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Review

Early intervention in bipolar disorders: Clinical, biochemical and neuroimaging imperatives

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Abstract

In the absence of clear targets for primary prevention of many psychiatric illnesses, secondary prevention becomes the most feasible therapeutic target, and is best encompassed by the concept of early intervention. This construct encompasses the goals of minimising diagnostic delay and the prompt initiation of clinically appropriate therapy. This paper develops the rationale for early intervention in bipolar disorder. Three interrelated themes are discussed; the clinical data supporting the value of prompt diagnosis and treatment in bipolar disorder, the putative biochemical mechanisms underlying the pathophysiological processes, and the parallel concept of neuroprotection, and the developing neuroimaging data that supports early intervention. Early initiation of appropriate therapy may potentially facilitate improved clinical outcomes, and further might allow the secondary prevention of the sequelae of untreated illness, which include the deleterious impact on family relationships, psychosexual and vocational development, identity and self-concept and self-stigma.

Keywords: Diagnosis; Early intervention; Bipolar disorders; Mania; Depression; Neuroprotection

Contents

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1. Introduction

At its inception bipolar disorder usually follows a stepwise, longitudinal trajectory, emerging from an at-risk asymptomatic period that gradually gives way to prodromal patterns. This prodromal milieu often crystallizes and eventuates in the form of a 'first episode' of illness, which if treated successfully, translates into remission. The illness can take a number of differing courses with some individuals experiencing complete inter episode recovery, and others having an unremitting or treatment refractory trajectory. However, in the majority of cases the illness usually progresses through successive stages. In clinical medicine, illness-staging is used widely with established models, for instance, in oncology and cardiology. These 'staged' models are all predicated on an underlying assumption that diseases follow a predictable course, with a better prognosis more likely if the illness is averted at an earlier stage, and that treatments are generally more effective than in later stages of disease. Implicit in this model is the thesis that early diagnosis and prompt initiation of therapy is the key factor in improving outcome. This paper will discuss lines of evidence supporting value of prompt diagnosis and treatment in bipolar disorder, the putative mechanisms that underlie the pathophysiological progression of the disorder, and the potential implications of these emerging findings.

1.1. The course of bipolar disorder and the need for early intervention

The course of bipolar disorder is such that the illness generally worsens over time, akin to medical illnesses, with respect to both increasing severity and frequency of episodes. Recently, a staging model for bipolar disorder has been developed. This attempts to explain the influence of vulnerabilities and progressive neurostructural changes on illness onset and progression, as well as serve as a treatment guideline for deciding upon stage appropriate medications and psychological interventions (Berk et al., 2007a, Berk et al., 2007c). For example, while the early stages of the illness are often associated with environmental stressors that are thought to precipitate episodes of illness based on triggering innate biological and genetic vulnerabilities, (Kraepelin, 2002, Frank et al., 1997, Frank et al., 2000, Hammen and Gitlin, 1997) later stages are more likely to be associated with endogenous factors and less closely coupled to environmental factors because of increased putative structural and functional brain 'scarring' (Monkul et al., 2005; Kapczinski et al., 2008). These initial episodes are generally depressive (Perugi et al., 2000) with a gradual transition to hypomania (bipolar II disorder) and/or mania (bipolar I disorder) as the illness matures (Berk et al., 2007b). The importance of early intervention is further highlighted by the fact that later illness states are generally more severe (Perugi et al., 2000, Angst and Preisig, 1995, Goldberg et al., 1995, Kessing et al., 2004, Roy-Byrne et al., 1985), as well as being more resistant to pharmacological treatment (Goodwin and Jamison, 1990, Swann et al., 1999) and less vulnerable to psychological intervention (Scott et al., 2006). Finally, having more episodes (especially depression) is associated with greater significant functional impairment (MacQueen et al., 2000) and confers a higher risk of relapse (Kessing and Mortensen, 1999). Together these factors provide a strong rationale for intervention as early as possible in the natural course of bipolar disorder.

In psychiatry, the concept of early intervention has been forged mainly by researchers in schizophrenia (McGorry, 2002). In bipolar disorders this approach has not yet received comparable attention, despite clear parallels with both medical models and schizophrenia (Berk et al., 2007a).

