when developing this class of compounds. GSK-3 isoforms are targets in several organ systems (more than 40 proteins are phosphorylated by GSK-3), and thus GSK-3 modulating compounds could have side effects across many organ systems.

**Mitochondria, endoplasmic reticulum, and calcium regulation**

Impaired regulation of calcium signalling, as well as increased intracellular calcium levels, are amongst the most widely reproduced cellular abnormalities in BD research (Akimoto et al. 2007; Kato 2008b; Sourial-Bassillious et al. 2009; Machado-Vieira et al. 2011). Calcium is a widespread second-messenger, and plays a major role in cellular ionic homeostasis, plasticity, and survival by directly affecting mitochondria and ER, both of which have been directly implicated in the pathophysiology of BD. One recent study found that the Bcl-2 gene polymorphism rs906572 variant AA was associated with higher basal and ER stimulated cytosolic calcium levels in lymphoblasts. In that study, basal intracellular calcium levels negatively correlated with Bcl-2 mRNA expression and protein levels (Machado-Vieira et al. 2011). These mechanisms are also involved in dysregulation of oxidative stress parameters (see Andreazza et al. 2008 for a review); oxidative stress, in turn, is commonly caused by mitochondrial calcium overload (Peng and Jou 2010). Recently, this Bcl-2 polymorphism AA was associated with faster
Mitochondrial dysfunction has also been associated with increased oxidative stress parameters and apoptosis. Altered oxidative stress parameters in BD have been consistently associated with the pathophysiology of BD, and are a putative therapeutic target (Andreazza et al. 2008; Berk et al. 2011). Further studies supporting the role of mitochondrial dysfunction in BD have shown lower mitochondrial respiration, changes in mitochondrial morphology, downregulation of nuclear mRNA molecules and proteins involved in mitochondrial function, and decreased high-energy phosphates/pH in the brain (Clay et al. 2011).

Mitochondrial dysfunction has also been associated with increased oxidative stress parameters and apoptosis. Altered oxidative stress parameters in BD have been consistently associated with the pathophysiology of BD, and are a putative therapeutic target (Andreazza et al. 2008; Berk et al. 2011). In individuals with BD experiencing a manic episode, acute lithium treatment both enhanced the antioxidant enzyme catalase, and reduced the pro-oxidant protein thiorbarbituric acid-reactive substances (Machado-Vieira et al. 2007a). It has been proposed that initial manic episodes are associated with both increased oxidative stress parameters and activation of antioxidant defences, which may be related to energy metabolism dysfunction (Machado-Vieira et al. 2007a). In addition, lithium’s neuroprotective properties have been hypothesized to result from its ability to increase the mitochondrial antioxidant protein glutathione in cultured cerebral cells (Shao et al. 2005; Cui et al. 2007). Enhanced lipid peroxidation and nitric oxide levels have also been observed in BD; both are linked to higher DNA damage associated with oxidative stress and altered antioxidant activity in the periphery; these effects were reversed by lithium treatment (Andreazza et al. 2008). Lithium has also been shown to improve oxidative stress parameters in healthy subjects (Khairova et al. 2012). Given the evidence of mitochondrial dysfunction in BD, a number of mitochondrial modulators are now being tested in preclinical and initial clinical studies (Nierenberg et al. 2012) as possible therapeutics for BD, particularly during depressive episodes. These include N-acetylcysteine, acetyl-l-carnitine, S-adenosylmethionine, coenzyme Q10, alpha-lipoic acid, and creatine monohydrate; however, clinical efficacy results to date remain unconvincing (Nierenberg et al. 2012).

