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The Role of Stress in Bipolar Disorder

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Contents

Abstract Stress is a major risk factor for bipolar disorder. Even though we do not completely understand how stress increases the risk for the onset and poorer course of bipolar disorder, knowledge of stress physiology is rapidly evolving. Following

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stress, stress hormones – including (nor)adrenaline and corticosteroid – reach the brain and change neuronal function in a time-, region-, and receptor-dependent manner. Stress has direct consequences for a range of cognitive functions which are time-dependent. Directly after stress, emotional processing is increased at the cost of higher brain functions. In the aftermath of stress, the reverse is seen, i.e., increased executive function and contextualization of information. In bipolar disorder, basal corticosteroid levels (under non-stressed conditions) are generally found to be increased with blunted responses in response to experimental stress. Moreover, patients who have bipolar disorder generally show impaired brain function, including reward processing. There is some evidence for a causal role of (dysfunction of) the stress system in the etiology of bipolar disorder and their effects on brain system functionality. However, longitudinal studies investigating the functionality of the stress systems in conjunction with detailed information on the development and course of bipolar disorder are vital to understand in detail how stress increases the risk for bipolar disorder.

Keywords Blunted response · Cognition · Cortisol awakening response (CAR) · Hypercortisolemia · Hypothalamus-pituitary-adrenal (HPA) axis · Network · Trier social stress test (TSST)

1 Introduction

1.1 Activation of Hormonal Systems After Stress

Situations of perceived threat, i.e., stressors, which are subjectively experienced as "stress," activate a cascade of events eventually resulting in the release of multiple stress hormones (Herman 2018; see Fig. 1). Thus, directly after stress, activation of the sympathetic nervous system causes the release of adrenaline from cells in the adrenal medulla. Adrenaline allows the individual to quickly respond to a stressor, in part by increasing heart rate, blood circulation, and respiration. Via indirect pathways, adrenaline also increases the release of noradrenaline in the brain, contributing to a quick cognitive response to the stressful situation.

Slightly later, a second system is activated, i.e., the hypothalamus-pituitary-adrenal (HPA) axis. Information about the stressful situation is funneled through the paraventricular nucleus of the hypothalamus (PVN), inducing the release of corticotropin-releasing hormone (CRH) – and to a lesser degree of vasopressin – from the median eminence into portal vessels surrounding the anterior pituitary gland. Corticotrophic cells in the anterior pituitary respond to CRH and vasopressin by releasing adrenocorticotropin releasing hormone (ACTH) into the circulation. In the adrenal cortex, ACTH stimulates the production of cortisol (the predominant adrenocortical hormone in humans) or corticosterone (the main hormone in most

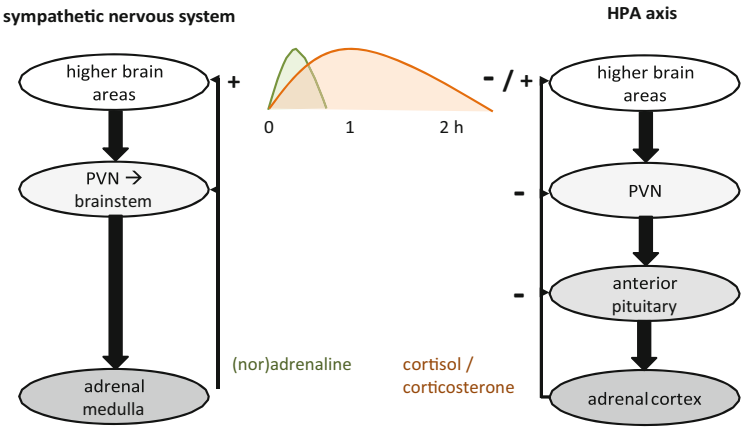

Fig. 1 Schematic representation of the hormonal systems activated after stress. Activation of the sympathetic nervous system causes the release of adrenaline. The end product of the hypothalamus-pituitary-adrenal (HPA) axis is cortisol (in humans) and corticosterone (in rodents). Adrenaline indirectly causes the release of noradrenaline in the brain. Corticosteroid hormones negatively feedback primarily on the hypothalamus and to a lesser degree on the anterior pituitary and higher brain areas. As a consequence of the hormone systems activated after stress, the brain is exposed to waves of hormones, i.e., a quick and short-lasting wave of (nor)adrenaline (in green) and a slower and longer-lasting wave of corticosteroids (in orange) which is normalized after approximately 2 h

rodents) which is then released into the bloodstream. Like adrenaline, cortisol and corticosterone affect numerous peripheral organs to promote and replenish resources that allow the individual to face the stressor. Corticosteroid hormones are lipophilic and therefore easily enter the brain where they reach virtually all cells. In the PVN – and to a lesser extent the anterior pituitary and higher brain regions – corticosteroids negatively impact cellular activity, thus turning down the release of CRH, ACTH, and eventually corticosteroid production. This occurs approximately 2 h after the onset of the stressful situation. Overall after stress, cells in the body, including the brain, are exposed to consecutive waves of stress hormones (Fig. 1). The corticosteroid wave occurs on top of circadian variations – which are determined by underlying ultradian pulses (Lightman et al. 2008), with a peak just before awakening and a nadir at the end of the active phase. The amount of corticosteroids reaching brain cells also depends on other factors, e.g., the expression of p-glycoproteins which determine the transport of particularly cortisol over the blood-brain barrier and the cellular plasma membrane (Pariante 2008).

