# Stress, Schizophrenia and Bipolar Disorder

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**Abstract** The role of stress in precipitating psychotic episodes in schizophrenia and bipolar disorder has long been acknowledged. However, the neurobiological mechanism/s of this association have remained elusive. Current neurodevelopmental models of psychosis implicate early dysfunction in biological systems regulating hypothalamic–pituitary–adrenal axis and immune function, with long-term effects on the development of the brain networks responsible for higher order cognitive processes and stress reactivity in later life. There is also increasing evidence of childhood trauma in psychosis, and its impact on the development of brain systems regulating stress. These findings are emerging in the context of a new era of epigenetic methods facilitating the study of environmental effects on gene expression. The evidence is thus converging: exposure to stress at critical periods in life may be an important factor in the development of the brain dysfunction that *represents* psychosis vulnerability, rather than merely interacting with an independent 'biological vulnerability' to manifest in psychosis.

**Keywords** Psychosis · Stress-vulnerability · Hypothalamic–pituitary–adrenal (HPA) axis · Epigenetics · Trauma

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# 1 The 'Stress-Vulnerability' Model of Psychosis

Schizophrenia and bipolar disorder are severe neuropsychiatric disorders that share some symptoms and cognitive deficits, and are likely caused by the interaction of multiple biological and environmental factors. Heritability estimates for both disorders approximate 80 % (van Winkel et al. 2008b; Sullivan et al. 2003; McGuffin et al. 2003), suggesting a strong genetic component that is not necessarily expressed with complete penetrance. In the largest genetic epidemiology study of heritability patterns to date, it was shown that the biological relatives of both schizophrenia and bipolar disorder had increased risk for both disorders, with an estimated 30–40 % shared genetic risk factors, and 3–6 % shared environmental risk factors (Lichtenstein et al. 2009). Notably, this evidence has emerged within an era of unparalleled genomic advances implicating common genetic loci in the development of the traditionally distinct 'non-affective' and 'affective' psychoses (Moskvina et al. 2009; O'Donovan et al. 2008; Craddock et al. 2005).

However, there remains a high level of interest in elucidating the undoubtedly complex effects of environmental stressors acting in concert with biological vulnerability for psychosis. Understanding how stress impacts the brain—its development and daily functioning—thus remains key to understanding the aetiology of psychosis. The treatment of stress-related features of illness will likely prove vital in preventing relapse in established cases, and may also assist in averting the onset of frank psychosis in vulnerable individuals.

Clinically, schizophrenia manifests in an episodic, and often deteriorating, course of illness. The overt expression illness includes phases in which the hallmark 'positive' symptoms of psychosis predominate (e.g. delusions, hallucinations and disorganisaton of thought and behaviour), while persistent 'negative' symptoms (impaired motivation and affect, social withdrawal, poverty of speech and impaired cognition) commonly increase over the course of illness, culminating in long-term disabling interpersonal and functional impairments (Liddle 1987). The

diagnosis of schizophrenia is confined to patients who experience remittent symptoms for a minimum of 6 months, with at least 1 month of persistent psychosis (APA 2013). Somewhat artificially, schizophrenia has been distinguished from schizoaffective disorder by the presence of significant mood symptoms, interspersed with periods of psychotic symptoms that account for a significant proportion of illness, and which occur also during periods without mood symptoms (APA 2013).

In contrast, bipolar disorder has been primarily understood as a mood disorder characterised by a (similarly) episodic course of illness that includes chronic and recurring episodes of mania (elated mood) and depression (low mood), interspersed by 'euthymic' periods in which the individual is neither affected by extremely high or low moods (Manji et al. 2003). Mania includes feelings of elation, irritability, impulsive behaviour, decreased need for sleep and can mimic a schizophrenia-like psychosis in severe cases (Manji et al. 2003; Berk et al. 2007). While mania and psychosis technically do not equate, psychotic symptoms (such as delusions) frequently occurs during mood episodes, with 20–50 % of patients with acute bipolar mania displaying symptoms of psychosis (Pope and Lipinski 1978). Despite many clinical and neurocognitive features in common (Tamminga et al. 2013; Hill et al. 2013), these mood and psychotic disorders remain as distinct categories of illness in the current DSM-V, with growing acknowledgement of the unequivocal evidence for shared genetic vulnerability and environmental factors contributing to their development.

