Chapter 5

Emotional and Motivational Processes in Bipolar Disorder: A Neural Network Perspective

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1. Introduction

Recurrent prominent mood swings are the most obvious characteristic of bipolar disorder. Thus it is not surprising that models of bipolar disorder emphasize the importance of disturbed emotion processing for the pathogenesis of this disorder. More precisely, models of bipolar disorder focus on abnormal unconscious and conscious evaluation of events (appraisal) relevant to the elicitation and regulation of emotions [1]. The close link between emotion and motivation has received less attention but appears equally important in bipolar disorder as evaluation of stimuli as appetitive (reward) or aversive (punishment) facilitates either approach or avoidance motivation and behavior [2]. Abnormal approach and avoidance behavior is observed in bipolar disorder patients in the manic and depressive states. During mania, patients seek rewarding outcomes more intensively despite potential negative consequences leading to such symptoms as an increase in goal-directed activity (at work, at school, or sexually) and excessive involvement in pleasurable activities. On the contrary, during depression, patients anticipate punishment rather than reward explaining why they show markedly diminished interest in almost all activities.

Despite these theoretical and clinical considerations, brain research in bipolar disorder has mainly focused on automatic emotional responses through the application of paradigms that use emotionally evocative stimuli like faces and words to elicit emotion during passive viewing, action choices, and facilitation or inhibition of responses. Most studies assess the activity of relevant brain regions using functional magnetic resonance imaging (fMRI) [3, 4], a technique that takes advantage of the different magnetic properties of oxygenated and deoxygenated blood. Measurement of this blood-oxygenated-level-dependent (BOLD) contrast reflects hemodynamic metabolic changes associated with neural activation, offering an indirect and complex representation of underlying neural processes [5, 6].

Based on the results of these studies, an imbalance between the activity of 'core emotional' brain regions and brain areas associated with both emotion and cognition has been proposed to underlie bipolar symptoms. Ventrally located 'core emotional' brain regions like the amygdala, the striatum, the orbitofrontal cortex, the subgenual and ventral anterior cingulate cortex, and the ventromedial prefrontal cortex are thought to be hyper-active in bipolar disorder, whereas regions belonging to the extended emotional and cognitive control network like the hippocampus, the anterior insula, the dorsal prefrontal cortex, and the posterior cingulate cortex are assumed to be hypo-active [7, 8]. Although the simplicity of this model is rather intriguing, one has to consider that each of these regions is itself a complex area that is connected to other regions forming different networks involved in numerous not exclusively emotional processes. In other words, each of these regions that showed abnormal activity in response to emotionally relevant stimuli in bipolar disorder patients is involved in multiple cognitive and emotional processes like emotion elicitation, emotion regulation, and motivation, which are carried out by several of these regions [9].

In the present chapter, we will review imaging literature examining both emotional and motivational processes as they are tightly linked psychological processes that represent two sides of the same coin. Whereas the focus on emotion implies a certain state of feeling, emphasis of motivation relates to a certain state of goal, pursuit like the achievement of pleasant feelings and the avoidance of unpleasant feelings. Imaging literature examining emotional processes in bipolar disorder will be reviewed, focusing on different stages of emotion processing (early emotional processes, elicitation of an emotional response, emotion regulation). Review of motivational processes will center on anticipation of positive and negative consequences and the delivery of these consequences. We will discuss volumetric alterations in relevant brain areas and we will also describe findings, which examine structural connectivity between these regions. Next we will address the question whether functional and structural abnormalities related to disturbed emotion and motivation processing in bipolar disorder are more likely to evolve during the course of the disease or rather constitute a vulnerability factor for bipolar disorder. We will also discuss current knowledge about the effects of mood states and psychotropic medication on emotional and motivational processes in bipolar disorder.

2. Emotional processes

Various theoretical accounts agree that emotion processing includes different mechanisms that vary with respect to the involvement of attentional and cognitive resources. In more detail, these mechanisms comprise a pre-attentive stage, attention allocation, sensory perception, transient and automatic emotional responses, experience and expression of emotion, higher-level appraisal of emotional stimuli, and finally the regulation of emotions [10]. From an experimental and clinical neuroscience perspective, it is important to make a distinction between these sub-processes in order to be able to validly characterize disturbed or maladaptive processes into psychopathologies. In this chapter, we will roughly divide these mechanisms into (1) early emotional processing, (2) emotional responses including

transient, automatic responses and the subjective emotional experience, and (3) expression of emotion and emotion regulation (see Figure 1).

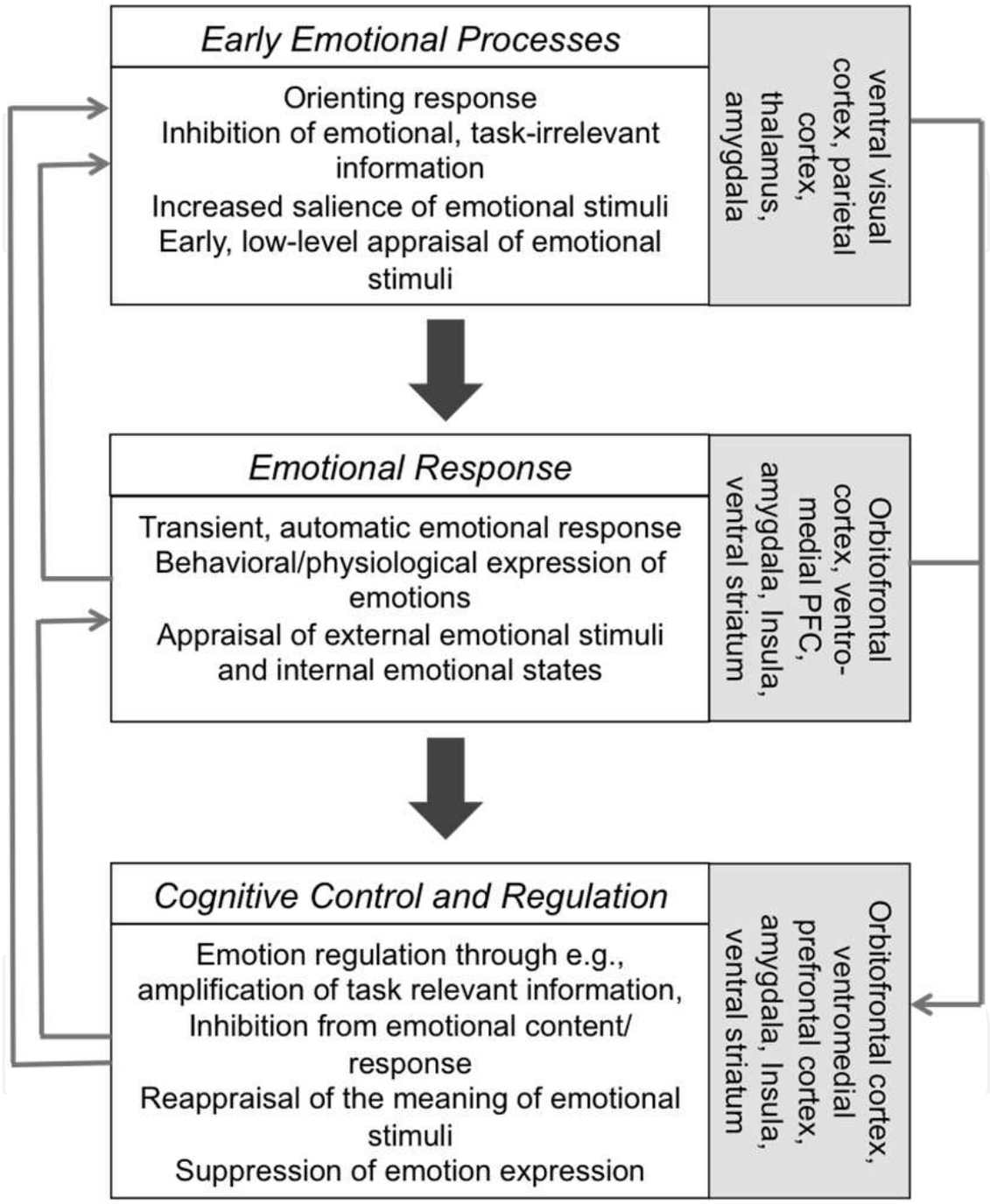

Figure 1. Schematic outline of the steps involved in emotional processing

2.1. Early emotional processes

Early emotional processes refer to the attribution of salience to motivationally relevant stimuli and the allocation of attentional resources to these stimuli. These processes are known to rely on the amygdala, thalamus, prefrontal cortex, parietal cortex, and visual

processing areas [9, 11, 12]. In bipolar disorder, the identification of disturbances in neural networks during these early stages of emotional processing is complicated by general attention deficits. Applying the Stroop color-word selective attention task, blunted activation in the ventral prefrontal cortex [13-16], anterior cingulate cortex [17], and parietal cortex [15] has been reported for bipolar disorder patients compared to healthy controls. Reduced activation in the anterior cingulate cortex and the parietal cortex has also been reported during high attentional control during a n-back task [18]. Furthermore, manic bipolar disorder patients displayed stable amygdala hyper-activation and striatal and thalamic deactivation during sustained attention compared to healthy persons [19].

