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# Neuroprogression: pathways to progressive brain changes in bipolar disorder



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## The progressive nature of bipolar disorder

Many psychiatric disorders, including bipolar disorder follow a progressive path, and manifest a variable but observable trajectory. While Kraepelin (1921) described a progressive dementing process in schizophrenia, and conceptualized the illness as a stepwise, progressive disorder, he saw bipolar disorder as having a more episodic pattern. Nevertheless, it has become clear that bipolar disorder too shares a temporal progression in phenomenology, treatment response, neurobiology and functional impairment. The notion of clinical staging, long used in oncology and medicine and more recently in psychiatry, postulates that there is a stepwise progression through a series of identifiable steps, which have characteristic features and potential treatment implications (Berk et al., 2007b; McGorry et al., 2006). The earliest stage, stage 0, applies to individuals who have known risk factors for the disorder such as genetic vulnerability, pregnancy and obstetric complications childhood psychological, physical or sexual abuse, proximal psychological stress, and substance abuse, but no overt symptoms. The prodromal stage, stages 1a and 1b comprise mild, non-specific and identifiable disorder-specific symptoms respectively. Stage 2 is the first episode of illness, and since mania is mandatory for a DSM-IV (APA, 2000) and ICD-10 (WHO, 2005) diagnosis of bipolar I, stage 2 is synonymous with the first

episode of mania or hypomania. Stage 3 is that of recurrence, and is subdivided into stage 3a, with the recurrence of subthreshold symptoms; stage 3b with threshold symptoms; and stage 3c with persistent relapses. Stage 4 is the stage of treatment resistance, manifest by a persistent unrelenting course.

Recurrence may be self-seeding, with illness begetting a further increased risk of recurrence. A reduction in inter-episode duration with increasing number of episodes, has been known since Kraepelin, and has been extensively replicated (Kessing et al., 1998; Kraepelin, 1921; Roy-Byrne et al., 1985; Zis et al., 1980). Further support for the progressive nature of the disorder comes from clinical, neuroimaging and neurocognitive studies. The characteristic and lengthy delay between the onset of bipolar disorder and the introduction of mood-stabilizing medication (Berk et al., 2007a), is associated with a potential reduction in the likelihood of response to treatment. Lithium (Franchini et al., 1999; Swann et al., 1999), and even psychotherapy (Scott et al., 2006) may be less useful if used later in the course of illness. Structural brain changes are not consistently found at illness onset, and appear to become more evident with chronicity (Lyoo et al., 2006; Strakowski et al., 2002). Cognitive deficits are well described in the disorder, and again there is again some evidence that this is related to number of episodes (El-Badri et al., 2001; Robinson and Ferrier, 2006), although the data is rather inconsistent. One report suggested that individuals after a first or second episode showed minimal cognitive differences compared to controls in terms of cognitive functioning (Lopez et al., 2008), whereas those with chronic illness showed significant deficits when compared to both controls and early episode bipolar patients on all scales. Recurrence is further associated with poorer social adjustment (Matza et al., 2005), more hospitalizations

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**Focus on:** Kauer-Sant'Anna et al. (2008). Brain-derived neurotrophic factor and inflammatory markers in patients with early- vs. late-stage bipolar disorder.

(Goldberg and Ernst, 2002), greater suicide risk (Hawton et al., 2005), higher rates of comorbidity, especially substance abuse (Brady and Goldberg, 1996), forensic complications, and failure to meet age-specific developmental tasks (Conus and McGorry, 2002).

### **Mechanisms underlying neuroprogression**

There are a number of models for understanding this change in the nature of the illness with course. Post (1992), in his neurosensitization model, suggests that multiple episodes lead to permanent alterations in neuronal activity, which may be transduced at the level of gene expression, and these in turn may form the neurobiological basis of a greater relapse liability, and potentially poorer response to medication. The allostatic load hypothesis (Kapczinski et al., 2008), models the cumulative 'wear and tear' of stressors, illness itself, and aggravating factors such as substance use, and suggests that these factors are transduced through modulation of brain circuits. This is hypothesized to result in the observed structural changes, the associated cognitive decline and the reported decreasing responsiveness to therapy. This process further increases the vulnerability to future illness episodes. In this model, mood stabilizers are hypothesized to exert an effect on neurons that opposes the impact of chronic stress.

The biochemical mediators of this process are incompletely understood, but are thought to include stress sensitization via cortisone, inflammatory processes, oxidative stress, mediation via GABA, thyrotropin-releasing hormone and Neuropeptide Y, and changes to neurotrophins including BDNF (Berk et al., 2008b; Post, 2007; Wadee et al., 2002). Post further hypothesized the failure of endogenous compensatory mechanisms over time as a component of the mechanism of neuroprogression.