Characteristically, the onset of bipolar disorder is during adolescence (Roy-Byrne et al., 1985), yet there remains a substantial delay in diagnosis, with 35% of patients with bipolar disorder waiting more than 10 years for the assignment of a correct diagnosis (Hirschfeld et al., 2003), and initiation of diagnostically appropriate therapy. Ironically, this delay is more pronounced in young people (Weller et al., 1995). Reasons for delays to diagnosis are widely documented and include factors such as misdiagnosis because of overlapping phenomenology with illnesses such as depression, personality disorders, ADHD; patients denying or misattributing symptoms; and patients failing to report or simply acknowledge pleasant or mild symptoms as an indication of bipolar disorder (Evans, 2000, Cassano et al., 1999). As a corollary there is a corresponding delay in commencement of evidence-based treatment that results in the frequent use of inappropriate therapies. Diagnostic delay also increases the risk of developing comorbidity, and the degree to which bipolar disorder interferes with the attainment of age dependant developmental tasks. Not surprisingly, all of these factors further compound the psychological and social consequences of the illness (Conus et al., 2008). In counterpoint, there is data suggesting that the earliest stages of many psychiatric disorders may present with overlapping and relatively non-specific phenomenology, and the full expression of the underlying disorder is often only manifest over time (Yung et al., 2007).

1.2. Improving early detection and diagnosis

Clearly, an accurate diagnosis is mandatory, and perhaps the greatest issue thwarting the successful early diagnosis of bipolar disorder is the fact that the initial presentation of the illness is most often with depressive symptoms (Perugi et al., 2000). This leads to a lag between the initial presentation of depression and the hallmark of bipolar disorder namely, mania or hypomania. It is worthwhile noting that patients spend the major proportion of their overall time ill in a depressive episode or with depressive symptoms (Judd et al., 2002). Specifically, the ratio of depressive to manic features in bipolar I disorder is 3:1 and as much as 47:1 for depression to hypomania in bipolar II. Consequently, an initial diagnosis of unipolar depression is highly likely and because of this patients with bipolar disorder are often treated with potentially non-efficacious medications (Sachs et al., 2007). The most common of these is antidepressant monotherapy, which can exacerbate the illness by precipitating mixed states, rapid cycling and mania in susceptible individuals (Post et al., 2001, Chunn and Dunner, 2004, Goldberg and Truman, 2003, Ghaemi et al., 2003, Altshuler et al., 2006), particularly in younger populations (Goldberg and Truman, 2003). Interestingly, antidepressant and substance induced manias are more likely to be dysphoric than euphoric, contributing to the risk that dysphoria and irritability are wrongly subsumed within a depressive syndrome because of confusion between mixed states and agitated depression (Berk et al., 2005). The likelihood of such misperceptions is further enhanced by the fact that in adolescence and early adulthood, mania is often atypical, mixed or dysphoric in contrast to euphoric mania that is more frequent in adult presentations (Goodwin and Jamison, 2007). Suicide is a particular risk in dysphoric and mixed presentations, and the contribution of undiagnosed mixed states to suicidal ideation, especially in younger individuals, is a theoretical risk (Berk and Dodd, 2005). The difficulty is that it is not possible to definitively know at this index depressive presentation that the presentation is due to a bipolar diathesis, that the person may not require or respond to antidepressants, or that their use will lead to a manic switch.

Some clues to the differentiation of unipolar and bipolar disorders can be gleaned from the subtle phenomenological distinctions between the disorders that are collectively referred to as the "signature" of bipolar depression (Mitchell et al., 2001, Berk et al., 2004). Features that point to a bipolar diathesis for a depressive presentation include hypersomnia or increased daytime napping, in consort with other "atypical" depressive symptoms such as "leaden paralysis" and hyperphagia. Additionally, psychotic features or pathological guilt, psychomotor slowing (Wahlund et al., 1998), "flatness" of affect, abrupt onset or offset of episodes and postpartum onset are all potential markers of bipolarity. A prodrome of cyclothymia or hyperthymia and a seasonal pattern of symptoms (Hallam et al., 2006, Cassidy and Carroll, 2002, D'Mello et al., 1995, Hakkarainen et al., 2003, Daniels et al., 2000) are other useful indicators, as are lability of mood and irritability (Benazzi et al., 2004). A family history of bipolar disorder is a clear prognosticator (Smoller and Finn, 2003, Mcguffin et al., 2003) whereas a history of lack of response to antidepressants (Calabrese et al., 2006, Moller et al., 2001, Gijsman et al., 2004, Joffe et al., 2005, Berk and Dodd, 2005, Ghaemi et al., 2000), and "poop out" response are thought to be suggestive of a bipolar diathesis. Many of these features have been incorporated into criteria for the bipolar spectrum (Ghaemi et al., 2000), and have been used in designing rating instruments specifically for bipolar depression (Berk et al., 2007d) (Table 1).