1.2 Stress Hormone Receptors

Noradrenaline binds to G-protein-coupled receptors in the plasma membrane and, through this pathway, exerts its actions in seconds to minutes. Secondarily to these

rapid actions, noradrenaline can also affect the transcriptional machinery and hence alter neuronal function over the course of hours. Although probably all adrenoceptor subtypes are involved in the mediation of changes in brain function after stress, pharmacological studies have demonstrated that particularly β-adrenoceptors are important for stress-induced effects on memory formation of adverse events (reviewed by (Roozendaal and McGaugh 2011)).

In contrast to noradrenaline – and peptides like CRH – corticosteroid hormones bind to intracellularly located receptors, which in their inactive state are bound to various proteins including heat shock protein 90. Upon binding of the hormone to the receptor, the receptor complex dissociates, and the hormone-receptor molecule translocates to the nuclear compartment. The activated receptor binds as a homodimer to palindromic recognition sites in the DNA of responsive genes and affects the transcriptional activity of that particular gene.

In addition, it has been shown that activated receptor monomers can bind to other transcriptional regulators and, in this indirect manner, change gene transcription. It has been shown that approximately 1–2% of all genes are potentially altered in their transcriptional activity when exposed to corticosteroids, which explains the pleiotropic action of the hormone. The transcriptional activity not only depends on the expression of receptors but is also determined by local expression of cofactors (Meijer 2002; Meijer et al. 2019). Due to these genomic signaling pathways, corticosteroid hormones generally exert actions that start with a delay of >1 h yet can last for hours to days. More recently, it has become evident that in some cases, corticosteroids can also evoke rapid effects, i.e., within minutes (Joëls et al. 2012). Presumably, these actions are mediated by receptors located in the vicinity of the plasma membrane and do not involve transcription and translation. Whether the receptor molecules mediating these rapid effects form a pool separate from the intracellular receptors has not been resolved to date.

Two types of corticosteroid receptors have been identified (for review see De Kloet et al. 2005). First, the high-affinity mineralocorticoid receptor (MR), which is identical to the receptor expressed in the kidney. Cells in the kidney express 11-β-hydroxysteroid dehydrogenase 2 (11βHSD2) which converts corticosterone and cortisol into their inactive 11-keto congeners (Seckl 2004). This allows the less prevalent adrenal hormone aldosterone to bind with high affinity to the MR, thus exerting its role in the maintenance of the mineral balance. Most cells in the brain, by contrast, express 11βHSD1 rather than 11βHSD2, which promotes the recovery of corticosterone and cortisol. Most brain MRs, therefore, bind corticosterone or cortisol instead of aldosterone; the affinity for corticosterone and cortisol is very high, causing the MR to be mostly in its active state, even with low (nadir) levels of corticosterone or cortisol. Expression of MRs is particularly high in all hippocampal subfields, in the lateral septum, in some motor nuclei in the brain stem, and, to a lesser degree, in amygdalar nuclei and neocortical layers. The second receptor type is the glucocorticoid receptor (GR), which is much more ubiquitously expressed, in neurons and glial cells. Neurons in the CA1 hippocampal region, the dentate gyrus, and classical feedback regions like the PVN contain high levels of GR. The GR has a tenfold lower affinity than MR for corticosterone and cortisol. In some cells that

express both MR and GR, e.g., hippocampal CA1 neurons, basal levels of corticosteroid hormones – such as circulate under rest at the circadian nadir – result in substantial activation of MR, while GR is only partly activated. Upon stress, the remainder of the available GR will be activated. These cells "shuttle" between a situation of predominant MR activation and a situation where both receptor types are substantially activated.

2 Stress Hormone Actions on the Brain in Healthy Individuals

2.1 Cellular Effects of Stress Hormones on Brain Circuits

As pointed out above, noradrenaline is released in specific pathways in the brain and locally exerts primarily rapid actions through pre- and/or postsynaptically localized receptors. Via β-adrenoceptors, neurons are mostly quickly excited (reviewed in (Joëls et al. 2012)), but the exact effect after stress depends on the concentration of noradrenaline, the local expression of receptor subtypes, and other processes such as reuptake. CRH acts in a similar fashion, through G-protein-coupled receptors. The expression of CRH receptor subtypes (CRH-R1 and CRH-R2) in particular cell populations but also, e.g., the availability of CRH-binding proteins, determines the overall outcome (Joëls and Baram 2009).