In contrast to 'pure' attentional tasks where bipolar disorder patients showed hypo-activation of the ventral prefrontal cortex, the anterior cingulate cortex, and the parietal cortex in response to non-emotional targets, studies examining attention to non-emotional targets while emotional distractors are presented have produced rather conflicting results in bipolar disorder patients. In response to emotional distractors, the medial orbitofrontal and medial prefrontal cortex were hyper- [20-22] and hypoactive [21, 23] in euthymic and manic bipolar disorder patients. Similar hyper- [18, 20, 24] and hypo-activity [25] of the anterior cingulate cortex as well as hyper- [18] and hypo-activity [21, 26, 27] of the dorsolateral prefrontal cortex have been observed during the presentation of emotional distractors. Furthermore, the hyper-activity of the insula [20, 21] and posterior regions such as the precuneus [20], parietal cortex [18], and posterior cingulate cortex [21] have occasionally been reported.

More consistently, striatal hyper-activity in response to emotional distractor, has been observed in euthymic bipolar disorder patients using various tasks such as an emotional go/no go task [20], an emotional Stroop task [28], an emotional n-back paradigm [18], and a task asking participants to direct attention to non-emotional aspects (age, gender) of emotional faces [22, 26, 27]. Furthermore, hyper-activation of the amygdala in euthymic bipolar disorder patients has also been frequently reported using different paradigms, testing the influence of emotion on attentional processes [18, 21, 24, 28, 29]. However, there have also been reports of no alterations in amygdala activity [27, 30] and hypo-activity of amygdala [23]. Interestingly, several authors reported reduced connectivity between the amygdala and various regions such as the dorsal anterior cingulate cortex [18], the perigenual anterior cingulate cortex [31], the posterior cingulate cortex, and the parahippocampal cortex [32] – all implicated in 'pure' attentional deficits of bipolar disorder patients.

Thus, in contrast to 'pure' attentional tasks associated with hypo-activity of frontal and parietal brain regions in bipolar disorder patients, attention allocation on non-emotional targets in the presence of emotional distractors is not clearly associated with hypo- or hyper-activity of the frontal and parietal areas. Inconsistencies concerning the activity of the frontal and parietal brain regions during attention allocation on non-emotional targets might be related to reduced connectivity between these regions and the amygdala, which was reported to be rather hyperactive during attention allocation on non-emotional targets. As most results stem from studies investigating euthymic bipolar disorder patients, reports of hyper-activity of frontal

and parietal brain regions might point towards a compensatory mechanism meant to down-regulate subcortical structures. Further, striatal hyper-activation during attention allocation on non-emotional targets was the most robust finding. Although this has not been investigated so far, altered connectivity between the striatum and frontal brain regions might also be of importance during attention allocation on non-emotional targets.

With regard to emotional targets of attention, studies have produced very discrepant results. When pediatric bipolar patients were asked to direct their attention towards emotional aspects of emotional faces, either hyper-activation of the amygdala [30] or no alterations in amygdala activity [33, 34] were observed. Furthermore, hypo-activation in the prefrontal cortex and the anterior cingulate cortex and hyper-activation in the right precuneus and the fusiform gyrus were reported [21]. Using an emotional go/no go task, enhanced response of the ventral prefrontal cortex to emotional targets was reported for manic bipolar disorder patients [35].

Some of the discrepancies described above are likely due to methodological variety as studies used paradigms addressing different psychological processes such as selective attention [21, 22, 26, 27, 30, 33, 34] and executive functions involving attention such as response inhibition [20, 35], set-shifting [28], and working memory [18] corresponding to different neural circuits. Furthermore, studies varied with respect to emotional valence of distractors – some used only negative and neutral distractors [23], whereas others applied positive, negative and neutral distractors [18, 20, 28, 30, 35]. In addition, bipolar disorder patients in different mood states were examined. Further, conflicting results might also be due to effects of psychotropic medication. However, this influence was not tested in three of the studies reviewed above [20, 28, 35], whereas others ruled out the possibility that psychotropic medication confounded the results [18, 22, 23, 27, 29-31, 33]. However, Hassel and colleagues (2009) showed that increased medication load was associated with decreased activity of the dorsolateral prefrontal cortex while directing attention away from fearful faces and increased activity of the ventral striatum while focusing attention away from the emotional content of happy faces.

In summary, it seems very interesting that although 'pure' attentional deficits in bipolar disorder seem to be related to hypo-activity in the ventral prefrontal cortex and anterior cingulate cortex, this pattern is likely to be reversed to hyper-activation in both structures in the presence of emotional distractors. On a cautious note, first results indicate that this change might be related to altered connectivity of these structures with the amygdala [18, 31], which showed hyper-activation in response to emotional distractors. As the striatum displayed rather robust hyper-activity in the presence of emotional distractors, altered connectivity between the striatum and frontal brain regions might also be of relevance and needs to be investigated in the future. Nevertheless, existing results underline that there is not one disturbed network in bipolar disorder, but that the task-dependent interaction between networks is of great interest and relevance.

Future studies should compare patients in different symptomatic states. This seems especially interesting, as it has been suggested that both mood states of bipolar disorder are

associated with a mood- congruent attentional bias. And indeed, some behavioral studies have reported a mood-congruent attentional bias in manic and depressed bipolar patients [36, 37] that might even persist during remission [38-40]. Although, there are also reports indicating a mood-congruent cognitive bias only for depressed bipolar patients [41] and mood-incongruent bias in manic and depressed patients [42].

2.2. Affective response and evaluation

With respect to the emotional response and appraisal of emotional stimuli, studies on bipolar disorder have mostly focused on the recognition of emotions and the reaction to emotional stimuli. As previous studies have demonstrated that neural responses to emotional stimuli are dependent upon the nature of the task performed during stimulus presentation and the valence of the emotional material used [43-46], we will review the existing literature grouped according to the involvement of cognitive processes and appraisal and valence of emotional stimuli.

Firstly, we will present results from passive viewing tasks instructing the participants to view the stimuli without drawing any cognitive interference. Independent of the valence of the emotional stimuli used, this task is known to activate networks involving the medial prefrontal cortex and the anterior cingulate cortex [44]. Secondly, results from affect matching tasks demanding to choose one out of two pictures matching the emotional valence of a target picture will be reviewed. This is a perceptual task with rather low involvement of cognitive appraisal known to activate the amygdala, the thalamus, and the fusiform gyrus [43]. Finally, evidence derived from affect recognition tasks asking participants to label emotional pictures will be discussed. In contrast to the other two paradigms, this task involves cognitive appraisal and was shown to deactivate the amygdala and to activate the prefrontal and temporal cortices [43, 45, 46]. For this task, we will differentiate between different emotional valence such as happiness, sadness, fear, and disgust.