## 1.1 Stress and the Development of Psychosis

Typically, overt psychotic symptoms emerge in late adolescence or early adulthood (Kessler et al. 2007) and often the onset of the first (and subsequent) psychotic episode/s can be linked to a significant life stressor (Canton and Fraccon 1985). Retrospective studies show that patients with schizophrenia tend to experience increased numbers of life events, especially before the onset of an acute episode (Bebbington et al. 1993; Canton and Fraccon 1985). Exposure to 'life events' may increase response to stress and predispose to subsequent reactions on later exposures (van Winkel et al. 2008b). Prospective studies of life events and psychosis reveal that, while the number of life events experienced by individual at high risk of psychosis are not particularly elevated, these individuals feel they do not cope with the stressors as well and report greater distress than controls (Mason et al. 2004; Phillips et al. 2006). Stress and inadequate social support have also been shown to predict recurrence in bipolar disorder (Cohen et al. 2004).

This accumulation of evidence might suggest that a core feature of psychosis may involve an aberrant neurobiological response to stress. At the same time, neurodevelopmental models assert the likely impact of early life stress on the developing brain, with accumulating evidence implicating the effect of early life exposures to numerous kinds of environmental insult during pre- or post-natal

periods, and/or during childhood or adolescence (Demjaha et al. 2012; Murray et al. 2004). These models highlight both similarities and distinctions in the neurodevelopmental trajectories of schizophrenia and bipolar disorder, that nevertheless point toward aberrant development of stress-related brain circuitry in the aetiology of both 'affective' and 'non-affective' forms of psychosis.

## 2 Neurobiology of Stress

The primary stress response system of the brain involves components of the hypothalamic–pituitary–adrenal (HPA) axis, which function together with multiple bodily systems to enable individual adaptation to the stressful/environmental situation (McEwen and Seeman 1999). After exposure to a stressor, release of serotonin from the amygdala stimulates the secretion of corticotropin-releasing hormone (CRH) and vasopressin through the medial parvocellular portion of the paraventricular nucleus (PVN) of the hypothalamus, which in turn stimulates the production of adrenocorticotropic hormone (ACTH) from the anterior pituitary gland (Jacobson and Sapolsky 1991; Munck et al. 1984; Sapolsky et al. 1986). ACTH acts on the adrenal cortices, stimulating the production of glucocorticoids, such as cortisol. Glucocorticoids in turn regulate their own release directly by action on both the hypothalamus (CRH) and pituitary gland (ACTH) via negative feedback cycles.

Within this system, cortisol is primarily involved in driving the stress response. It binds to glucocorticoid receptors (GR) to both induce and restrain the stress response. These receptors are expressed throughout the brain with concentrated expression in the PVN, hippocampal area and dentate gyrus, amygdala and lateral septum and prefrontal cortex (PFC) (Pillai et al. 2012). Mineralocorticoid receptors (MR), expressed only in the hippocampus and the lateral septum, have a tenfold greater affinity for cortisol and are primarily active at basal level and important in modulating the circadian pulsatile rhythm of cortisol (Deuschle et al. 1998; Heuser et al. 2000).