1.3. Clinical consequences of diagnostic delay

In addition to commencing inappropriate antidepressant pharmacotherapy, an important corollary to diagnostic delay is the lack of initiation of an appropriate mood

Table 1
Features differentiating bipolar from unipolar depression

	Unipolar depression	Bipolar depression
Depressive symptoms	"Typical" depressive symptoms predominate – Insomnia – Reduced appetite Additional symptoms may include – Anxiety – Tearfulness – Less substance use compared to bipolar depression – Long episodes	"Atypical" depressive symptoms predominate – Hypersomnia – Leaden paralysis – Hyperphagia Melancholic symptoms more common Additional symptoms may include – Psychotic features – Pathological guilt – Psychomotor slowing – Flatness of affect – Irritability/mixed states/lability
Family history	Various mental illnesses predominantly unipolar depression	Various mental illnesses predominantly bipolar depression
Onset	– Onset usually in early adulthood – Episodes often preceded by a period of subthreshold symptoms – Predominantly females	– Onset usually during adolescence – Postnatal onset – Seasonal pattern – Abrupt onset or offset of episodes – Equal numbers of males and females – Highly recurrent pattern
Psychomotor		Psychomotor retardation – Slowed movement – Delayed verbal response

stabilizer. Published gaps range from 9.3 to 10 years (Post et al., 2003, Baethege et al., 2003) and such a significant delay in initiation of suitable treatment has a number of documented consequences. For instance, lithium is thought to be less effective if prescribed later in the course of bipolar illness, (Post et al., 2003) although this finding has not been consistently replicated across all studies (Baethege et al., 2003, Baldessarini et al., 2003). Olanzapine has also been reported to have preferential efficacy in the earlier stages of the disorder (Ketter et al., 2006) and these stage related changes in efficacy perhaps also apply to psychotherapeutic interventions. For example, in a trial of cognitive behavioural therapy (CBT) for bipolar disorder, there was no overall difference between CBT and treatment as usual, however a significant improvement was observed in those with fewer episodes, whereas those with more than 12 episodes deteriorated with CBT (Scott, 2006). This suggests that clinical response to adjunctive psychological treatment is perhaps less likely as the disorder becomes more chronic, an effect that has been shown in the unipolar literature (Scott, 2006) and one that reinforces the importance of early intervention.

1.4. Summary

From a clinical perspective it is fairly clear that bipolar disorder is difficult to detect early and diagnose with confidence. This delays the initiation of suitable treatment strategies and creates a period early in the course of bipolar disorder in which unchecked the illness can exact significant functional damage. Indeed, lengthy gaps between symptom onset and treatment initiation are associated with worsening social adjustment (Matza et al., 2005), an increased risk of hospitalisation (Cassano et al., 1999, Weller et al., 1995), and suicide (Hawton et al., 2005), increasing comorbidity, particularly substance abuse (Brady and Goldberg, 1996), greater risks of conflicts with the law (Barzman et al., 2007, Senon et al., 2006, Birmaher and Axelson, 2006) and impairment in age specific developmental tasks (Lewinsohn et al., 2002, Birmaher and Axelson, 2006, Berk et al., 2007a). Therefore, in the absence of robust clinical markers of bipolar disorder it is imperative that researchers pursue neurobiological indices that may assist in early detection, diagnosis and treatment.

2. Aims and methods

The aim of this article is to briefly discuss the biological imperatives for early intervention drawing upon the emerging literature from the fields of neurochemistry neuroimaging and cognitive neuroscience. A selective search of articles pertinent to early intervention and neuroprotection was conducted using recognised database search engines along with the retrieval of literature known to the authors. Due to the paucity and diversity of the

literature reviewed a systematic approach was not possible. The article is therefore selective, and focuses on recent findings from studies of cellular mechanisms and brain imaging.