In limbic neurons, such as in the CA1 hippocampal area, dentate gyrus, and basolateral amygdala, corticosterone was shown to rapidly increase spontaneous glutamatergic transmission, via a nongenomic MR-dependent pathway (Joëls et al. 2012). These rapid nongenomic effects of corticosteroids are state- and region-dependent. Thus, basolateral amygdala neurons of mice that were earlier stressed respond to corticosterone with a rapid nongenomic *suppression* of glutamate transmission, which involves GR. Similarly, parvocellular neurons in the PVN show a rapid nongenomic GR-dependent suppression of glutamatergic transmission (see Levy and Tasker 2012).

Rapid non-genomic signaling in hippocampal cells is complemented by slow-onset gene-dependent effects, which in all cases investigated involved the GR. These GR effects promote the signal-to-noise ratio, by enhancing specific glutamatergic signals while suppressing background activity of neurons. The latter has not only been described for hippocampal CA1 (and CA3) neurons but also principal neurons in the prefrontal cortex.

The waves of stress hormones to which neurons are exposed partly overlap in time, which could mean that cells are subject to concomitant actions of several stress hormones. In addition, consecutive waves may affect each other's action. A clear example is the effect of stress hormones on neurons in the basolateral amygdala (Karst and Joëls 2016). These neurons respond in vitro to a moderate to high concentration of the β-adrenoceptor agonist isoproterenol with a short-lived burst

of glutamate-mediated excitatory activity, followed approximately 1 h later by suppression of glutamate signaling. However, if the wave of isoproterenol was followed 20 min later by a wave of corticosterone (at a high concentration), the secondary inhibitory phase did not occur; instead, a prolonged period of excitation was observed: The delayed brake on amygdalar activity was in this case "overruled" by the subsequent wave of corticosterone.

All in all, waves of stress hormones change brain function in a time-, region-, and receptor-dependent manner. To what extent local receptors are being activated depends on the type and severity of the stressor. Although it is not simple to translate this body of knowledge to an overall picture how stress affects entire brain circuits, it nevertheless did guide an extensive series of studies examining time-dependent effects of cortisol and/or stress on cognitive function in rodents and humans.

2.2 Neuronal Circuits and Cognitive Function

To test time-dependent effects of stress hormones on cognitive function, one can administer, e.g., yohimbine (which indirectly causes the release of noradrenaline in the brain), hydrocortisone (in humans), or corticosterone (in rodents), and test changes in cognition after various intervals. Preferably, the effect of stress (rather than exogenous hormone exposure) is studied. To examine rapid nongenomic and delayed gene-mediated effects, respectively, circuit activity and cognitive function were probed directly after stress exposure or >1 h later, allowing to distinguish between rapid nongenomic and delayed gene-mediated actions, respectively. To focus on the contribution of a particular receptor type, exogenous hormone administration or stress was in some cases combined with pretreatment with specific receptor antagonists or, in the case of rodents, with the use of brain-selective receptor knockout.

Functional neuroimaging and behavioral studies revealed that directly after stress, the activity of the salience network (SN), and particularly of the amygdala, is strongly increased, involving β-adrenoceptors (Hermans et al. 2011). Interestingly, stress also increases the connection of the amygdala nuclei with striatal areas, at the cost of pathways to higher brain areas such as the hippocampus (Vogel et al. 2016; Schwabe 2017). This connection with the striatum was shown to depend on MR function and to be required for optimal behavioral performance under stress. The rapid β-adrenergic and MR-dependent phase is important for alertness, vigilance, emotion, and rapid decisions necessary for the immediate survival of stressful situations.

These rapid actions are complemented by effects that appear with a delay of at least 1 h. At that time, amygdala activity is normalized (or even suppressed), while behavior involving the hippocampus or frontal cortex is facilitated compared to non-stressed controls. Rational decision-making, driven by the executive control network (ECN), is improved. In rodents, these later behavioral effects were found to depend on GR; this has not been tested specifically in humans to date. Behaviorally,