Chronic exposure to glucocorticoids results in significant changes in neurophysiology (Belanoff et al. 2001), through genomic and non-genomic pathways, [see (Joels et al. 2012) for review] in brain regions which plays an important role in memory and cognition (Eichenbaum et al. 1992; Herman et al. 2005). Elevated levels of glucocorticoids or cumulative exposure can lead to hippocampal degeneration (McEwen and Sapolsky 1995; Sapolsky et al. 1986). The hippocampus plays an important role in explicit memory, and the interaction between glucocorticoids and the hippocampus may explain its effect on cognition (Belanoff et al. 2001). Indeed, longitudinal study of associations between childhood cognitive performance and later cortisol levels in adulthood have shown that lower cognitive ability in childhood predicted lower morning levels of cortisol and a blunted cortisol awakening response later in life (Power et al. 2008). Prefrontal cortex and amygdala housing of substantial corticosteroid receptors may similarly

account for variability in cognitive domains; executive function, working memory and emotion regulation (McCormick et al. 2007; Wingenfeld et al. 2011).

Both abnormally high and low cortisol levels, reflecting aberrant HPA function, have been linked with early life stressors including severe childhood abuse, and post-institutionalisation (Doom et al. 2013; Quevedo et al. 2012), with recent evidence of heightened cortisol levels in adult schizophrenia participants with a history of childhood trauma (Braehler et al. 2005). In accordance with the diathesis stress model, evidence also suggests there may be an ability in healthy individuals to 'bounce back' from childhood trauma, confirmed by an attenuated Dexamethasone/CRH response in individuals exposed to early trauma (Klaassens 2010).

## 3 Levels of Cortisol in Schizophrenia and Bipolar Disorder

Cortisol levels have been found to be higher in chronic sufferers of schizophrenia compared to healthy controls, irrespective of age (Muck-Seler et al. 2004). Similarly, higher cortisol levels are evident in bipolar disorder in the morning and afternoon, relative to healthy controls (Gallagher et al. 2007). Possible explanations of these results come from evidence incorporating symptom severity and disease progression. One study found that first-episode psychosis participants' reduction in cortisol over a 12-week period was directly related to improvements in depressive, negative and positive psychotic symptoms (Garner et al. 2011). Similarly, a longitudinal study found that adolescents followed for 4 years from the onset of prodrome to psychosis demonstrated a pronounced increase in cortisol secretion over the course of the study period (Walker et al. 2010).

Several studies have also shown that repeated administration of corticosteroids to participants initially free of psychiatric illness results in approximately 25 % of individuals meeting diagnostic criteria for mania (Brown et al. 2002; Bolanos et al. 2004; Naber et al. 1996); in addition, those with a greater number of episodes demonstrated more dysfunctional cortisol patterns than those with relatively less severe bipolar disorder. These studies suggest similar relationships to those in schizophrenia where illness stage, and symptom severity, may be moderators of cortisol dysfunction.

One important factor that may contribute to elevated cortisol levels in psychotic disorders is psychotropic medication. A recent meta-analysis also shows that, while medicated schizophrenia patients had elevated cortisol compared to healthy controls, the cortisol levels of patients that were medication-free were greater still (Girshkin et al. 2014). This meta-analysis also found no increase in cortisol level in first-episode medication-naïve participants compared to healthy controls, consistent with reports of normal pituitary volume in first-episode participants before after antipsychotic treatment (Gruner et al. 2012). These findings in first-episode samples suggest that antipsychotic medication may have less impact on cortisol

levels in the early stage of illness. Other studies have identified an increase in cortisol from baseline after a 12-day period of withdrawal from psychotropic treatment (Naber et al. 1985; Albus et al. 1985). Unlike antipsychotics, mood stabilisers, including lithium carbonate, have been shown to increase cortisol levels in a dose dependent manner (Platman and Fieve 1968; Bschor et al. 2011; Eroglu et al. 1979).