3. Discussion

3.1. Neurochemical basis of neuroprotection and rationale for early intervention

Current theories suggest that bipolar disorder is associated with disturbances in neuroplasticity and cellular resilience within brain circuits involved in mood regulation (Manji et al., 2001). Consonant with this it has been postulated that treatment intervention may activate intracellular signalling systems that are associated with neuroprotection (Coyle and Duman, 2003). Supporting these hypotheses, numerous postmortem studies have reported reduced neuronal and glial density in discrete regions of the prefrontal cortex (Drevets et al., 1998, Rajkowska et al., 2001, Uranova et al., 2001, Vostrikov et al., 2007) and a reduction in the density and number of glial cells in both bipolar disorder and depression postmortem studies is a consistent finding. Brain regions most often affected include specifically the dorsolateral prefrontal, orbitofrontal and anterior cingulated cortices and amygdala. In addition, a recent study has found increased DNA fragmentation in non-GABAergic cells in the anterior cingulate cortex of individuals with bipolar disorder (Buttner et al., 2007), suggesting that in this illness, these cells may be particularly prone to illness-related metabolic stress.

3.2. Oxidative stress

The central nervous system (CNS) is intrinsically extremely vulnerable to peroxidative damage, because it is rich in oxidizable substrates and has a high oxygen tension (metabolizes 20% of total body oxygen) with relatively low antioxidant capacity (Halliwell, 2001, Takuma et al., 2004). In addition, the CNS has a high demand for oxygen due to very high neural ATP consumption that is needed for neuronal cells, the maintenance of membrane potentials through the Na+/K+ pump, and the release and storage of neurotransmitters (Halliwell, 2001, Halliwell and Gutteridge, 1999). The mitochondrial disorders, which are inherited abnormalities of energy generation, are overwhelmingly neurological disorders.

Recently it has been shown (Machado-Vieira et al., 2007) that unmedicated manic patients have increased levels of serum TBARS, a marker of lipid peroxidation, and that these increases in serum TBARS are present across all phases of bipolar disorder (manic, depressed or euthymic) (Andreazza et al., 2007). These studies suggest that increased levels of lipid peroxidation may damage membrane phospholipids. Such tissue insults affect neuronal functioning by exacting changes to either membrane fluidity or by alteration to membrane receptors (Mahadik et al., 2001). This in turn leads to impairment in neurotransmitter uptake and release that can eventuate in cell death. Much of the focus of research thus far on antioxidant defence mechanisms has been on the key scavenging antioxidant enzymes namely, superoxide dismutase (SOD) that is responsible for detoxification of the free radical superoxide, and catalase and glutathione peroxidase (Gpx) that are responsible for the metabolism of peroxide hydrogen (Halliwell and Gutteridge, 1999). Supporting the involvement of oxidative damage in bipolar disorder, studies conducted with peripheral blood have demonstrated that bipolar disorder is associated with significant alterations in the activity of these antioxidant enzymes (Ng et al., 2008, Berk et al., 2008a).

In interpreting the results of antioxidant enzymes in bipolar disorder, it is important to consider the phase of illness as a range of studies have been conducted examining bipolar disorder patients in various phases. Andreazza et al. (2007) for instance evaluated antioxidant enzyme activity in manic, depressed and euthymic patients, whereas Machado-Vieira et al. (2007) and Gergerlioglu et al. (2007) examined manic bipolar disorder patients, and Savas et al. (2006) studied euthymic patients. Others such as Ranjekar et al. (2003), Kuloglu et al. (2002) and Abdalla et al. (1986) have not specified or characterised the phase of the illness in their respective studies. Nevertheless, it has been reliably shown that superoxide dismutase activity is increased in bipolar disorder patients (Abdalla et al., 1986, Andreazza et al., 2007, Kuloglu et al., 2002, Savas et al., 2006, Machado-Vieira et al., 2007). Further, Andreazza et al. (2007) found that this increase occurs during the manic and depressed phases of bipolar disorder, but not in euthymia. This is corroborated in part by Machado-Vieira et al. (2007) who report increased activity of SOD in unmedicated manic bipolar disorder patients. However, Savas et al. (2006) have identified increased SOD levels in 27 euthymic bipolar patients, and Gergerlioglu et al. (2007) report a decrease in levels of SOD in 29 manic patients. Unfortunately, this inconsistency of enzyme level changes extends to other oxidative enzymes. For instance, catalase levels have been found to be decreased in euthymic patients (Andreazza et al., 2007) and increased in unmedicated manic patients (Machado-Vieira et al., 2007). Kuloglu et al. (2002) also found decreased levels of catalase in bipolar patients however, the phase of illness is

not specified. Andreazza et al. (2007) has noted increased levels of GPx in euthymic bipolar patients, while others have not found significant alterations of this enzyme in bipolar disorder (Ranjekar et al., 2003, Kuloglu et al., 2002, Abdalla et al., 1986).