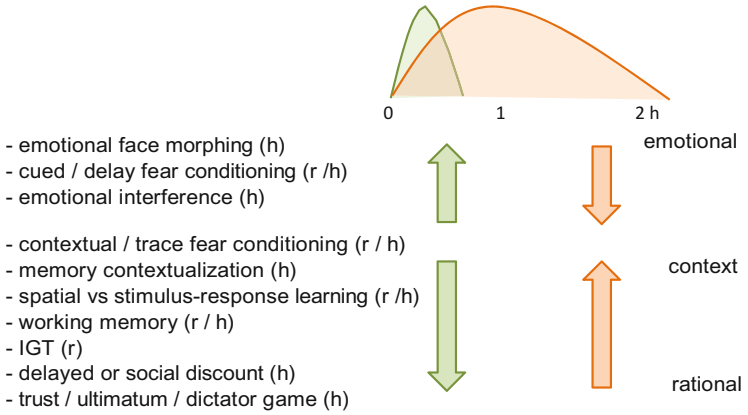

Fig. 2 Summary of behavioral observations in rodents (r) and human subjects (h) directly after stress/corticosteroid administration (rapid) and >1 h after stress/corticosteroid administration (delayed). The tests are arranged from those involving primarily amygdalar/striatal circuits (top), through hippocampal circuits (middle) to prefrontal circuits (bottom). Directly after stress monoamines (green) and corticosteroids acting primarily via MR promote emotional processing, at the cost of higher cognitive functions such as contextual memory formation or reward-based decision-making. At a longer interval >1 h after stress or corticosteroid administration (orange), the reverse is seen. *IGT* Iowa gambling task

this late phase is associated with stronger (than in control conditions) contextualization of information and more rational/less emotionally driven decision-making. Late, as opposed to early, effects of stress were also shown to promote altruistic behavior. In general, delayed actions of stress and corticosteroids promote cognitive processes that are beneficial for the future survival of the individual.

Figure 2 summarizes the time-dependent effects of stress and/or corticosteroid hormones on cognitive function. It is assumed that a good balance between both phases is important for optimal survival of individuals in the face of stress, i.e., one needs to react quickly for immediate survival but also needs storage, contextualization, and rationalization of stressful information to restore cognitive performance and to be well-prepared for similar challenging conditions in the future.

3 Changes in Stress Responsiveness in Bipolar Disorder

3.1 Imbalance in the Stress System: Importance of Genetic and (Early) Life History

The effect of stress hormones depends on many factors, including the age, sex, health, and medication of the individual. Also, the genetic background is of eminent importance. For instance, multiple single nucleotide polymorphisms (SNPs) have been reported for both MR and GR; some combinations are inherited as haplotypes

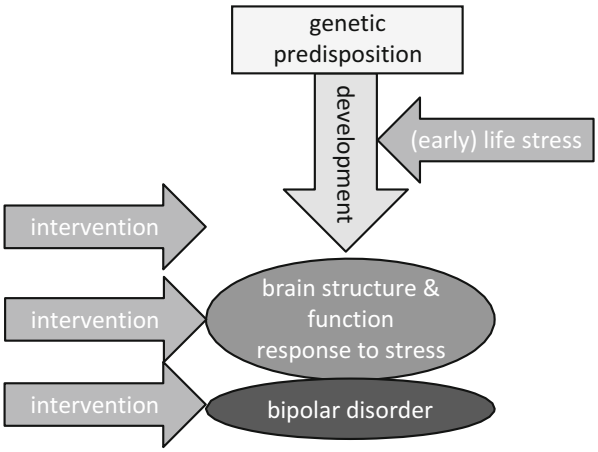

Fig. 3 Development of the brain and the stress system is determined to an important extent by an individual's genetic background. The effect of small genetic variances that predispose to a hyper- or hyporesponsive stress system may be amplified in the face of multiple life events, especially when these are experienced early in life when both the stress system and brain connections are still developing. This may have lasting consequences for brain structure and function as well as the response of individuals to stress (and the impact thereof on the brain). These changes may form an added risk factor for the precipitation of bipolar disorder in genetically vulnerable individuals. Based on these insights, intervention aimed at normalization of the stress system could be effective

(Koper et al. 2014; ter Heegde et al. 2015). Particular SNPs or haplotypes may be associated with a higher incidence of psychopathology. Given the role of corticosteroids in the negative feedback loop, it is to be expected that such genetic variants also affect the stress-induced release of cortisol and hence the exposure of the brain to waves of hormones after stress. For instance, a low functionality of the GR may cause insufficient feedback, resulting in a prolonged wave of cortisol after stress. Such elevated hormone levels, in turn, may downregulate receptor expression, which further exacerbates the insufficient feedback. This may eventually result in a vicious circle. A mild genetic predisposition to less (or more) functional GR or MR may become amplified when life events frequently challenge the stress system of the individual. Especially when these events take place during the sensitive period of development, this may not only have an impact on a stress system that has not yet stabilized but also on brain circuits that are still being shaped. Over (or under) exposure of the brain to corticosteroids during that time may have lasting consequences for the balance in the stress system and the way in which brain regions are interconnected and thus for their role in cognitive performance (see Fig. 3).

In agreement with this view, adverse conditions experienced early in life are generally reported to be a risk factor for the development of brain disorders, including psychiatric disorders such as bipolar disorder or schizophrenia (Turecki et al. 2014; Jawahar et al. 2015; Cancel et al. 2019).

In the following sections, we first summarize the current evidence for the altered function of the HPA axis in bipolar disorder and next highlight how the disorder affects time-dependent cognitive effects of stress. We compare the characteristics reported for bipolar disorder (BD) with those seen in relation to schizophrenia.