The manipulation of cortisol levels via the administration of glucocorticoid antagonists provides interesting results at odds with the growing list of similarities among schizophrenia and bipolar disorder: in a series of elegant investigations using mifepristone (a glucocorticoid antagonist), both schizophrenia and bipolar disorder individuals demonstrated a rise in cortisol and decrease in brain-derived neurotrophic factor (BDNF) in response to administration, compared to controls; however, it was only the schizophrenia participants whose changes in cortisol were associated with peripheral BDNF levels (Mackin et al. 2007). Another study by this group found that, following administration of mifepristone, the cortisol awakening response of bipolar disorder participants increased from baseline, and predicted improvement in spatial working memory over the course of treatment (Watson et al. 2012; Young et al. 2004). There was no similar effect of mifepristone on cognition in schizophrenia, despite the effects of mifepristone in increasing plasma levels of cortisol in schizophrenia (Gallagher et al. 2005). Together, these investigations implicate differential neurobiological mechanisms underlying the aberrant stress responses reflected in their abnormal heightened cortisol levels. Further work is clearly required to disentangle the similarities from differences with respect to abnormal HPA function in the psychotic and mood disorders.

The biological mechanisms of elevated cortisol levels in schizophrenia and bipolar disorder may be associated with the predisposition to psychosis, environmental effects or an interaction of the two (Wang et al. 2011; Aina 2013; Perroud et al. 2011). Predisposing genetic factors may include common variants on single nucleotide polymorphisms (SNPs) in genes associated with cortisol metabolism (SRD5A2) (Steen et al. 2010), the regulation of cortisol (glucocorticoid receptor, NR3C1) (Schatzberg et al. 2014), dopamine catabolism (catechol-o-methyltransfease COMT; dopamine D4 receptor gene (DRD4) (Jabbi et al. 2007), inhibitory neurotransmittors (GABA α6 receptor subunit gene; GABRA6) (Uhart et al. 2004) and stress-vulnerability (serotonin transporter-linked polymorphic region; 5-HTTLPR) (Miller et al. 2013). Similarly, environmental factors such as substance abuse (Lopez-Larson et al. 2011; Gavrieli et al. 2011), sleep deprivation (Spiegel et al. 1999), dietary changes (Cheng and Li 2012), lower socioeconomic status (Rudolph et al. 2014) and a lower level of education (Karlamangla et al. 2013) may contribute to the increased cortisol. While it remains unclear whether elevated cortisol levels are a risk factor for these disorders or a consequence of onset, recent studies suggest that it may be an interaction of the two (Wang et al. 2011; Aina 2013; Perroud et al. 2011).

Notably, the meta-analysis by Girshkin et al. (2014) revealed a positive relationship between duration of illness and cortisol levels in schizophrenia; that is, the

magnitude of increase in cortisol level in established schizophrenia was greater than that for first-episode psychosis, relative to healthy controls. Increasing cortisol with illness chronicity may be accounted for by several factors such as an inability to habituate to stimuli that, therefore, are perceived as salient (potentially threatening), and therefore tax the HPA system (Kirschbaum et al. 1995; Braunstein-Bercovitz et al. 2001). This constant experience of events perceived to be salient may create lasting neural changes resulting hypersensitivity to external stimuli (J. Wang et al. 2005; Tognin et al. 2012; Zimmermann et al. 2011; McEwen 2000; Rao et al. 1989; Starkman et al. 1992; Lupien et al. 1998; Tessner et al. 2007; McGowan et al. 2009), which over time, may amass to a state of extreme sensitivity to both internal and externally driven stress (De Kloet et al. 1998; Holsboer 2000). The heightened levels of cortisol in bipolar disorder and schizophrenia not seen in earlier stages of illness may thus be due to a lack of accumulated stressful experiences, in combination with the effects of continued medication.

## 4 Inflammation and Stress

Stress-mediated immune activation is well known to affect HPA axis function, and can result in chronic inflammation capable of altering neural networks and brain morphology (van Winkel et al. 2008b; McEwen 2007). Notably, one of the most commonly implicated genetic markers of schizophrenia is in the Major Histocompatibility Complex (MHC) locus, which encodes more than 400 genes critical to immune functions (Corvin and Morris 2014); MHC-mediated immune molecules are highly expressed in neurons and regulate key aspects of brain development (McAllister 2014).