Finally, as glutathione is the brains predominant free radical scavenger, research has attempted to examine if redressing oxidative stress using the glutathione precursor, *N*-acetyl Cysteine (NAC) reduces core symptoms of bipolar disorder. In a placebo-controlled design, NAC was associated with a large effect size in the treatment of depressive symptoms, quality of life and functioning (Berk et al., 2008b).

3.3. Brain-derived neurotrophic factor (BDNF)

As previously mentioned, the pathophysiology of bipolar disorder may be associated with impaired synaptic plasticity with consequent alterations of neurotrophins. Brain-derived neurotrophic factor (BDNF) is the most widely distributed neurotrophin in the CNS. It has many critical important biological functions including neuronal survival, differentiation, and synaptic plasticity (Neves-Pereira et al., 2005, Neves-Pereira et al., 2002). In addition it is essential to long-term memory, and BDNF also acts as one of a series of neurotrophic factor receptors (tyrosine kinases) (Post, 2007). Previous studies have suggested that variants in the BDNF gene may increase the risk for bipolar disorder (Lohoff et al., 2005, Neves-Pereira et al., 2002). In particular, one single nucleotide polymorphism (val66met) has been associated with poorer neuropsychological performance in patients with bipolar disorder (Rybakowski et al., 2003). Decreased serum BDNF levels have been reported in first-episode bipolar disorder and schizophrenia (Palomino et al., 2006), and in bipolar subjects during depressive and manic episodes (Cunha et al., 2006, Machado-Vieira et al., 2007). Interestingly, a negative correlation between serum BDNF levels and scores of psychopathology has been found in bipolar individuals (Cunha et al., 2006).

Given the key role of BDNF in cognitive functions such as learning and memory, together with pharmacological studies demonstrating that chronic administration of mood stabilizers lithium and valproate (Frey et al., 2006a, Fukumoto et al., 2001) and antipsychotics quetiapine (Park et al., 2006), clozapine and olanzapine (Bai et al., 2003) increase BDNF expression in rat brain, it is conceivable that early pharmacological intervention in bipolar disorder may prevent early cell death and diminish the cognitive deterioration observed in this illness. Likewise, the fact that lithium and valproate exert antioxidant effects in vitro and in vivo (Shao et al., 2005, Frey et al., 2006a), the preliminary evidence suggesting that oxidative damage may be normalized by pharmacological treatment (Frey et al., 2007), may open a new avenue and rationale for early intervention in bipolar disorder.

There is preliminary evidence that the biochemical changes discussed previously might be dependant on stage of illness (Berk et al., 2007a). Kauer-Sant'anna et al. (2008) has shown that BDNF is decreased only in the later stages of the disorder, but not at the first episode. In addition, the pro-inflammatory cytokines IL6 and TNFα were elevated in both early and late-stage disorder, while the anti-inflammatory cytokine IL10 was increased at the first episode but not in the later stages of the disorder. Andreazza et al. (2008) have reported that the activity of key enzymes in the glutathione pathway, glutathione reductase, and glutathione S-transferase are increased in late-stage patients compared to early stage patients and controls. This fits with Post's (2007) theory, that a failure

Table 2
Comparison of biochemical markers between Bipolar patients in early and late state

Measures	Early state	Late state	Reference
BNDF	NS [a]	Decreased	Kauer-Sant'anna et al. (in press)
Interleukine-10	Increased	NS	Kauer-Sant'anna et al. (in press)
Interleukine-6	Increased	Increased	Kauer-Sant'anna et al. (in press)
TNF-alpha	Increased	Increased	Kauer-Sant'anna et al. (in press)
Glutathione peroxidase	NS	NS	Andreazza et al. (personal communication)
Glutathione reductase	NS	Increased	Andreazza et al. (personal communication)
Glutathione S-transferase	NS	Increased	Andreazza et al. (personal communication)
3-Nitrotyrosine	Increased	Increased	Andreazza et al. (personal communication)
Protein carbonyl	NS	NS	Andreazza et al. (personal communication)

Reference
Kauer-Sant'anna, M., Kapczinski, F., Andreazza, A. C., Bond, D. J., Lam, R. W., Young, T. and Yatham, L. N. (2008) Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder. International Journal of Neuropsychopharmacology, (In Press).
[a] Not significant.

of compensatory mechanisms occurs with progression of the disorder (Table 2).