2.2.1. Passive viewing

Bipolar disorder patients display hypo-activation of the ventrolateral prefrontal cortex during mania [47, 48], euthymia [49], and depression [48, 50] when passively viewing pictures of negative emotional valence. With regard to the amygdala, hyper-activation during mania [51], euthymia [49], depression [50] and in a mixed sample [52] have been reported. However, hypo-activation during mania and euthymia [48], and no alterations during mania [47] have also been reported. Further reports include increased activity of the anterior cingulate during mania when viewing fearful faces [47], euthymia when viewing angry and happy faces [49], and in a mixed sample when viewing happy faces [53]. Also, striatal hyper-activity during mania when viewing fearful faces [47] and in a mixed sample when viewing happy faces [53] was observed. Hyper-activation of the prefrontal cortex, superior temporal gyrus, thalamus, and hypothalamus when viewing pictures of negative valence and increased activity of the prefrontal cortex, superior temporal gyrus, fusiform gyrus, parahippocampal gyrus, and thalamus when viewing pictures of positive valence

have been reported in depressed bipolar disorder patients [50]. Unfortunately, none of the studies using passive viewing of emotional pictures in bipolar disorder patients examined the effects of psychotropic medication. Nevertheless, hypo-activation of the ventrolateral orbitofrontal cortex is a very robust finding in bipolar disorder patients during passive viewing of emotional stimuli. In addition, hyper-activation of the anterior cingulate cortex and the striatum have been frequently and consistently reported across mood states.

2.2.2. Face matching tasks

Interestingly, both manic [54, 55] and depressed [56] patients showed hypo-activation of the ventrolateral prefrontal cortex during this task, but during euthymia, hyper-activation of the lateral prefrontal cortex was observed, although anticonvulsants showed some normalizing effect [57]. When manic bipolar disorder patients were asked to match facial expressions, they displayed hyper-activation of the amygdala [54, 55]. Euthymic patients did not show any hyper-activation of the amygdala, which might be attributed to antidepressants [57]. Furthermore, increased activity of the thalamus and the ventral anterior cingulate cortex during mania [55], and increased activity of the dorsolateral prefrontal cortex during depression [56] have been observed. However, as only four studies used this paradigm to investigate bipolar disorder patients, it is difficult to draw any clear and valid conclusions. Although the possible influence of psychotropic medication has not been frequently tested, hypo-activation of the ventrolateral prefrontal cortex has been repeatedly shown across mood states during this task [54-56].

2.2.3. Affect recognition tasks

When asked to recognize happy facial expressions, neuronal activity in manic [36], euthymic [58], and depressive [58] bipolar disorder patients did not differ from controls. However, others reported hypo-activation of the parahippocampal gyrus during euthymia [59] and depression [60] but hyper-connectivity between parahippocampal gyrus and subgenual anterior cingulate cortex during euthymia [59]. Further, depressed bipolar disorder patients showed hyper-activity of the striatum, ventral prefrontal cortex [42, 60], superior frontal gyrus, middle temporal gyrus, visual cortex, thalamus, and dorsal and posterior cingulate gyrus [42], and they showed hypo-activation of the thalamus and amygdala [60] while recognizing positive affect. Thus, altered activation during appraisal of positive stimuli appears to be rather state dependent in bipolar disorder.

When asked to recognize sad facial expressions, manic bipolar disorder patients showed hyper-activity in the posterior cingulate cortex, nucleus caudate, posterior insula, temporal cortex [36], and fusiform gyrus [42], but they showed hypo-activation in the subgenual anterior cingulate and parahippocampal gyrus [36]. Euthymic bipolar disorder patients displayed hypo-activation in the prefrontal and cingulate cortex but hyper-activation in the parahippocampal gyrus [61]. Depressed bipolar disorder patients showed increased activity of the amygdala [58, 59], hippocampus, and ventral prefrontal cortex [60] but decreased activation of the orbitofrontal cortex, putamen, and dorsolateral prefrontal cortex [60].

Further, connectivity between the amygdala and the orbitofrontal cortex was increased in depressed bipolar disorder patients during recognition of a sad facial expression [62]. However, no altered brain activation was also reported for euthymic [58] and depressed [42] bipolar disorder patients. Similarly to reports concerning appraisal of happiness, altered brain activation in response to appraisal of sadness also seems to be rather state dependent.

When labeling fearful facial expression, manic, euthymic, and depressed bipolar disorder patients showed hyper-activation of the parahippocampal gyrus and the temporal cortex [42, 63]. Further, hyper-activity of the prefrontal cortex, nucleus caudate, putamen, thalamus, and brainstem was observed during mania and depression [42]. There are also reports of increased activity in the amygdala in depressed bipolar disorder patients [58, 60] and hyper-activity of the hippocampus, the parietal cortex, and lingual cortex as well as hypo-activity of the precentral gyrus in euthymic bipolar disorder patients [63]. However, no alterations were also reported for manic [36] and euthymic [58] bipolar disorder patients. Comparable to reports for happy and sad affect, altered brain activation in response to fear appraisal seems to be rather state dependent in bipolar disorder except, potentially, hyper-activation of the parahippocampal gyrus, which has been reported to be hyper-active across mood states.

Labeling disgust has only been investigated in euthymic bipolar disorder patients. Disgust appraisal was reported to be associated with increased activity of the nucleus caudate, hippocampus [64], occipital cortex, and lingual cortex [63]. Furthermore, hypo-activity of the prefrontal cortex [63, 64], anterior cingulate cortex, thalamus [64], insula, fusiform gyrus, and precuneus was observed [63].

Studies combining different emotions during data analysis also showed rather heterogeneous results of hyper-activity in the orbitofrontal cortex and in the nucleus caudate during mania [65], and hyper-activity of the amygdala, hippocampus, orbitofrontal cortex, and insula during euthymia [65]. Further, in a sample of mixed states, hyper-activation of the dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, insula, and superior temporal gyrus when labeling negative pictures also occurred [66]. When recognizing positive pictures, hyper-activation of the medial prefrontal cortex, anterior cingulate cortex, nucleus caudate, thalamus, and precuneus was observed [66].

Regarding appraisal of affective stimuli, no clear pattern of hyper- and / or hypo-activation has emerged so far. Reports are especially inconsistent for frontal brain regions. During all mood states, hyper-activity of the prefrontal brain regions [42, 55, 65] but also no altered activity in the prefrontal cortex [36, 58, 59, 62, 67] has been reported. Furthermore, there are also reports of hypo-activity in the prefrontal cortex during mania and euthymia [55, 63, 64]. When ignoring the valence of the emotional stimuli, hyper-activation of the striatum [36, 42, 64-66] and amygdala [55, 58, 59, 65] are most consistently found across mood states. However, one has to keep in mind that many studies also reported no activation differences for the striatum [55, 58, 59, 62, 63, 67] and amygdala [36, 42, 62, 63, 67].

In part, medication effects might explain heterogeneity of the results. Unfortunately, many authors did not test whether there was a significant influence of psychotropic medication

[36, 42, 55, 63, 64, 66]. Whereas some studies ruled out such influence [59, 65, 67], others reported negative correlation between medication load and amygdala activation [58] and an influence of psychotropic medication on the functional connectivity between the amygdala and orbitofrontal cortex [62] during labeling of sad affect.

2.2.4. Summary

Interestingly, when tasks like passive viewing and stimulus matching, which do not explicitly ask for appraisal of emotional stimuli, are used, hypo-activity of the ventrolateral prefrontal cortex independent of the emotional valence of the stimuli is consistently observed across mood states. Furthermore, abnormal activity of the anterior cingulate cortex has been frequently reported for 'appraisal-free' tasks, although it seems that hypo- or hyper-activity of this region is more related to current mood state and psychotropic medication. However, when using affect recognition tasks, which ask for appraisal of emotional stimuli, a different picture evolves. In case of appraisal, which always implicates a certain personal relevance, hyper-activity of the ventral striatum is the most robust finding across mood states. Although altered activity of the prefrontal brain regions, parahippocampus / hippocampus, insula, and thalamus has also be repeatedly observed, it seems to depend on mood states and medication. It is also important to note that, independent of the mood state, hyper-activation of the amygdala has been consistently observed during both 'appraisal-free' and 'appraisal-demanding' tasks.