Altered ER stress response has been described in the neurobiology of BD (Table V). Diverse ER chaperones were found to be impaired in peripheral cells from BD patients, an effect reversed by lithium treatment (Kato 2008a). For instance, the chaperone X-box-binding protein 1 (XBP-1) is a basic leucine zipper transcription factor involved in cellular plasticity. A promoter polymorphism of XBP1 was found to reduce ER stress responses less effectively in lymphoblasts from subjects with BD (Kakiuchi et al. 2003; So et al. 2007). Interestingly, the attenuated response of XBP-1 to ER stress in BD was reversed by lithium and valproate. Also, changes in the chaperones GRP78, GRP94, and calreticulin have been described in BD, and these may increase the risk of deleterious effects associated with malfolded proteins (Shao et al. 2006). An increased response to stimulation of ER calcium release and altered expression of several ER stress proteins were also observed in peripheral cells from patients with BD (Kato et al. 2003; Machado-Vieira et al. 2011). In sum, diverse cellular (and even environmental) stressors may increase unfolded ER proteins and ER stress. Mood stabilizers, in turn, induce chaperones that prevent potential cellular atrophy and death in BD. Overall, mitochondrial and the ER are important potential targets for the development of new treatments in BD, possibly through integrative regulation of ER chaperones.

Table V. Mitochondria and endoplasmic reticulum in BD.

<table>
<thead>
<tr>
<th>Mitochondria</th>
<th>*Important imaging data support mitochondrial dysfunction (e.g., ATP, lactate)</th>
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<tr>
<td></td>
<td>*mtDNA deletions in the brain might cause depression and might be associated with BD</td>
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<td></td>
<td>*Mitochondrial disorders comorbid with BD and MDD</td>
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<td>*Global downregulation of mitochondria-related nuclear</td>
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<td>Endoplasmic reticulum</td>
<td>*Attenuated response of XBP-1 (ER chaperone) to ER stress in BD</td>
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<td>*Decreased XBP1 and GRP78 expression in BD monozygotic twins compared with their discordant siblings</td>
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<tr>
<td></td>
<td>*Lithium and valproate increase expression of the ER chaperones GRP78, GRP94, and calreticulin</td>
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<tr>
<td></td>
<td>*High prevalence of manic and/or depressive symptoms associated with ER genetic disorders</td>
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</tbody>
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BD, bipolar disorder; ATP, adenosine triphosphate; mtDNA, mitochondrial DNA; ER, endoplasmic reticulum; MDD, major depressive disorder.
intracellular calcium, the mitochondrial oxidative phosphorylation system, and Bcl-2 metabolism.

The glutamatergic system

Glutamate is the most abundant excitatory neurotransmitter in the brain, and is known to regulate synaptic plasticity via diverse mechanisms (Genoux and Montgomery 2007). Altered glutamatergic neurotransmission has been implicated in the pathophysiology of BD. Broadly, most studies have noted increased glutamate levels in the plasma, serum, and cerebrospinal fluid of subjects with BD (Zarate et al 2010). Similarly, both MRS (Ongur et al. 2008; Soeiro-de-Souza et al. 2012) and postmortem (Hashimoto et al. 2007; Machado-Vieira et al. 2012) studies have found increased glutamate levels in diverse brain areas of individuals with BD.

Therapeutic agents that affect glutamate levels have been shown to have rapid antidepressant effects in individuals with BD. The best known of these, ketamine, is a noncompetitive NMDA antagonist with antidepressant effects in major depressive disorder (Berman et al. 2000; Zarate et al. 2006b; Machado-Vieira et al. 2009b). In addition, two double-blind, placebo-controlled ketamine studies have been conducted in individuals with bipolar depression; both found that ketamine had rapid and sustained antidepressant effects, as well as antisuicidal effects, in bipolar depression (DiazGranados et al. 2010; Zarate et al. 2012). These effects manifested within approximately 40 min of a single ketamine infusion and persisted on average for 3 days post-infusion. Notably, these studies were the first to demonstrate that therapeutic effects can be achieved in BD by directly targeting a specific brain target.

The blood–brain-penetrant glutamatergic modulator riluzole has also been tested as a putative therapeutic agent in BD. Riluzole, currently approved for the treatment of amyotrophic lateral sclerosis, has neuroprotective and anticonvulsant properties. It inhibits glutamate release and increases AMPA trafficking by enhancing membrane insertion of GluR1 and GluR2, and increases glutamate reuptake and neurotrophic factor synthesis (Mizuta et al. 2001; Frizzo et al. 2004). One 8-week, open-label trial that investigated the effects of riluzole as an add-on to lithium in patients with bipolar depression found that it had consistent antidepressant effects (Zarate et al. 2005). Another small, open-label, add-on study of 14 subjects with bipolar depression found that riluzole significantly improved depressive symptoms (Brennan et al. 2010). However, a recent 4-week, double-blind, placebo-controlled study showed that riluzole, when used as an add-on to ketamine therapy, was not effective in individuals with treatment-resistant depression (Ibrahim et al. 2012a). The search for the next generation of more selective glutamatergic modulators is underway (e.g., the glutamate NR2B receptor antagonist MK-0657) (Ibrahim et al. 2012b), and may ultimately provide new, improved therapeutics for BD.