3.4. Summary of neurochemical findings

The role of oxidative stress in bipolar disorder pathophysiology is supported by evidence from biochemical and genetics studies. Oxidative stress mechanisms likely play a pivotal role in the early development of a number of neuropsychiatric disorders — in particular mood and anxiety disorders that are clinically associated with emotional and social distress. The potential role of neurotrophic factors is exemplified by BDNF, which is reduced in acute illness, increased by mood stabilizers and implicated as impacting upon bipolar cognition.

3.5. Neuroimaging data supporting disease progression and early intervention

Neuroimaging studies in bipolar disorder are proving pertinent as they have the potential to shed light on the evolving structural and neurochemical changes in the disorder. They have promise in clinical practice for identifying individuals likely to develop bipolar disorder and also to monitor treatment response. Findings from structural, functional and spectroscopic studies in bipolar disorder patients indicate limbic-thalamo-cortical and limbic-thalamo-striatal dysfunctions. However, the key question concerning bipolar disorder neuroimaging research is whether these changes are state or trait related and whether they are modified by disease progression and if so to what extent they also reflect the impact of treatment.

Strategies that have been used to identify changes that are related to the early stages of bipolar disorder include examining patients that are at high-risk of developing the illness (Chang et al., 2003). This entails studying the children of patients with bipolar disorder. However, not all those within this so called 'high-risk' population will eventually go on to develop bipolar disorder and although the rate of emergent bipolarity is higher in this group than in the general population it is not clear how confidently findings attributed to this group can be generalised (Singh et al., 2007). Thus another strategy is to examine patients that have experienced their first episode of bipolar disorder. This approach allows researchers to examine diagnostic factors with respect to psychosocial outcome. It is reasonable to assume that in first-episode patients the diagnosis is much clearer and confounds such as the direct impact of repeated episodes of illness and the effects of long-term medication are yet to take hold. This strategy has already borne some fruit, however it is noteworthy that even first-episode patients by the time they are identified have usually been subject to a significant duration of subsyndromal symptomatology (Conus and Mcgorry, 2002, Conus et al., 2006). In the specific context of bipolar disorder first-episode studies suffer some unique limitations, for instance the necessity for mania to be manifested before a diagnosis of bipolarity can be assigned means that in many instances first-episode "bipolar patients" have often endured a number of depressive episodes. Further, first-episode mania studies often subsume a proportion of patients suffering from psychosis, many of which can only be partitioned from bipolar disorder through follow up. Hence, the generalisability of such studies is also of some concern, as many patients with bipolar disorder do not report psychotic symptoms (Peh and Tay, 2008). Yet another potential approach to examine the origins of bipolar disorder is to dissect the prodromal phase of the illness. Unfortunately, in practice, conducting prospective studies that survey a population with a view to capturing the prodromal phase and subsequent full blown illness is extremely difficult, not only because of the cost of such a project and the time it would take in terms of follow up but also because it is not yet possible to identify prodromal symptoms with sufficient sensitivity and specificity.

Few neuroimaging studies have been conducted within high-risk bipolar populations even though modern techniques, such as voxel-based morphometry and diffusion tensor imaging offer potentially promising insights (Malhi and Lagopoulos, 2008). Proton spectroscopy studies examining bipolar disorder offspring as compared to healthy subjects have found no significant differences in the levels of *N*-acetylaspartate (NAA) in the dorsal lateral prefrontal cortex even though changes in this metabolite have been identified in the hippocampus (Gallelli et al., 2006, Atmaca et al., 2007b, Blasi et al., 2004). NAA is a neural metabolite that serves as a marker of neuronal integrity (Malhi et al., 2002). It is of interest in bipolar disorder along with myoinositol, glutamate and GABA, all of which can be sampled in vivo using proton spectroscopy (Malhi and Lagopoulos, 2008). As noted previously, some studies of subjects at high-risk for bipolar disorder necessarily encompass those that are likely to develop psychosis instead and therefore the findings of such studies (Velakoulis et al., 2006) are limited in terms of extrapolating to bipolar disorder. Researchers have therefore attempted to investigate first-episode mania patients so as to identify putative developmental neuroimaging abnormalities. Reiterating the advantage of this strategy, it enables the examination of patients that are relatively drug naïve and those that overall have been subjected to a lesser burden