2.3. Emotion regulation

The inability to effectively regulate emotions within an adequate range and to adapt to the respective context has been proposed to be at the core of bipolar disorder [1, 8]. Until now, however, neural correlates of voluntary emotion regulation have not been investigated in bipolar disorder. One major problem in emotion regulation research in general is a very heterogeneous conceptualization of emotion regulation and, consequently, diverse operationalization in experimental research.

According to Gross and Thompson (2007), emotion regulation refers to the process of increasing or decreasing current affect. Such a process may occur consciously or unconsciously on a continuum from effortless and automatic (unconscious) to effortful and controlled regulation (conscious). Within their model of emotion regulation, the authors [68] differentiate five types of emotion regulation strategies which can be broadly divided into (1) antecedent-focused strategies, occurring before full-blown emotional responses are elicited (situation selection, situation modification, attentional deployment, and cognitive change), and (2) response-focused strategies, occurring after emotional responses are generated (response modulation). In experimental emotion regulation, research focus has been placed on the investigation of a few strategies, particularly on distraction as an example for attentional deployment, on reappraisal as an example for cognitive change, and on suppression as an example for response modulation. Whereas distraction refers to redirecting attention away from the emotional features of the situation to different,

potentially non-emotional aspects of the situation, reappraisal refers to changing the meaning of a situation or how we think about a situation in order to alter its emotional significance.

In a way, some of the studies reviewed in the section of early emotional processes might also be considered to have examined deployment of attention as participants were asked to ignore emotional distractors and focus on the task. These studies most consistently showed hyper-activity of the striatum and the amygdala during distraction, yet there is a difference between emotional distractors presented during a cognitive task and conscious perception of an emotional stimulus followed by the 'decision' to redirect attention in order to prevent in depth processing of this stimulus.

Recently, our research group completed a study on the neural correlates of two different voluntary emotion regulation strategies, namely distraction and reappraisal in patients with bipolar-I disorder (unpublished manuscript). Bipolar disorder patients showed impaired down-regulation of amygdala activity in response to positive and negative stimuli during reappraisal when compared to healthy controls, but not during distraction. This impaired amygdala down-regulation was mediated by a relatively reduced negative connectivity between the amygdala and the lateral orbitofrontal cortex. These first results concerning emotion regulation mechanisms in bipolar disorder underline the importance of appraisal mechanisms for understanding emotional disturbances in bipolar disorder. However, more studies are needed to draw further conclusions.

2.4. Summary

In summary, consideration of appraisal might be essential in understanding altered brain activation in response to emotional stimuli in bipolar disorder. If the task does not ask for appraisal of the emotional stimuli but allows emotional content without assigning any meaning to it (passive viewing: "just look what is there"; face matching: "compare whether you see the same"), hypo-activity of the ventrolateral prefrontal cortex is observed independent of the emotional valence of the stimuli or the current mood state. However, as soon as the task labels the emotional content as important with either a positive (affect recognition: "correct labeling of emotion means mastering the task") or negative (emotional distractors: "affect is an information that might prevent the person from mastering the task") connotation, hyper-activity of the striatum implicated in learning and evaluation [69] is the most consistent finding across mood states. Further, in case of negative appraisal, the ventral prefrontal cortex known to encode behavioral significance [70] and the anterior cingulate cortex shown to process choice predictions and prediction errors [71] have been reported to be rather hyper-active. In contrast, positive appraisal of emotional content is not clearly associated with hyper- or hypoactivation of ventral prefrontal structures or anterior cingulate cortex.

Interestingly, hyper-activation of the amygdala has been reported during both 'appraisal-free' and 'appraisal-demanding' tasks independent of the mood state. Further, euthymic bipolar disorder patients also showed hyper-activation of amygdala activity during

reappraisal of positive and negative stimuli. Further, there are several reports of altered functional connectivity between the amygdala and various regions such as the lateral orbitofrontal cortex [62], the dorsal anterior cingulate cortex [18], the perigenual anterior cingulate cortex [31], the posterior cingulate cortex, and the parahippocampal cortex [32], which itself has been shown to be differentially connected to the subgenual anterior cingulate cortex in bipolar disorder [59]. However, only a few studies have examined functional connectivity during emotion processing in bipolar disorder, so definite conclusions cannot be drawn.

It would be interesting to see the results of a meta-analysis that considers the proposed differentiation between 'appraisal-free' and 'appraisal-demanding' tasks. To date, meta-analyses included tasks using emotional stimuli irrespective of the task given to the patients. Results of recent meta-analyses consistently showed hypo-activation of the ventrolateral prefrontal cortex during emotional processes [72-74]. Further, meta-analyses showed hyper-activity of the parahippocampal gyrus [72-74], striatum [73, 74], and amygdala [72, 73] in bipolar disorder patients compared to healthy controls. However, a recent review on emotion processing and regulation in bipolar disorder concluded that amygdala activation is rather likely to vary as a function of mood state [75].

These results have already been incorporated in a 'condensed' neurobiological model of bipolar disorder suggesting that impaired prefrontal-limbic modulation in two networks: (1) a network originating in the ventrolateral prefrontal cortex and (2) a network starting from ventromedial prefrontal cortex underlies bipolar disorder [76]. Both networks are thought to be similarly organized, building iterative feedback loops that process information and modulate activity of the amygdala, the ventral striatum, and the thalamus. Whereas the first network is assumed to be involved in the modulation of external emotional cues such as emotional faces, the second network supposedly regulates internal emotional states [77, 78]. Although the simplicity of this hypothesis is rather intriguing, it remains unclear how complex processes of appraisal and reappraisal might be integrated in this model. Further, this model does not account for motivational aspects of the bipolar symptomatology.

3. Motivational processes

In general, motivation is defined as the process of initiating, controlling, and maintaining behavior with the goal of maximizing pleasant outcomes [79; see Figure 2]. Thus, motivation has been closely linked to the human reward network [80], whose key structures are the midbrain dopamine neurons, the ventral striatum representing reward anticipation [81], the orbitofrontal cortex embodying the value of possible outcomes, and the anterior cingulate cortex coding the value of actions to guide future behavior [71]. However, information about the incentive value alone is not sufficient to actually receive the reward but must be combined with planning, decision-making, troubleshooting, learning, and the overcoming of strong habitual responses. Consequently, other structures, including the dorsolateral prefrontal cortex guiding the allocation of attentional resources and the learning of stimulus-response contingencies [71], the habenula and the amygdala involved in the devaluation of previously

rewarding stimuli [82, 83], and the thalamus integrating information about reward from different brain areas are involved in motivation regulation [80].