Neurotrophic pathways

Neurotrophins – including BDNF, nerve growth factor (NGF), glial cell line-derived neurotrophic factor (GDNF), and neurotrophin (NT)-3, NT-4, NT-5, and NT-6 – are essential for neuronal survival and functioning (Mocchetti and Brown 2008; Skaper 2008). Altered neurotrophin signalling has been described in BD, with most findings drawn from studies using plasma/serum samples. Decreased BDNF levels have been observed during manic and depressive episodes, a finding that has also been related to symptom severity and antidepressant response (Machado-Vieira et al. 2007b; Kapczinski et al. 2008). Altered BDNF gene transcription has also been described in individuals with BD, and appears to be regulated by stress, neuronal dysfunction, and mood episode state (Grande et al. 2010).

With regard to therapeutics, chronic lithium treatment was found to alter brain concentrations of NGF and GDNF in animal models of depression (Angelucci et al. 2003). Evidence further suggests that the neuroprotective effects of lithium in cortical neurons requires BDNF expression (Hashimoto et al. 2005). Other studies found that lithium upregulated ERK1/2 activation after ischaemia, and significantly increased cell proliferation in the hippocampal dentate gyrus (Yan et al. 2007). A recent study from our laboratory found that lithium increased plasma BDNF levels after 1 month of treatment in BD subjects (de Sousa et al. 2011), but little is known about the clinical relevance of lithium’s ability to enhance neurotrophins (reviewed in Machado-Vieira et al 2009a).

Conclusions and perspectives

Synaptic plasticity plays a key role in the pathophysiology and therapeutics of BD in multiple ways (Figure 1). The consistent evidence described herein supports the concept that BD involves structural and functional impairments related to dysfunctions in cellular plasticity and resilience in targets such as cellular organelles (particularly mitochondria and ER) and intracellular signalling cascades. These, in turn, have been directly associated with changes in neurotrophic factor regulation, energy metabolism,
neurotransmission, and inflammation; all of these directly impact brain structure and neurochemical parameters. As noted above, the deleterious central and peripheral biological effects associated with BD may be prevented or even reversed with the use of mood stabilizers (particularly lithium), but the effects of these drugs are subtle, non-specific, and in some cases not related to clinical efficacy, eventually affecting only some of the components implicated in cellular resilience and plasticity.

Looking ahead, it is likely that obtaining further insights into the pathophysiology of BD – particularly as applied to developing novel therapeutics – may involve the use of new in vivo imaging techniques, as well as gene interaction and and comprehensive gene expression analyses conducted using DNA microarrays. Studies exploring the effects of lithium and other mood stabilizers in responsive-gene networks related to neuroprotection are promising, and may ultimately expand our understanding of critical nuclear downstream pathways and targets expressing key proteins and peptides. The search for neurobiological predictors of response, as well as state and trait markers, is critically relevant to this work, and may provide new insights about potential biomarkers associated with the biological effects of mood stabilizers that could also be relevant to clinical and translational paradigms. In this respect, the use of dimensional approaches and the implementation of personalized psychiatry may be key.

The study of systems and endophenotypes is also important for the development of new, improved therapeutics for BD. In addition, future studies evaluating patients during their first episode and/or in early onset are critical to avoiding a variety of biases, including treatment, lifestyle, number and type of episode, and substance abuse. Overall, a variety of approaches, drawing on various multimodal tools and methods in BD research, will ultimately be necessary to collect information at all levels of systems biology in the translational paradigm (Figure 1).

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Statement of Interest

Dr Zarate is listed as a co-inventor on a patent application for the use of ketamine and its metabolites in major depression. Dr Zarate has assigned his rights in the patent to the US government but will share a percentage of any royalties that may be received by the government. The other authors have no conflict of interest to disclose, financial or otherwise.

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