of illness, as compared to those that have had multiple episodes during their lifetime. This type of analysis therefore allows partitioning of deficits that are developmental from those that are accrued because of illness-related factors. Conducting such research, recent studies have identified grey matter volume increases in the ventral prefrontal and anterior cingulate cortices in bipolar patients early in the course of their illness as compared to healthy subjects (Adler et al., 2005). Interestingly, when examining this same region in first-episode patients no such abnormality is evident indicating that any increase in grey matter is likely to be a consequence of dysfunctional maturation that occurs later in the course of the illness (Adler et al., 2007). Studies of first-episode bipolar patients have identified a number of regions with changes in size including for instance the thalamus, anterior cingulate, fusiform gyrus and cerebellum all of which are increased in volume and have grey matter abnormalities (Adler et al., 2007). Interestingly, decreases have also been identified, notably in the cingulate gyrus of first-episode patients with affective psychoses (Hirayasu et al., 1999), and especially in those with a family history of mood disorders. Over time, the anterior cingulate cortex has been shown to undergo progressive volumetric loss in grey matter as demonstrated by a recent study of first-episode psychotic bipolar patients (Farrow et al., 2005).

Striatal structures are also of interest in bipolar disorder as they form part of the limbic circuitry and have been reliably implicated in bipolar pathology (Malhi and Lagopoulos, 2008). For instance, in first-episode bipolar patients the putamen is found to be larger as compared to healthy subjects (Strakowski et al., 2002). Similarly the amygdala is emerging as a key structure in the regulation and generation of mood. Amygdala volume changes lack consistency with both decreases and increases having been found in right amygdala volumes in first-episode subjects as compared to controls (Atmaca et al., 2007a, Velakoulis et al., 2006) and similar ambiguity surrounds changes in ventricular volume in first-episode mania patients (Strakowski et al., 2002, Strakowski et al., 1993). However, other structures, such as the cerebellum and hippocampus that are implicated in emotional circuitry have not been found to differ.

White matter hyperintensities are a consistent finding in bipolar populations and have been associated with changes in cognition and illness characteristics such as severity and chronicity (Swayze et al., 1990, Bearden et al., 2001). Interestingly white matter hyperintensities have been identified in younger bipolar patients and patients with first-episode mania (Strakowski et al., 1993, Lyoo et al., 2002). The new technology of diffusion tensor imaging that specifically examines white matter tracts has been useful in corroborating white matter pathology. In bipolar disorder, changes in fractional anisotropy that suggest white matter disorganisation have been identified in the superior prefrontal regions of bipolar patients (Adler et al., 2007) and these changes have also been found in the corpus collosum of first-episode bipolar patients. This suggests that disruption of white matter that affects cortical connectivity is perhaps core to the cognitive deficits observed in bipolar disorder (Brambilla et al., 2003). Somewhat perplexing however, is the finding that white matter hyperintensities increase with age and are also associated with late-onset mood disturbance. Their potential utility therefore as markers of early onset bipolar remains limited but warrants further exploration.

In recent years functional neuroimaging studies of bipolar patients, both across mood states and euthymia, have begun to identify prefrontal regions of diminished activity in conjunction with hyperactivity in subcortical structures (Malhi et al., 2004, Phillips and Vieta, 2007). This “pattern” of activity in adults is subject to many factors and few functional MRI studies have been conducted to date in the prodromal phase of bipolar disorder or in high-risk or first-episode patients. Studies that have examined paediatric and adolescent bipolar populations suggest that the pattern of functional activity contrasts to that found in adults (Blumberg et al., 2003). Whether this reflects the complexities of brain maturation or indicates illness-related functional changes is yet to be discerned. Clearly functional imaging affords a unique opportunity for examining cognition in vivo and permits mentation to be localised to specific brain regions (Malhi and Lagopoulos, 2008). However, there are inherent limitations to the inferences that can be drawn from the findings of neuroimaging studies because of variability in sampling (voxel placement in spectroscopy), grey–white matter partitioning (structural imaging) and analysis techniques (fMRI). Data from structural and functional studies that contest the findings reported in this paper (Malhi et al., 2004, Hauser et al., 1989, Hoge et al., 1999, Critchley, 2003, Pearlson et al., 1997) highlight the ongoing need for further corroborative studies in this rapidly developing field of research.