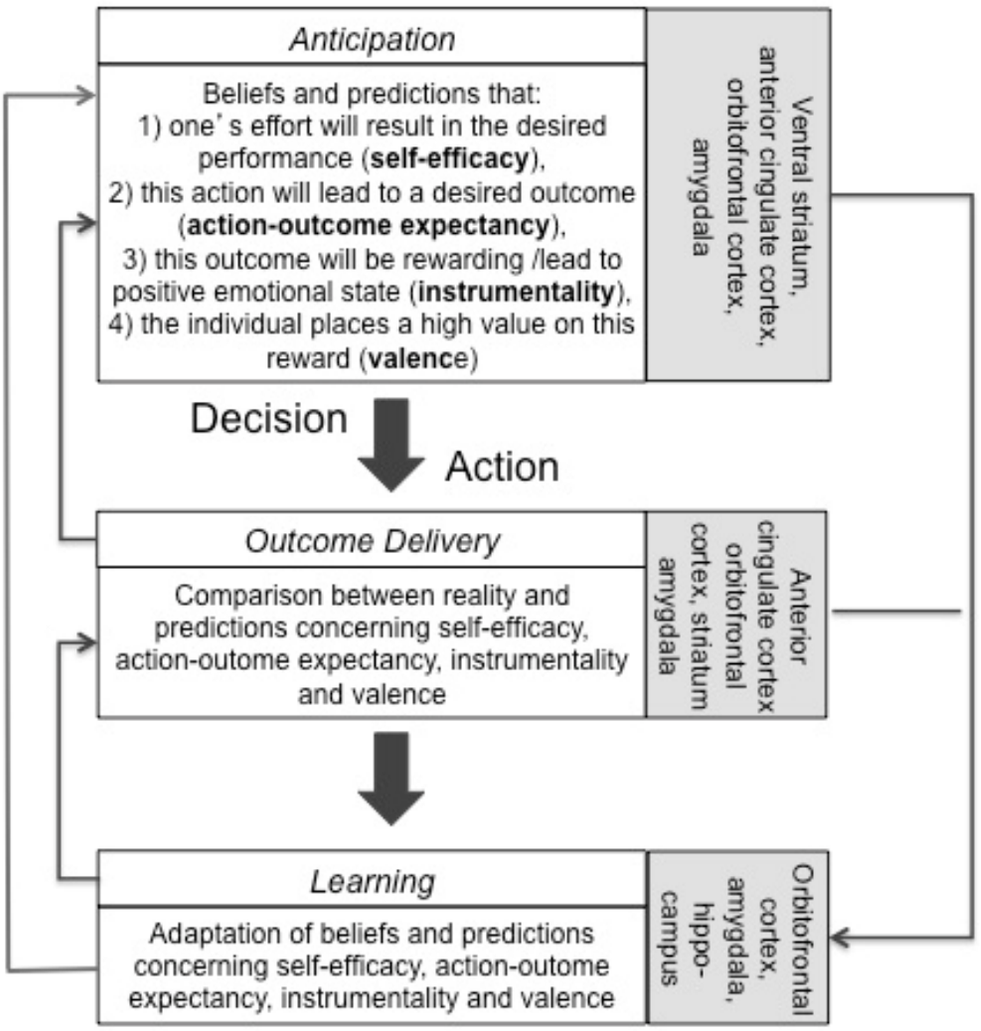

Figure 2. Schematic outline of the steps involved in motivational processing

Most of the structures comprising neurobiological models of bipolar disorder are innervated by dopaminergic projections ascending from the ventral tegmental area to the mesolimbic system, including the ventral striatum, the amygdala, and the hippocampus, as well as the mesocortical system, which includes, among others, the dorsomedial prefrontal cortex, the anterior cingulate cortex, and the orbitofrontal cortex [84]. These dopamine-irrigated structures are the neural correlate of the behavioral activation system, which mediates individual differences in sensitivity and reactivity to appetitive stimuli. High behavioral activation system sensitivity is associated with enhanced appetitive stimuli processing and approach-motivation as well as the diminished processing of aversive stimuli. However, the behavioral activation system might also facilitate active avoidance when safety is perceived

as a reward and aggression when reward acquisition is blocked [85]. Thus, hypersensitivity of the behavioral activation system refers to extreme reactions of this system in response to motivationally relevant stimuli also depending on the pre-event state of the behavioral activation system [2, 84, 86]. Extreme fluctuations in activation and deactivation of the behavioral activation system are then reflected in such bipolar symptoms as "excessive involvement in pleasurable activities that have a high potential for painful consequences e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments" during mania and "markedly diminished ... pleasure in all, or almost all, activities" during depression [87].

Whereas the reaction to primary emotional stimuli such as fear, anger, disgust, and happiness has been extensively investigated in bipolar disorder patients, neuroimaging studies on reward processes and motivation in patients with bipolar disorder are extremely rare, although altered reward processing has recently been hypothesized to represent an important mechanism of the alternating phases of mania and depression [88]. On a behavioral level, a reduced and delayed response bias towards more frequently rewarded stimuli was reported in euthymic patients with bipolar disorder [89]. In addition, previous studies have shown that euthymic bipolar disorder patients need more time when the consequence of a decision leads to reward or punishment [90-92]. This might indicate a general deficit in responding to motivationally relevant stimuli in bipolar disorder patients.

3.1. Anticipation of positive and negative consequences

In general, anticipation of positive consequences (reward) has been linked to the concept of incentive motivation [93]. The most important brain structures involved in the anticipation of reward are dopaminergic and include midbrain regions (substantia nigra, ventral tegmental area) projecting to the striatum (nucleus caudatus, putamen, nucleus accumbens) and the frontal cortex [94, 95].

To date, only three studies have examined the anticipation of positive and negative consequences in bipolar disorder patients. During a delayed-incentive paradigm, no differences were observed in a small sample of twelve manic patients in response to expected rewards compared to healthy controls and schizophrenic patients [96]. In a second study, manic patients showed increased activation of the orbitofrontal cortex when expecting increasing gain and decreased responses of the orbitofrontal cortex when expecting increasing loss, which normalized in a subsample of seven patients after remission [97]. In the third study, greater activation in the right ventral striatum and the right lateral orbitofrontal cortex was observed in euthymic bipolar disorder patients compared to healthy controls during reward anticipation. However, no significant group differences were observed during anticipation of loss [98]. All studies tested whether results were influenced by psychotropic medication, but this was not the case.

As there are only a few studies with conflicting results, no definite conclusions can be drawn. However, first evidence suggests that the orbitofrontal cortex is especially relevant for alterations in reward anticipation in bipolar disorder.

3.2. Delivery of positive and negative consequences

Similarly, only a few studies have investigated the neural correlates of reward and punishment delivery. During a delayed-incentive paradigm, manic patients showed significantly decreased activation of the nucleus accumbens in response to the receipt or omission of expected rewards, which was interpreted as deficits in prediction error processing [96]. However, other studies have failed to replicate this result in a different sample of manic patients [97]. Errors made during a behavioural task with changing reward contingencies correlated negatively with activity in orbitofrontal and striatal brain regions in bipolar disorder patients when measured during a separate language-processing task [99]. In addition, increased activation in the frontal polar region close to the orbitofrontal cortex was reported in manic patients during reward processing [100]. However, in euthymic pediatric bipolar disorder patients applying the same task with changing reward contingencies, increased activation in parietal and frontal brain regions, but not in the orbitofrontal cortex, have been reported [101]. Further, adding more inconsistency, a study comparing a small sample of twelve depressed bipolar disorder patients to healthy controls observed no difference in neuronal activations during the same task [102]. Furthermore, decreased activation of the ventral prefrontal cortex and increased activation of the anterior cingulate cortex in response to the receipt of reward during a gambling task were reported for euthymic bipolar disorder patients [103]. In a recent study of our group, greater activation in response to reward and decreased deactivation in response to reversal of reward contingencies were observed in the medial orbitofrontal cortex in euthymic bipolar patients [104]. Further, activation of the amygdala in response to reversal of reward contingencies was increased. In response to reward, there was a significant negative correlation between medication and amygdala activation in bipolar disorder patients. Heightened activation of the medial orbitofrontal cortex and the amygdala during wins was interpreted as heightened sensitivity toward reward, whereas greater activation of the amygdala and reduced deactivation of the medial orbitofrontal cortex during rule reversal was suggested to represent an attenuated prediction error signal. Interestingly, heightened reward sensitivity and reduced prediction error signal, as coded by the medial orbitofrontal cortex, was significantly correlated with the score of the behavioral activation system scale, lending further support to the behavioral system dysregulation model [2]. Last but not least, increased activity in the lateral orbitofrontal cortex, the dorsal anterior cingulate cortex, and the putamen in response to changing reward contingencies was also observed; it was suggested that this might represent a compensatory mechanism that aids in suppressing previously rewarded responses, thus allowing adequate performance during euthymia [104]. Interestingly, despite the significant negative correlation between amygdala response and psychotropic medication observed by Linke and coworkers (2012), no influence of psychotropic medication on brain responses upon delivery of reward or punishment have been observed in other studies [96, 97, 99, 101].