The paper of Kauer-Sant'Anna et al. (2008) provides mechanistic support for this hypothesis, and is the first published data that shows a stage-dependent change in neurochemistry in bipolar disorder. This is of particular relevance, as more than perhaps any major psychiatric disorder, bipolar disorder lacks a coherent pathophysiological hypothesis. As a consequence, rational drug discovery has been markedly restricted, with almost all agents in current use either discovered serendipitously, or borrowed from other indications. The presence of known targets opens the door to the development of strategic interventions. The principal finding of the paper was that BDNF was decreased only in the late stage of the disorder; this is concordant with the prediction of Post (2007), who argued that

a failure of compensatory mechanisms occurs with neuroprogression in the disorder. Given the role of BDNF in neuronal survival and proliferation, this provides support for role of neurotrophins in neuroprogression. The paper also examined pro- and anti-inflammatory cytokines, in particular TNF- $\alpha$ , IL-6 and IL-10. The pro-inflammatory cytokines IL-6 and TNF- $\alpha$  were elevated in both early- and late-stage disorder, while the anti-inflammatory cytokine IL-10 was increased early but not late in the disorder. TNF- $\alpha$ , while elevated throughout the course, was higher later than earlier in the disorder. This confirms the presence of an inflammatory state (Wadee et al., 2002), that is greater later in the disorder, and could be due to progression of the primary underlying process, or due again to failure of homeostatic mechanisms consequent to episode progression. There is a suggestion that some elements of the inflammatory process may be state dependent, as Kim et al. (2007) reported that IL-6 elevation in mania resolves with clinical remission, while TNF- $\alpha$  did not change with clinical remission.

There is unpublished data on stage-dependent changes in oxidative parameters. Glutathione is the brain's principal free radical scavenger, and dysregulation of the glutathione system is implicated in bipolar disorder (Berk et al., 2008b; Ng et al., 2008). Andreazza et al. (2007) 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. They hypothesized that the change in antioxidant enzymes in late-stage patients may be an adaptive result of the cumulative effect of oxidative stress with progression of the disorder. This again is concordant with the prediction of Post (2007).

Other mediators of neuroprogression have been examined. In depression, the CSF metabolome differs between responders and non-responders to treatment, although specific biomarkers have not yet been identified. A tendency for individuals to switch from unipolar to a bipolar phenomenology with time is well described. It has been hypothesized that this conversion from depression to a bipolar phenotype may be due to epigenetic modification as part of the disease process, and may be associated with treatment resistance. This may be a result of histone acetylation or DNA methylation altering gene expression (Holsboer, 2008).

### **Neuroprotective effects of mood stabilizers**

Mood stabilizers impact the pathways and mechanisms that are associated with neuroprogression in

bipolar disorder, via the prevention of the biochemical mediators of the tissue damage, that manifests as the observed staged structural, cognitive and clinical changes. Both lithium and valproate increase levels of the anti-apoptotic protein bcl-2 in animal studies (Chen et al., 1999; Manji et al., 2000). Atypical antipsychotics also increase bcl-2 levels (Bai et al., 2004). Glycogen synthase kinase-3 (GSK-3), a cytoprotective protein that regulates apoptosis, cellular plasticity and resilience is inhibited by lithium (Gould and Manji, 2005; Klein and Melton, 1996). Lithium protects against excitotoxic apoptosis, which contributes to hippocampal atrophy, and increases *N*-acetylaspartate, a marker of neuronal viability (Malhi et al., 2002; Malhi and Yatham, 2007). Lithium treatment increases grey matter in individuals with bipolar disorder (Moore et al., 2000a,b).

Oxidative stress is increased in bipolar disorder. There is evidence that lithium and valproate reduce oxidative stress (Ng et al., 2008). Similarly, lithium, valproate, and atypical antipsychotics such as quetiapine, increase BDNF (Bai et al., 2003; Martinowich et al., 2007). These common properties of otherwise biochemically diverse mood stabilizers provide tentative support for a shared mechanism of action, that further correlates with the neuroprogressive changes documented by Kauer-Sant'Anna et al. (2008).

The biochemical mechanisms of neuroprogression appear to include illness stage-related alterations in inflammatory cytokines, neurotrophins and oxidative stress. These data further support the principle of neuroprotection, and the possibility of secondary prevention of the disorder as viable therapeutic targets. The clinical implications of these findings suggest that there may be an opportunity early in the course of the disorder, whereby the progressive trajectory of the disorder could be modified. This evidence further supports the imperative to reduce the lengthy delay to diagnosis and initiation of appropriate therapy. A focus on early intervention at a service level would support the development of specialized early intervention services. Last, these biochemical findings might additionally provide rational intervention targets (Berk et al., 2008a).

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