3.6. Summary of neuroimaging findings

The extant literature and the convergent findings from different imaging modalities implicate neural circuits known to underpin mood generation and regulation. The exact timing of when these changes/deficits emerge and how these impact upon individuals functionally, with

respect to cognitive and social functioning remains to be elucidated. Key subcortical and prefrontal structures including for instance the amygdalae, hippocampi, anterior cingulate and prefrontal cortex are likely to yield changes and patterns of activity on neuroimaging that eventually serve as neurobiological markers and help identify the early onset of bipolar disorder. As this potential is realised the findings will also afford the possibility of modifying the disease process and thereby create opportunities for assessing the impact of treatments.

3.7. Conclusion

Bipolar disorder is associated with marked morbidity that impairs psychosocial functioning and can result in mortality. It is increasingly evident that many individuals with bipolar disorder may not fully 'recover' between episodes of illness, but instead have residual neuropsychological and functional compromise. Post's (1992) neurosensitisation model, suggests that multiple episodes lead to permanent alterations in neuronal activity. This may alter gene expression, and provide a neurobiological mechanism whereby recurrence leads to a greater relapse liability, and a potentially poorer response to medication. This is being underpinned by findings from neuroimaging and neurochemical studies, which albeit at times inconsistent, have prompted inquiry into earlier intervention. Clinically, diagnostic issues limit early detection and despite strategies of examining high-risk populations and first-episode subjects, capturing the prodromal phase of the illness reliably has proven difficult to date. Findings from neuroimaging studies point to brain changes that may precede clinical signs and symptoms suggesting that in practice even earlier intervention is perhaps needed. This is clearly an ambitious goal, but one perhaps worth pursuing, given the accumulating neurochemical evidence that suggests avenues for pharmacological intervention that may offset the effects of oxidative stress.

Early intervention however, has a number of inherent challenges. Insight is often compromised in young, first-episode individuals, and this tends to worsen with the experience of multiple episodes. As a consequence, poorer medication adherence and greater risks of other behaviours that pose health risks are therefore not infrequent. These difficulties are compounded by high rates of comorbidity with alcohol and other substance misuse, suicidal behaviour and psychotic symptoms. Illness at this crucial developmental stage poses risks of interference with age specific education, social and psychosexual development and not infrequently, symptom severity is greater with early onset. The clinical presentations at the earliest stages may be non-specific, dominated by depressive, behavioural and substance use issues, although there is a potential signal derived from the "signature" phenomenology of bipolar depression. The reliability of this signal needs to be validated using prospective studies. A further challenge is that of false positive diagnoses; while there are clear risks to non-diagnosis, there are risks too of false positives, including inappropriate use of medication with significant tolerability issues, self-stigmatisation, illness-role issues, and the fact that the treatment opportunities of the underlying disorder will equally be missed. The neuroimaging and cognitive changes that are reported further overlaps with those in related disorders, including schizophrenia and depression.

Balanced against this background is data that medication may be at its most effective in first episode, and that psychosocial interventions similarly may share that efficacy profile. In this regard psychosocial therapies have a core base in addressing the contribution of medication non-compliance, disrupted social and biological rhythms, stressful life events and dysfunctional coping styles. However, in young adults, further clinical consideration should be placed on factors such as engagement, educational and vocational counselling and discussion of the progress through age appropriate developmental tasks to encourage development. Early intervention is the critical ingredient if the promise of neuroprotection is to be actualised. Early initiation of optimal therapy similarly allows the secondary prevention of the sequelae of untreated illness including impacts on family relationships, psychosexual and vocational development, identity and a concept of self.

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Conflicts of interest

Professor Berk has received grants, served on advisory boards and have received honoraria for talks and presentations from Bristol Myers Squibb, Eli Lilly, Glaxo SmithKline, Organon, Novartis, Mayne Pharma, Pfizer, Sanofi Synthelabo, Servier, Janssen Cilag, Lundbeck, Astra Zeneca, Solvay and Wyeth. Professor Malhi has served on a number of pharmaceutical industry advisory boards for Wyeth, Astra Zeneca, Eli Lilly, Pfizer, Lundbeck, Organon and Jansen Cilag in the past 3 years and have received honoraria for talks and presentations and grants for research. Dr Hallam has received a grant for research from Astra Zeneca. Dr Dodd has received honoraria for talks from Eli Lilly and research funding from Mayne Pharma, Organon, Eli Lilly, Servier, Astra Zeneca, Pfizer and Novartis. Dr Gama, Dr Andreazza, Dr Frey and Professor Kapczinski have no conflicts of interest.

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