To sum up, in bipolar disorder, the orbitofrontal cortex seems to react differently upon delivery and omission of reward in a way that suggests a heightened reward sensitivity and deficient prediction error signal of this brain structure, which might even be a vulnerability

factor for bipolar disorder. Furthermore, other key structures of the human reward system, namely the ventral striatum, the anterior cingulate cortex, and amygdala, seem to react differently upon reward delivery in bipolar disorder patients compared to healthy controls. However, the connection between these alterations needs to be investigated in more depth in the future.

3.3. Summary

In patients with bipolar disorder and individuals with an increased risk to develop bipolar disorder, reward anticipation and reward delivery seems to elicit a more pronounced response in the orbitofrontal cortex, which is known to code the positive value an individual places on rewards [71]. Furthermore, if a previously rewarding stimulus has lost its rewarding properties, it will still be more likely to elicit a response in the medial OFC, similar to the response upon reward in euthymic bipolar disorder patients and high-risk individuals. This combination of heightened reward sensitivity and attenuated prediction-error signals in response to changing reward contingencies might facilitate the pursuit of immediate rewards despite the negative consequences in the medium or long term. Further, increased motivation to approach rewarding, or at least formerly rewarding, stimuli is likely to be present before the onset of bipolar disorder and could therefore be a vulnerability factor for this disease.

4. Structural alterations in networks associated with emotion and motivation

4.1. Gray matter alterations

In bipolar disorder, regional abnormalities of gray matter volume have been reported for all regions involved in the described emotional and motivational networks. But, as most studies have been performed on heterogeneous samples with respect to illness subtype, medication status, comorbidity, and mood state, they have produced conflicting findings.

Results have been especially inconsistent for the ventral striatum, the amygdala, the anterior cingulate cortex, the thalamus, and the hippocampus. Studies have reported larger caudate volumes in males [105] and in both affected and unaffected monozygotic bipolar twins [106] compared to controls. However, other studies have found no differences in the caudate of bipolar disorder patients [107-113] or decreased caudate volume [114]. Similarly, putamen enlargement was reported [112, 115, 116], but other studies found no differences in the putamen [105, 107, 113] or decreased volume [117]. Studies also showed reduced volume in the nucleus accumbens [118, 119]. With respect to the amygdala, findings indicate an enlargement of this structure [120-124], but reductions of amygdala volume have also been reported [118, 125-129]. There were also frequent reports of enlargement of the anterior cingulate cortex [130-133]; however, other studies found volume reductions of the anterior cingulate cortex [134]. Studies reported increased volume of the thalamus [123, 131], while others showed no differences [108] or reduced volume of the thalamus [119, 135]. Regarding

the hippocampus, some studies reported increased volume [136] as well as decreased volume [119, 137]. By contrast, reports of gray matter abnormalities for dorsolateral prefrontal cortex [118, 134, 138-140] and the habenula [141] have been infrequent but show a more consistent pattern of reduced volume. For the orbitofrontal cortex, decreased volume [117, 134, 142] and neuronal size reduction [143] have been reported, in addition to no alterations [144].

Interestingly, there has been evidence suggesting that abnormal gray matter volumes in the amygdala, hippocampus, thalamus, anterior cingulate cortex, and orbitofrontal cortex are not pervasive characteristics of bipolar disorder but may instead be associated with specific clinical features. Mood-stabilizers, such as lithium, were shown to increase the gray matter volume of the amygdala, hippocampus, and anterior cingulate cortex in bipolar disorder [116, 145-149]. In contrast, antipsychotics and anticonvulsants do not seem to influence gray matter volume of structures involved in emotional and motivational processes [150]. In addition, a longer duration of illness has been associated with increased gray matter in the basal ganglia, the anterior cingulate cortex, and the amygdala [146] as well as loss of hippocampal gray matter [151]. Further, depressive episodes have been associated with gray matter density increases in the orbitofrontal cortex and gray matter density decreases in the prefrontal cortex and anterior cingulate cortex [152].

Based solely on the empirical evidence reviewed above, it is difficult to draw conclusions about potential morphological alterations associated with emotional and motivational circuits as there is either insufficient data on volumetric alterations (habenula, dorsolateral prefrontal cortex) or the results are too heterogenic (striatum, amygdala, thalamus, hippocampus, and orbitofrontal cortex). However, on an important note, a meta-analysis of gray matter alterations in bipolar disorder revealed gray matter reductions in the rostral anterior cingulate cortex [146], which, in addition, seems to be specific to bipolar disorder but not schizophrenia [153]. Hence, gray matter loss in the anterior cingulate cortex, which was also shown in a recent meta-analysis [74], might be the most promising correlate of aberrant emotional and motivational processes emerging from volumetric studies of gray matter alterations.

4.2. White matter alterations

The different gray matter regions constituting networks related to emotional and motivational processes are connected through white matter, which is composed of axons. Deviation from normal axonal organization can be investigated using diffusion tensor imaging, a technique that quantifies the restricted diffusion of water in white matter through scalars, such as fractional anisotropy (FA). Fractional anisotropy is known to be positively correlated with the directionality and coherence of white matter bundles [154]. Although studies of bipolar disorder using diffusion tensor imaging lag behind other psychiatric diseases such as schizophrenia, the existing body of evidence strongly suggests that the loss of white matter integrity in fronto-limbic and cortical-striatal-thalamic circuits is a biological vulnerability factor for bipolar disorder [155]. In more detail, it has been

hypothesized that impaired development of white matter, such as altered prefrontal pruning, leads to decreased connectivity within emotional and motivational networks. This is further thought to result in impaired top-down and bottom-up modulation of prefrontal-limbic circuits eventually leading to symptoms of bipolar disorder [76, 156].

With regard to motivation, the integrity of the anterior corpus callosum providing interhemispheric connections between the left and right ventral prefrontal cortex and the anterior limb of the internal capsule, which contains fibers interconnecting the thalamus, striatum, amygdala, hippocampus, anterior cingulate cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex [157, 158], seems to be of particular relevance. In more detail, risky decision-making has been shown to be negatively correlated with the integrity in the corpus callosum [159-161] and the integrity of the anterior limb of the internal capsule [162]. Interestingly, pathological gambling was also negatively related to the integrity of the anterior limb of the internal capsule itself and the uncinate fasciculus [163]. On an important note, the integrity of the uncinate fasciulus is also positively associated with recognition of fearful facial expression [164], harm avoidance [165], and neuroticism [166], pointing towards its relevance for emotional processes.

During depression, mania, and euthymia, reduced white matter integrity, especially in the anterior corpus callosum in children and adolescents [167-170] as well as in adults [171-177] suffering from bipolar disorder, has been described. Interestingly, a normalizing effect of lithium on the volume of the corpus callosum has been observed [178], and a study of euthymic bipolar disorder patients even reported increased integrity of the corpus callosum [179]. Furthermore, all but one [180] tractography study showed reduced white matter integrity in the anterior thalamic radiation [181-183], which passes through the anterior limb of the internal capsule [184] in depressed, euthymic, and manic patients. In line, reduced white matter integrity in the anterior limb of the internal capsule has also been repeatedly observed in bipolar patients [173, 185, 186]. Similar, reduced integrity of the uncinate fasciculus, which interconnects the amygdala with the orbitofrontal cortex and the anterior cingulate cortex [187], has also been frequently observed in depressed and euthymic bipolar disorder patients [173, 180, 182, 183, 188, 189]. Although, increased white matter integrity and increased number of fibers have also been reported for the uncinate fasciculus [180, 190]. On an important note, the integrity of the uncinate fasciculus was shown to influence functional coupling between the anterior cingulate cortex and the amygdala [31]. Reports of reduced white matter integrity of the orbitofrontal cortex [191, 192], which were shown to be related to impulsivity and suicide attempts [12], are of further interest for the understanding of neurobiological underpinnings of emotional and motivation processes in bipolar disorder.

The effect of psychotropic medication on white matter integrity has been less thoroughly investigated than its influence on gray matter integrity. There are some studies stating that psychotropic medication such as lithium, antidepressants, or antipsychotics do not affect the corpus callosum [167, 173, 176, 177, 179, 192-195], although thickening of the corpus callosum has also been observed after lithium treatment [196]. Similarly, the white matter integrity of the anterior limb of the internal capsule and the uncinate fasciculus were not influenced by psychotropic medication [173, 180, 183].