Inflammation has been linked to psychosis (Bergink et al. 2014), as well as depression, mania and cognitive impairment (Laan et al. 2009; Wadee et al. 2002; Larson and Dunn 2001). Interestingly, monocyte genomic profiling of mRNA has shown that inflammatory markers in bipolar disorder were overlapping with almost all those associated with schizophrenia (Drexhage et al. 2010). Positron Emission Tomography (PET) imaging studies in schizophrenia patients experiencing psychosis have also identified an increase of activated microglia in the hippocampus, suggesting focal neuroinflammation of this region of the brain (Doorduin et al. 2009).

The immunosuppressive and anti-inflammatory actions of antipsychotic drugs such as chlorpromazine suggest that inflammation has a role in altering central nervous system (CNS) function (Drzyzga et al. 2006). Similarly, antidepressants such as imipramine work by suppressing pro-inflammatory responses (cytokine production) and increasing BDNF (Sairanen et al. 2005; Kenis and Maes 2002). In healthy individuals pro-inflammatory cytokines modulate apoptotic and neurotrophic processes as well as prevent morphological brain changes (de Vries et al. 1997). However, evidence for immune dysregulation in schizophrenia and bipolar disorder suggests that inflammatory mechanisms shift from being neuroprotective

to neurotoxic (Potvin et al. 2008; Kapczinski et al. 2011). As interactions between immune, gene and neural networks are complex, it remains unclear to what extent the pro-inflammatory response might contribute to the neuropathology of psychosis; however, a number of interesting models are emerging as new evidence shapes our understanding of these relationships (Girgis et al. 2014; Corvin and Morris 2014; Bergink et al. 2014).

## 4.1 Pro-Inflammatory Markers in Schizophrenia and Bipolar Disorder

Cytokines are pro-inflammatory markers which accompany immune responses to stress and have diverse roles in immunomodulation and cellular function (Kunze et al. 2013). Elevated levels of cytokines are evident in the peripheral blood of schizophrenia and bipolar disorder patients, relative to healthy controls (Kunze et al. 2013; Kim et al. 2007). Specifically, increased levels of serum interleukin (IL)-1, IL-2, IL6 and tumour necrosis factor-alpha (TNF-$\alpha$) have been found in schizophrenia (Potvin et al. 2008; Theodoropoulou et al. 2001), and elevated plasma cytokine levels of IL-2, IL-4, IL-6, IL-8 and TNF-$\alpha$ are also evident in bipolar disorder (Brietzke et al. 2011; O'Brien et al. 2006).

Chronically elevated levels of cytokines can cause increased oxidative stress and alter neuronal function (Brietzke et al. 2011; Schafers and Sorkin 2008), and may also contribute to the grey matter loss seen in schizophrenia and bipolar disorder (Viviani et al. 2004). Pro-inflammatory cytokines can also stimulate excess secretion of corticotrophin-releasing hormone, which has an inverse relationship with the adaptive stress response (Sauvage and Steckler 2001). Thus, long-term increase in cytokines can further exacerbate the molecular changes associated with stress-induced HPA dysfunction.

In a balanced immune system, cytokines provide neurotrophic support to neurons and play a role in learning and memory via their effect on the hippocampus (Wilson et al. 2002). However, in bipolar disorder, cytokines have been shown to be positively correlated with symptom severity during active manic and depressive episodes (Kim et al. 2007; O'Brien et al. 2006) and with paranoid–hallucinatory symptoms in schizophrenia (Muller et al. 1999). As such, altered levels of cytokines implicate inflammatory processes in the pathophysiology of schizophrenia and bipolar disorder. The timing of inflammation (particularly whether before or after the onset of illness), and the precise effects on the brain are yet to be fully explicated. Perhaps not surprisingly, on the basis of the current evidence, preliminary studies of the use of common anti-inflammatory pharmacological agents to improve psychotic symptoms show promise as adjunct treatments for schizophrenia (Sommer et al. 2014).