3.2 Changes in the HPA Axis in Bipolar Disorder Patients

A common finding in psychiatry is the disruption of the HPA axis in mood disorders, with most studies reporting hypercortisolemia in depressed patients (Gold et al. 1988; Gillespie and Nemeroff 2005). As for patients diagnosed with BD, high levels of basal cortisol were previously reported to be prevalent when the measurements were taken in the morning, before 10:00 AM (Girshkin et al. 2014). The difference between cortisol levels in BD patients compared to controls is even more pronounced when the cortisol awakening response (CAR) is determined (Belvederi Murri et al. 2016). However, basal cortisol levels were also found to be augmented in the afternoon and night hours, as recently demonstrated by a meta-analysis performed by Belvederi Murri et al. (2016) including 37 studies on basal cortisol levels in BD patients.

It would be an oversimplification to determine stress (cortisol levels) in BD patients regardless of the phase of the disease in which the samples were taken. Therefore, Belvedere Murri and colleagues also assessed effects sizes (Hedges's g) of basal cortisol levels (at various moments of the day) during the different phases of the illness. The subgroup analyses showed that in BD patients during the depressive episodes, hypercortisolemia were only evident in the studies which samples were continuously obtained throughout the day (Hedges's $g = 0.44$). The studies in which samples were obtained during the euthymic phase indicated significant high cortisol levels at wakening ($g = 0.59$), morning ($g = 0.41$), afternoon ($g = 0.31$), and 24-h continuous sampling ($g = 0.28$). When samples were obtained during the manic phase, significant hypercortisolemia was found at morning ($g = 0.66$), night ($g = 0.15$), and 24-h continuous sampling ($g = 0.64$). Additionally, meta-regression analyses pointed out that assessing basal cortisol levels during the manic phase was associated with higher effects sizes (Belvederi Murri et al. 2016).

Although the literature points to increased cortisol levels in BD patients under basal conditions, there might also be differences during real-life stress, but cortisol levels are difficult to determine and standardize under such conditions. Nevertheless, one study did assess cortisol level in response to negative life events and found no significant differences between BD and controls (Havermans et al. 2011). There are several studies suggesting that under a controlled stressful laboratory situation, such as the Trier social stress test (Kirschbaum et al. 1993), the cortisol response of BD patients is *blunted* compared to controls (Wieck et al. 2013; Houtepen et al. 2015). Houtepen and colleagues found that from 20 to 90 min after the TSST, BD patients presented a blunted cortisol response compared to healthy controls, whereas BD

patients' unaffected siblings showed a cortisol response that was similar to the healthy controls.

As high levels of basal cortisol are observed in BD patients, this could point to impaired negative feedback control of the HPA axis possibly due to diminished GR sensitivity, as previously indicated in pharmacological studies (Schmider et al. 1995; Rush et al. 1996; Rybakowski and Twardowska 1999; Watson et al. 2004). The blunted response to the TSST does not seem to support this idea. Yet Houtepen et al. (2015) argued that the chronically elevated cortisol levels of BD patients might gradually impair the HPA axis' ability to respond to stress, eventually resulting in a blunted stress response. Unfortunately, studies that closely follow the functionality of the stress response and the development of BD are scarce.

Many BD patients are under medication. Houtepen et al. (Houtepen et al. 2015) showed that BP patients under antipsychotics treatment presented a flat cortisol response to the TSST compared to BD patients under non-antipsychotics (anticonvulsants, benzodiazepines, and antidepressants) treatment and healthy controls, suggesting a substantial influence of antipsychotics on the stress response measured under these circumstances. Interestingly, prior to the start of the TSST in this study, no antipsychotic effects were observed, suggesting that they might exert no effect on basal cortisol level. However, a meta-regression analysis indicated that the use antipsychotics is associated with a reduction of basal hypercortisolemia in BD patients compared to controls; no association was observed between basal cortisol in BD patients and antidepressants, lithium, or mood stabilizers (Belvederi Murri et al. 2016). The latter finding is in line with a study by Girshkin et al. (2014), who evaluated morning cortisol data of BD patients who were under treatment mostly with antidepressants and mood stabilizers (or medication-free) and found no significant differences compared to controls.

Antipsychotics are mostly prescribed for schizophrenia (SZ), another psychiatric condition in which the HPA axis is dysregulated (Brenner et al. 2009). Similar to what was found in BD patients, SZ patients also present high basal cortisol levels in early stages of the disease (Chaumette et al. 2016), high morning cortisol levels (Girshkin et al. 2014), and a blunted cortisol response to social stress (Ciufolini et al. 2014; Zorn et al. 2017). However, in contrast to BD patients, SZ patients show a reduced CAR compared to controls (Berger et al. 2016). Data on cortisol levels in BD and SZ patients are summarized in Table 1.