Based on the empirical findings reviewed above, we conclude that white matter tracts connecting emotional and motivational circuits are disturbed in bipolar disorder. Thus it is very likely that this reduced structural connectivity underlies functional alterations, particularly in the orbitofrontal cortex and amygdala, and emotional and motivational symptoms in bipolar disorder. However, to date, association between impaired white matter integrity in the corpus callosum, the anterior limb of the internal capsule, or the uncinate fasciculus and altered early emotional processes, disturbed generation of an emotional response, or emotional and motivational dysregulation has not been shown.

5. The chicken or the egg

So far, empirical data provide evidence that bipolar disorder is a disorder of emotion and motivation. Furthermore, disturbances in these tightly linked but distinct psychological processes are related to impairments in similar neural networks involving prefrontal brain regions such as the orbitofrontal cortex and the anterior cingulate cortex and subcortical structures like the amygdala and the ventral striatum. However, it appears that neural networks associated with emotional and motivational disturbances in bipolar disorder are not uniformly hypo- or hyperactive. Instead, the ongoing psychological process (e.g. early emotional processes, emotion regulation, motivation) and the current mood state crucially interact with neural activation patterns. In addition, psychotropic medication was also repeatedly reported to influence the neural correlates of emotional and motivational processes in bipolar disorder on a structural and functional level (for review see [197]). Therefore, it is difficult to distinguish whether the neural abnormalities in emotional and motivational networks represent biological vulnerability factors for bipolar disorder or a consequence of the disease. Despite the lack of longitudinal studies, this issue might in part be clarified by studies examining healthy persons at high risk of developing bipolar disorder, such as first-degree relatives of patients with bipolar disorder.

5.1. Early emotional processes

Using the emotional Stroop task on a behavioral level, an increased emotional interference effect that was specifically associated to disease-related words was reported for first-degree relatives of bipolar disorder patients compared to healthy controls [198], whereas the 'regular' Stroop task did not reveal any deficits in relatives of bipolar disorder patients [198, 199]. However, on a neural level, relatives of bipolar disorder patients displayed reduced activity in the parietal cortex; unaffected relatives also displayed this reduced activity in the nucleus caudate during the Stroop task [15]. In addition, relatives also showed significantly reduced functional connectivity between the ventrolateral prefrontal cortex and the insula compared to healthy controls during the Stroop task [200]. On a descriptive level, connectivity between the ventrolateral prefrontal cortex and the ventral anterior cingulate cortex appeared to be weaker in relatives. Further, connectivity between the ventrolateral prefrontal cortex and the nucleus caudatus appeared weaker in relatives suffering from major depression but not in healthy relatives of bipolar disorder patients, who showed a negative coupling between ventrolateral prefrontal cortex and dorsolateral prefrontal cortex, which was absent in healthy controls and

was interpreted as a compensational mechanism [200]. Interestingly, when directing attention away from fearful and happy faces, hyper-activation of the amygdala, the medial prefrontal cortex, and by trend also of the putamen but only during presentation of fearful faces as distractors was also reported in adolescent relatives of bipolar disorder patients [22]. Despite the interesting results of this first imaging study examining early emotional processes in relatives of bipolar disorder patients, no conclusions can be drawn concerning the question whether abnormal early emotional processes constitute a vulnerability or a consequence of bipolar disorder. Thus, future studies should examine these processes in relatives of bipolar disorder patients preferably using imaging techniques.

5.2. Affective response and evaluation

Fortunately, the generation of an emotional response has been studied more extensively in relatives of bipolar disorder patients. On a behavioral level, relatives of bipolar disorder patients showed significant deficits in recognizing and labeling emotional faces correctly [201-203], yet no difference in emotional responsiveness operationalized by choosing the emotion that would best fit the description of a real-life situation was observed [203]. While rating their fear of fearful faces, unaffected subjects at-risk for bipolar disorder exhibited amygdala hyperactivity [204]. After induction of a sad mood, siblings of bipolar disorder patients showed hyper-activity in the dorsal anterior cingulate cortex and the anterior insula but hypo-activation in the orbitofrontal cortex [205]. Interestingly, siblings also showed hyper-activity in the medial prefrontal cortex, which distinguished this group from bipolar disorder patients and was hence interpreted as protective compensatory mechanism [205]. It is difficult to draw any conclusions based on the existing evidence as both imaging studies in relatives of bipolar disorder used very different paradigms – rating of emotion intensity and mood induction through recall of autobiographical life events. Thus, inconsistencies are likely to be related to different experimental operationalization. Further studies are, therefore, needed examining the neurobiological correlates of affective response and evaluation in relatives of bipolar disorder patients.

5.3. Emotion regulation

Similar to early emotional processes, emotion regulation has been rarely studied in first-degree relatives of bipolar disorder. One behavioral study investigated the use of different emotion regulation strategies and reported more frequent use of maladaptive strategies such as catastrophizing and self-blame among relatives, which correlated with higher scores in measures of depression, anxiety, and hypomanic personality [206]. Concerning the mechanisms underlying this preference of mal-adaptive emotion regulation strategies, our workgroup recently observed impaired down-regulation of amygdala activity in response to positive and negative stimuli during reappraisal, but not during distraction in first-degree relatives of bipolar disorder patients, when compared to healthy controls (unpublished manuscript). Similar to the results already reported for bipolar disorder patients, this impaired amygdala down-regulation was mediated by a relatively reduced negative connectivity between the amygdala and the lateral orbitofrontal cortex. These results are the

first evidence that deficits in emotion regulation through reappraisal might be a vulnerability marker for bipolar disorder. The underlying neural mechanisms include impaired control of amygdala reactivity in response to emotional stimuli and dysfunctional connectivity of the amygdala and regulatory control regions in the orbitofrontal cortex. Such impaired functional connectivity might result from impaired white matter development disturbing fronto-limbic circuits [76, 207].

Thus, reports of aberrant emotion regulation in first-degree relatives of bipolar disorder patients need to be replicated and imaging studies investigating the neural basis of these alterations are warranted.

5.4. Motivation

To the best of our knowledge, anticipation of reward or punishment has not been studied so far in healthy individuals to develop bipolar disorder. However, there is one study investigating the neural responses to the delivery of reward and punishment in healthy first-degree relatives of bipolar disorder patients. Similar to bipolar disorder patients, the authors observed greater activation in response to reward in the medial prefrontal cortex and the amygdala, which was interpreted as heightened reward sensitivity [104]. Further, in response to negative feedback, which was followed by a change in behavior (reversal of reward contingencies), decreased deactivation in the medial orbitofrontal cortex and increased activation in the amygdala was observed, which is thought to represent an attenuated prediction error signal. This attenuated prediction error signal was particularly pronounced during negative feedback that was not followed by a behavioral change. It was speculated that this might be the underlying mechanism of a behavior frequently observed in manic bipolar patients: the pursuit of immediate rewards despite negative consequences because on a neural level, they are not coded as punishment. Furthermore, heightened reward sensitivity and reduced prediction error signal as coded by the medial orbitofrontal cortex were significantly correlated with the score of the behavioral activation system scale in the healthy relatives of bipolar disorder patients.

Although results need to be replicated, existing empirical evidence from bipolar disorder patients and their relatives suggests that hyper-activation of the amygdala and the medial orbitofrontal cortex in the context of motivational processes constitute a vulnerability for bipolar disorder. This idea is further supported by another study that showed increased amygdala activation in response to reward in carriers of the risk allele of *CACNA1C* rs1006737, a genome-wide supported risk variant for bipolar disorder [208].

5.5. Gray matter alterations in networks associated with emotional and motivational processes

Similar to the results in bipolar disorder patients, the literature is very inconsistent with respect to alterations of gray matter volume in relatives of bipolar disorder patients. Although gray matter reduction in the anterior cingulate cortex appeared to be the most robust finding in bipolar disorder patients [146], the picture is less clear in their relatives as

there are both reports of reduced volume [209] and no volumetric alterations [210, 211]. Other cortical regions, which were investigated in relatives of bipolar disorder patients, are the medial prefrontal cortex where the volume was found to be reduced [212] and the insula with conflicting results of decreased [212] and increased volume [213, 214].