## 5 Early Life Stress and Psychosis

Childhood trauma and other types of adversity are now well established as significant risk factors for the development of several mental disorders, including schizophrenia and bipolar disorder (Janssen et al. 2004; Kessler et al. 2010; Read and Bentall 2010; Cutajar et al. 2010; Etain et al. 2010; Hyun et al. 2000; Read et al. 2005; Matheson et al. 2013; Varese et al. 2012; Schafer and Fisher 2011). Childhood adversity refers to a number of experiences in the early stages of life including maltreatment (encompassing physical, sexual or emotional abuse and various forms of neglect), parental loss or divorce, parental substance abuse and poverty (Rosenberg et al. 2007). While sexual abuse has been reported as a significant risk factor for psychosis alone (Cutajar et al. 2010), a recent meta-analysis shows no evidence that any particular type of trauma is a stronger predictor of psychosis than the others (Varese et al. 2012). However, one recent study reports higher rates of emotional neglect in psychotic patients, with higher rates of physical abuse and neglect differentiating individuals with schizophrenia from those with bipolar disorder (Larsson et al. 2013).

A recent review of the neurobiological and clinical features of maltreatment across a variety of mental disorders concludes that sufficient evidence points towards the utility of examining subtypes of cross-disorder clinical cases who share a history of childhood trauma, as a phenotypic specialisation of environmental adversity, or ‘*ecophenotype*’ (Teicher and Samson 2013). For example, neuroimaging studies of maltreated individuals within various clinical categories included in this review, report alterations in the size and integrity of the corpus callosum, hippocampus, cerebellum, and primary sensory cortices; as well as in sub-cortical region including the striatum/basal ganglia; and neocortical regions including the anterior cingulate cortex (ACC), the orbitofrontal cortex and the dorsolateral prefrontal cortex. More recently, Teicher et al. (2013) showed that maltreatment was associated with *decreased* connectivity among regions involved in emotion regulation and in theory of mind skills (left ACC, right medial frontal gyrus, right occipital pole and left temporal pole), and *enhanced* centrality among regions involved in emotion perception, self-referential thinking, self-awareness [right superior temporal gyrus (STG), right anterior insula] (Craig 2009). These regions are commonly implicated in the neuropathology of both schizophrenia and bipolar disorder, such that further examination of the effects of stress on these brain systems is warranted.

Only few studies have investigated brain abnormalities associated with childhood adversity in psychotic disorders. In individuals with first-episode of psychosis, exposure to childhood trauma has been associated with worse cognitive function and smaller amygdala (Aas et al. 2012), or decreased hippocampal volume (Hoy et al. 2012). Sexual abuse has been specifically associated with reduced (total) grey matter volume in psychotic patients compared to healthy participants (Sheffield et al. 2013), whereas, in line with Carrion et al. (2001), psychotic cases with a history of childhood trauma showed bilateral reduction of the PFC relative

to cases without trauma history. Results of a functional neuroimaging investigation of the effects of childhood adversity on brain networks for working memory, in a combined sample of patients with schizophrenia and bipolar disorder, demonstrate failure to deactivate the posterior cingulate cortex (PCC) in patients with a history of severe childhood trauma; in contrast, psychotic patients without a history of childhood trauma show aberrant brain activation of the visuo-motor/attentional network (pre-post central gyrus, cuneus/visual areas) (Quidé et al. 2014). Interestingly, Quidé et al. also demonstrated the effects of childhood trauma on brain regions involved in salience and threat detection (amygdala, thalamus), as well as directed attention (amygdala, cuneus/lingual gyrus), and emotion regulation (amygdala, thalamus, superior temporal gyrus). Findings from neuroimaging studies thus converge with the implications of neurobiological investigations (reviewed above), in both suggesting that long-term changes in brain systems responsible for salience and threat detection may coincide with chronic HPA axis dysregulation. Determining the primary antecedent of these mechanisms requires further investigation of psychotic samples with due diligence in relation to the characterization of pre-term birth complications and early adverse life events.