4 Changes in Cognitive Function in Bipolar Disorder Related to Stress

As described in Sect. 2, glucocorticoids modulate neuronal activity and network function and, when chronically elevated, also morphology, as was shown already some decades ago in preclinical experiments (Magariños and McEwen 1995; Magariños et al. 1996). Neurons in the medial prefrontal cortex are also sensitive

Table 1 Overview of cortisol levels in bipolar disorder and schizophrenic patients compared to controls under basal condition and in response to awakening social stress

Cortisol levels	BD vs controls	SZ vs controls	Type of study	Reference
Basal (overall)	Augmented[1]	Augmented[2]	[1, 2]Meta-analysis	[1]Belvederi Murri et al. (2016); [2]Chaumette et al. (2016)
Basal (morning)	Augmented[1]	Augmented[1]	[1]Meta-analysis	[1]Girshkin et al. (2014)
Basal (afternoon)	Augmented[1]	N/A	[1]Meta-analysis	[1]Belvederi Murri et al. (2016)
Basal (night)	Augmented	N/A	[1]Meta-analysis	[1]Belvederi Murri et al. (2016)
Cortisol awakening response (CAR)	Augmented[1]	Diminished[1]	[1]Meta-analysis	[1]Berger et al. (2016)
Stress-induced cortisol (TSST)	Blunted[1, 2]	Blunted[3, 4]	[1, 2]Original research [3, 4]Meta-analysis	[1]Wieck et al. (2013), [2]Houtepen et al. (2015), [3]Ciufolini et al. (2014), [4]Zorn et al. (2017)

Illness phase and medication effects on cortisol levels in BD patients	BD vs controls	SZ vs controls	Type of study	Reference
Depressive	Augmented[1] (only if 24 h measurements were taken)	N/A	[1]Meta-analysis	[1]Belvederi Murri et al. (2016)
Euthymia	Augmented[1]	N/A	[1]Meta-analysis	[1]Belvederi Murri et al. (2016)
Mania	Augmented[1]	N/A	[1]Meta-analysis	[1]Belvederi Murri et al. (2016)
Medication (antipsychotics)	Blunted TSST response[1], lower hypercortisolemia[2]	N/A	[1]Original Research [2]Meta-Analysis	[1]Houtepen et al. (2015), [2]Belvederi Murri et al. (2016)

Illness phases and medication effects on cortisol levels are also shown for bipolar patients. Most of the data summarized in this table were obtained from meta-analyses published in the last few years Superscript numbers indicate from which studies data were obtained

to high glucocorticoid levels and, similar to CA3 neurons, show decreased dendritic complexity even after a mild stress paradigm (Brown et al. 2005). In contrast, pyramidal and stellate neurons in the amygdala, as well as pyramidal neurons in the orbitofrontal cortex, show increased dendritic arborization (Vyas et al. 2002; Mitra et al. 2005). Overexposure to glucocorticoids as generally seen in BD patients – at least under basal (non-stressed) conditions – might thus result in altered morphology and function of limbic structures such as the hippocampus and amygdala, areas that are important for (emotional) memory. In agreement, hippocampal

atrophy has been found in BD patients, particularly the CA3 area of the hippocampus (Bertolino et al. 2003; Konradi et al. 2011; Mathew et al. 2014).

4.1 Time-Dependent Changes in Cognitive Processing Following Stress in BD Patients

Given the changes observed in BP patients regarding circulating cortisol levels and the potential consequences thereof for neuronal function and morphology, one might expect that neuronal circuits are altered as well as the cognitive processes for which these circuits are crucial. BD is indeed related to dysfunction of several brain networks, including the salience network, executive control network, the default mode network, and the reward circuitry (Bora et al. 2010; Mamah et al. 2013; Whitton et al. 2015; Goya-Maldonado et al. 2016; Schreiter et al. 2016; Gong et al. 2019; Karcher et al. 2019). We will first discuss the evidence for disturbed reward processing in BD patients, under basal and stress conditions.

Reward processing is affected during the acute and recovery phase of stress. During and directly after stress in healthy controls, reward-seeking is increased and anticipatory responses in the brain's reward circuitry amplified, including in the orbitofrontal cortex and ventral striatum (Kumar et al. 2014; Lewis et al. 2014); responses to reward consumption are reduced (Bogdan and Pizzagalli 2006; Porcelli et al. 2012; Berghorst et al. 2013; Kumar et al. 2014). By contrast, in the late aftermath of stress – i.e., during stress recovery – anticipatory reward responses are reduced (Montoya et al. 2014), whereas neural responses to reward outcomes are increased (van Leeuwen et al. 2019a, 2019b).