## 6 Genetic Interactions with Early Traumatic Experiences

Several investigations have recently examined the effects of trauma in the context of common genetic variation, as reviewed by van Winkel et al. (2013). Study of the additive interaction of genes and trauma demonstrate worse cognitive functioning in first-episode patients with a history of physical childhood trauma (neglect or abuse) carrying the short-version of the serotonin transporter (5-HTTLPR) gene (Aas et al. 2012); in addition, four studies have shown increased symptoms in psychotic individuals homozygous for the Met allele of the *COMT* Val[158]Met genotype in response to daily stress or in those with a history of childhood trauma (van Winkel et al. 2008a; Collip et al. 2011; Peerbooms et al. 2012; Green et al. 2014). These and other emerging studies of epigenetic processes highlight the likely interaction of genetic variations with traumatic experiences that may be also affected by epigenetic processes.

Epigenetic mechanisms refer to functionally relevant modifications to the genome that do not involve changes in nucleotide sequence; in contrast to examinations of stable DNA sequences, epigenetic processes are highly dynamic and can be modified by environmental factors (Weaver 2007). While the epigenetic mechanisms influencing the expression of genes in the human brain are yet to be fully understood, a series of elegant studies in rodents have shown methylation changes to sites of DNA in association with maternal rearing behaviours; these studies also demonstrated the ongoing genetic heritability, and potential reversibility, of epigenetically determined brain changes set in motion by early social experiences (Weaver et al. 2004, 2007).

A growing number of investigations of DNA methylation in humans have demonstrated epigenetic regulation of genes relevant to the function of the HPA axis, in the context of childhood trauma (Uher and Weaver 2014). For example, a recent study demonstrates increased risk of developing stress-related psychiatric disorders in association with allele-specific, childhood trauma-dependent DNA demethylation in the FK506 binding site protein 5 (FKBP5) gene, known to regulate glucocorticoid response functions (Klengel et al. 2013); in this study demethylation at this site was also associated with stress-dependent gene transcription alterations, leading to long-term dysregulation of the HPA system and a global effect on the function of immune cells and brain areas associated with stress regulation. Another earlier study showed aberrant methylation of a neuron-specific glucocorticoid receptor (NR3C1) promoter in the human brain, in association with childhood trauma (McGowan et al. 2009). Notably, increased methylation of this site has also been recently associated with the number and severity of childhood maltreatment (sexual, physical, emotional) in patients with bipolar disorder (Perroud et al. 2014). Evidence for aberrant DNA methylation patterns in schizophrenia patients have been reported for genes implicated in molecular genetic and neurobiological investigations of this disorder (Wockner et al. 2014). Interestingly, there has also been recent demonstration of common genomic sites of hypomethylation among twins with bipolar disorder and schizophrenia (Dempster et al. 2013); although this study did not examine associations with childhood trauma, their results imply common biological features of schizophrenia and bipolar disorder that likely result from common environmental effects on existing neurobiological vulnerabilities. These studies converge to suggest a crucial role of epigenetic mechanisms in modulating neurocognitive development that will be important for our understanding and treatment of psychotic disorders (Champagne et al. 2009).

## 7 Summary and Conclusions

Current neurodevelopmental models of psychosis implicate early dysfunction in biological systems regulating hypothalamic–pituitary–adrenal axis and immune function, with long-term effects on the development of the brain networks responsible for higher order cognitive processes and stress reactivity in later life. There is also increasing evidence of childhood trauma in psychosis, and its impact on the development of brain systems regulating stress, at the same time as new epigenetic methods facilitating the study of environmental effects on gene expression. The evidence is converging to suggest that exposure to stress at critical periods in life may be a critical factor in the development of the brain dysfunction that *represents* psychosis vulnerability, rather than stress merely precipitating the expression of an independent 'biological vulnerability' to psychosis.

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