In BD patients, though, these acute and late effects of stress on the reward circuitry are absent (see Fig. 4). More specifically, reward-related responses were not decreased directly after stress (Berghorst et al. 2016) and were not increased in the aftermath of stress (van Leeuwen et al. 2019b). These findings suggest that neurobiological adjustments after stress are necessary for the maintenance of good mental health. Frequent exposure to stressors may ultimately lead to generally impaired reward processing. Indeed, the number of stressful life events was negatively associated with striatal responses after stress (van Leeuwen et al. 2019b). Reduced upregulation of the reward circuitry following stress was also observed in siblings of schizophrenia patients (van Leeuwen et al. 2019a), suggesting diagnosis spanning alterations in the reward circuitry in relation to stress in psychiatric disorders.

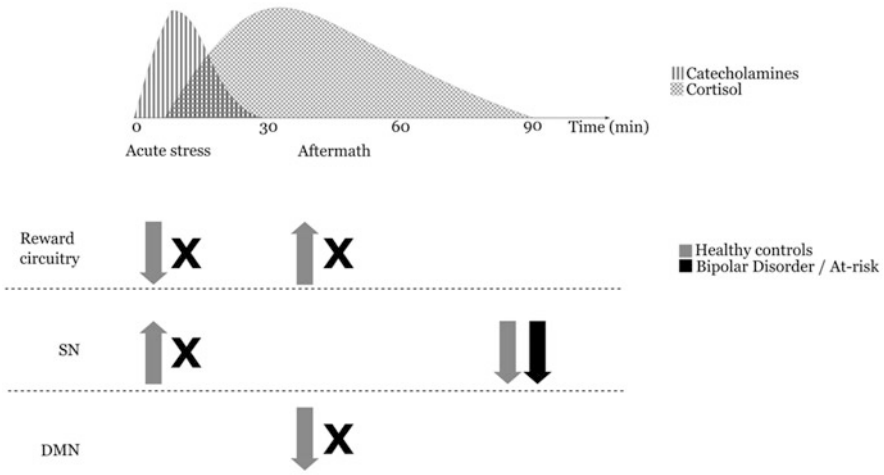

Fig. 4 Model illustrating the time-dependent effects of stress on brain functioning in healthy controls and individuals at risk for/suffering from bipolar disorder. The studies summarized in this review implicate that resilience to stress most likely requires active regulation of neurocognitive processes aimed to effectively cope with and recover from environmental stressors, rather than the absence of a reaction to such stressors. *SN* salience network, *DMN* default mode network

4.2 Network Function in BP Patients and Individuals at Risk for Psychopathology

Connectivity within and between the salience network (SN), executive control network (ECN), and default mode network (DMN) that also play a role in response to stress has consistently been shown to be affected in bipolar disorder, even in the absence of stress (Öngür et al. 2010; Chai et al. 2011; Gong et al. 2019; Sha et al. 2019).

Unfortunately, there are currently no published studies that looked at the effects of stress on these networks in BD patients. However, studies are focusing on the effects of stress in individuals with an *increased familiar risk* for BD. Studies have revealed etiological relationships between schizophrenia and BD and found that family background is the largest risk factor for both disorders (Merikangas et al. 2007). Indeed, relatives of schizophrenia patients have a higher chance to develop BD compared to the general population (Cheng et al. 2017). Given the large heritability of both schizophrenia and BD and their interaction with environmental factors, investigating the neural responses to stress in family members of schizophrenia patients could be a valuable paradigm to investigate the gene-environment interactions in bipolar disorder. Here we summarize previous findings on the effects of stress on these networks in vulnerable individuals.

First, the results on the salience network (SN). The activation of the sympathetic nervous system and the release of (nor)epinephrine during and directly after stress increase connectivity within the SN in healthy individuals, leading to increased threat detection and thereby aiding active coping (van Marle et al. 2009; Oei et al. 2012; Hermans et al. 2014; van Oort et al. 2017). In contrast, SN functional connectivity in siblings of schizophrenia patients is lower during acute stress, indicating impaired detection of relevant stimuli and inadequate response selection under stressful circumstances (van Leeuwen et al. 2018). In addition, salivary alpha-amylase level, an indirect marker of adrenergic activity (Van Stegeren et al. 2006), was higher in at-risk individuals exposed to a placebo test than in healthy controls, which did not further increase in response to stress, suggesting higher chronic levels of norepinephrine. The (late) aftermath of stress is characterized by downregulation of SN activity (Hermans et al. 2014), which did not differ between controls and siblings (van Leeuwen et al. 2018). Overall, these findings suggest reduced responsiveness to changes in the environment, possibly caused by a reduced dynamic range in the sympathetic/noradrenergic response. Evidence that BD patients also display exaggerated adrenergic signaling at trend level (van Leeuwen et al. 2019b) could point to a potentially reduced SN activation after stress as well.

Second, the default mode network (DMN). Previous studies showed that acute stress temporarily increases activity in the DMN, increasing interference from internal emotional states (Qin et al. 2009); deactivation was observed in the aftermath of stress (Van Leeuwen et al. 2018). Several studies have already demonstrated that the inability to downregulate the DMN in the absence of stress is associated with poor clinical outcome in BP and schizophrenia and with rumination in depression (Grimm et al. 2009; Pomarol-Clotet et al. 2012; Bartova et al. 2015; Wang et al. 2017). Moreover, there is one case report in the literature that shows normalization of DMN activity after successful treatment in a BD patient (Landin-Romero et al. 2013), suggesting a role for DMN dysregulation in the course of the disorder. In individuals at risk for schizophrenia, it was indeed found that DMN activity does not decrease in the aftermath of stress (Van Leeuwen et al. 2018). These findings indicate that good mental health requires a dynamic shift away from the DMN in the aftermath of stress. In vulnerable individuals, sustained activity within the DMN may result in increased rumination following stress and maybe a precipitating factor in the development of BD.

Finally, the executive control network (ECN). Only a few studies found altered ECN functional connectivity in BD. Regarding the situation after stress, ECN functional connectivity is reduced during and directly after stress but increased in the (late) aftermath of stress, the latter presumably through genomic actions of cortisol (Arnsten 2009; Qin et al. 2009; Henckens et al. 2011; Hermans et al. 2014). To date, no functional MRI studies have examined the effects of stress on ECN connectivity in BD. We previously observed an increase in functional connectivity between the ECN and the cerebellum in healthy controls but also in individuals at risk for schizophrenia in the aftermath of stress (van Leeuwen et al. 2018). The role of the ECN and its relation to stress in BD require further investigation.

5 Concluding Remarks

In this overview, we highlighted that stress causes consecutive yet overlapping waves of hormones to reach the brain. These hormones change neuronal function in a time-, region-, and receptor-dependent manner. While it is difficult to predict how this affects entire circuits and thereby cognitive processing, an extensive series of studies point to an overarching picture: During and directly after stress, the salience network and default mode network are increased in activity, at the cost of networks involved in contextualization. In the aftermath of stress (starting at least 30 min after stress onset), the earlier activation of these networks is dampened, while networks involved in executive control and contextualization are enhanced in their activity. Both phases are necessary for (quick) correct appraisal of the situation at hand and (later) rational decision-making and context-related storage of information for future use.

If the stress-induced release of hormones is altered, as appears to be the case in BD, this in itself will already change any functional process resulting from hormonal actions. The effects that have been described in terms of cortisol release are not entirely consistent, though. Basal levels generally seem to be increased, yet there may be diminished stress-induced cortisol release, at least under laboratory stress conditions. How BD patients respond to real-life stress is still unresolved. Moreover, cortisol levels are not the only factor determining the effect of stress on brain function. Other factors of relevance comprise, e.g., the extent to which cortisol gets into the brain, what happens to receptor expression, and potential effects downstream of the receptors. In addition, stress causes the release of multiple hormones that potentially interact with each other, and many of these hormones have not (yet) been determined in relation to BD.

Importantly, how HPA function alters along the course of the disease is largely unknown. Possibly, hyperactivity of the system occurs early on in the disorder, which could slowly evolve into hypoactivity in the face of prolonged overexposure of the brain and body to cortisol. Precise measurement of both the stress system and the development of BD is necessary to address this issue. This might also give insight whether HPA disturbances are the cause or consequence of the disorder. There is some evidence for a causal role. Longitudinal studies revealed that in BD patients relapse of depressive and (hypo)manic episodes is preceded by a higher number of stressful life events, compared to euthymic periods (absence of depressive or (hypo)manic symptoms) (Lex et al. 2017). Moreover, patients reported increased emotional reactivity to daily life stressors compared to controls (Myin-Germeys et al. 2003; Havermans et al. 2010). These findings suggest that an impaired initial response to stress and/or a poor recovery from stress may play a role in the development and clinical course of bipolar disorder.

Related to the disease and/or alterations in the stress system, brain circuits may be altered in BD patients. We supplied some evidence for this notion in Sect. 4, although there is clearly a paucity in information, particularly with regard to studies investigating time-dependent effects of stress on cognitive processing in BD patients

versus controls. While most human stress studies focus on the acute phase of stress, it is becoming clear that it is important to include all phases of the stress response, particularly the recovery period which has not received much attention. We observed quite striking differences between controls and both at-risk individuals and patients in the early aftermath of stress. In general, healthy controls displayed stress-dependent changes in neuronal activity during cognitive tasks (e.g., emotional information or reward processing), while this was diminished in at-risk individuals and BD patients. We propose that resilience to stress most likely requires active and dynamic regulation of neurocognitive processes aimed to effectively cope with and recover from environmental stressors, rather than the absence of a reaction to such stressors. These findings could provide a starting point for more research elucidating the mechanisms of stress vulnerability in BD, to identify who is at risk, and make the first steps toward preventive rather than reactive therapeutic interventions.

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