The literature also remains inconsistent for subcortical structures. Comparable to patient data, there is also evidence of decreased caudate volume in relatives of bipolar disorder patients [209, 215]. However, increased volume [106] and no alterations [216] in caudate volume have also been reported. Whereas there seem to be no volumetric alterations in the amygdala of relatives of patients with bipolar disorder [217, 218], there are reports of reduced hippocampal volume [218] and also reports of no apparent alterations in the hippocampus [217]. Furthermore, one study observed reduced thalamic volumes in relatives of bipolar disorder patients [215].

Due to the heterogeneity of the gray matter alterations in bipolar disorder patients and their unaffected relatives, no final conclusion whether alterations are the cause or the consequence of the disease can be drawn. However, considering the variance of the obtained results, it seems more likely that gray matter alterations are more related to certain endophenotypes like altered early emotional processes, impulsivity, working-memory, or reward processing than the illness itself. If at all, the volume of the anterior cingulate cortex seems to be the most promising candidate for a vulnerability factor of bipolar disorder.

5.6. White matter alterations in networks associated with emotional and motivational processes

Similar to the results obtained in patients, decreased integrity of the corpus callosum was also reported for adult and adolescent first-degree relatives of patients with bipolar disorder [186, 219, 220], although others observed no differences in the corpus callosum of relatives of bipolar disorder patients [193, 196]. Also corresponding to the abnormalities reported in patients, unaffected relatives displayed reduced integrity of the internal capsule [186, 220], even though not all research groups replicated this finding [185]. Interestingly, white matter integrity in the anterior limb of the internal capsule was also inversely related to cyclothymic temperament [220]. To date, we are not aware of any study replicating the finding of decreased integrity of the uncinate fasciculus observed in bipolar disorder patients in unaffected relatives of bipolar disorder patients.

The empirical findings of reduced inter-hemispheric and prefrontal-subcortical connectivity in children, adolescents, and adults that are independent of the current mood state and are also observable in unaffected first-degree relatives of bipolar disorder patients support the hypothesis that impaired development in white matter precedes functional alterations in networks relevant for emotion and motivation. Although causality still needs to be proven, there is notable evidence suggesting that impaired white matter integrity in the corpus callosum, the anterior limb of the internal capsule, and the uncinate fasciculus might be biological vulnerability factors of bipolar disorder. However, enthusiasm for this assumption has been limited by the fact that reductions of white matter integrity, especially

of the corpus callosum [221-228], the anterior limb of the internal capsule, and the uncinate fasciculus, have also been reported for schizophrenia and unipolar depression [173, 183, 229-233]. Thus, reported white matter abnormalities might not be a vulnerability specific to bipolar disorder, but they seem linked to clinical features like impulsivity, psychosis, and depressive mood as well. Consequently, impaired development of inter-hemispheric and prefrontal-subcortical connectivity seems to be a necessary but not a sufficient condition for the development of bipolar disorder.

5.7. Summary

Supporting the view that impaired white matter development in early life might precede the onset of bipolar disorder [76], reduced white matter integrity in the corpus callosum and the anterior limb of the internal capsule was observed in children, adolescents, and adults suffering from bipolar disorder as well as in unaffected first-degree relatives of bipolar disorder patients. Further, it has been hypothesized that the impaired development of white matter results in impaired prefrontal-limbic modulation in two networks comprising either the ventrolateral or ventromedial prefrontal cortex as well as the amygdala, ventral striatum, and thalamus [76]. And, indeed, hyper-activation of the amygdala has also been observed during early emotional processes [22], generation of an affective response [204], emotion regulation (unpublished manuscript of our group), and motivational processes [104] in unaffected relatives. Thus, we conclude that both impaired white matter of the corpus callosum and the anterior limb of the internal capsule likely disturb fronto-limbic feedback- and feedforward-loops, leading to hyper-activity of the amygdala that precede bipolar symptoms. Further, abnormalities in prefrontal brain regions such as hyper-activity of the medial prefrontal cortex in response to emotional distractors [22] and sad mood [205], hyper-activity of the anterior cingulate cortex [205], hyper-activity of the orbitofrontal cortex in response to reward and omission of reward [104], and reduced functional connectivity between the lateral orbitofrontal cortex and the amygdala (unpublished manuscript of our group) have been observed. However, results are rather inconsistent, implying that these abnormalities might be either protective [205] or risk factors [104]. However, it might be of great interest to examine potential alterations in frontal brain regions in more detail in unaffected relatives. This is especially true as white matter alterations were shown to be not specific for a certain mental disorder, raising the question which neurobiological alterations make the difference between uni- and bipolar affective disorder or bipolar disorder and schizophrenia. However, we like to emphasize that these reflections are rather speculative and that more studies examining emotional and motivational processes in relatives of bipolar disorder patients as well as longitudinal studies are warranted in order to definitely clarify the question which neurobiological abnormalities are risks or consequences of the disease.

6. Conclusion and future perspectives

The interpretation of the above-reviewed results is hampered by a large heterogeneity of results, which is likely to arise from the investigation of heterogenic samples with respect

to (1) current symptomatic states, (2) main diagnosis of bipolar I, bipolar II, or bipolar spectrum disorder, (3) psychotropic medication, and (4) life time as well as current psychiatric comorbidities. In the past years, authors started to investigate effects of psychotropic medication more regularly and it seems that functional magnetic resonance imaging and diffusion tensor imaging is rather not influenced by medication [150]. However, the effect of current symptomatology and especially of comorbidity has not been investigated in depth. Thus, future research should address how current symptomatology and comorbidity influences emotional and motivational processes. Further, it would be of great interest to compare patients of bipolar I, bipolar II, and bipolar spectrum disorder.

Despite all heterogeneity, the presented synopsis of empirical results on the neural underpinnings of emotional and motivational processes in bipolar disorder show that bipolar disorder clearly is a disorder of emotion and motivation. As Figure 3 shows, these two psychological processes are closely interrelated and cannot be separated when studying the psychological and neurobiological mechanisms underlying bipolar disorder. This notion is underlined by the fact that emotional and motivational disturbances in bipolar disorder partly share one neural basis. Several structures that are part of the emotion-motivation circuit (ventral prefrontal/orbitofrontal cortex, dorsolateral prefrontal cortex, anterior cingulate cortex, parietal cortex, amygdala, striatum, thalamus, hippocampus) show deviant activation patterns in bipolar patients compared to healthy controls; however, the direction of deviance (hyper- or hypo-activity) depends on the underlying ongoing psychological process. One example is the ventral prefrontal/orbitofrontal cortex: this structure appears to be (1) hypo-active during passive perception of emotions without being asked to actively deal with the emotional content (e.g., correct labeling of emotion) and (2) hyper-active during reward anticipation and reward delivery. From a systems neuroscience perspective, bipolar disorder might therefore be well described on the basis of a neural network dysfunction mainly originating from the amygdala and the ventral prefrontal/orbitofrontal cortex [76]. However, from a psychological and psychotherapeutic perspective, the reviewed results also imply that the underlying psychological processes are the crucial determinants of neural dysfunctions on the one side and of bipolar symptoms during mania and depression on the other. Integrating the systems neuroscience and psychological perspective suggest that alterations in the described emotional and motivational processes, for example, through psychotherapy would accordingly result in neural changes. Thus, in the case of successful therapy, behavioral modifications should result in normalization of disturbed functioning of the emotion-motivation brain network. Consequently, research on modifications of emotional and motivational processes in bipolar patients with neuroimaging methods would be worthwhile and timely.

Finally, although existing data clearly show that a neural network of several brain structures and not single structures on their own forms the pathophysiological basis of bipolar disorder symptoms, more studies on altered functional connectivity during emotion and motivation processing combined with and related to measures of structural connectivity are warranted.

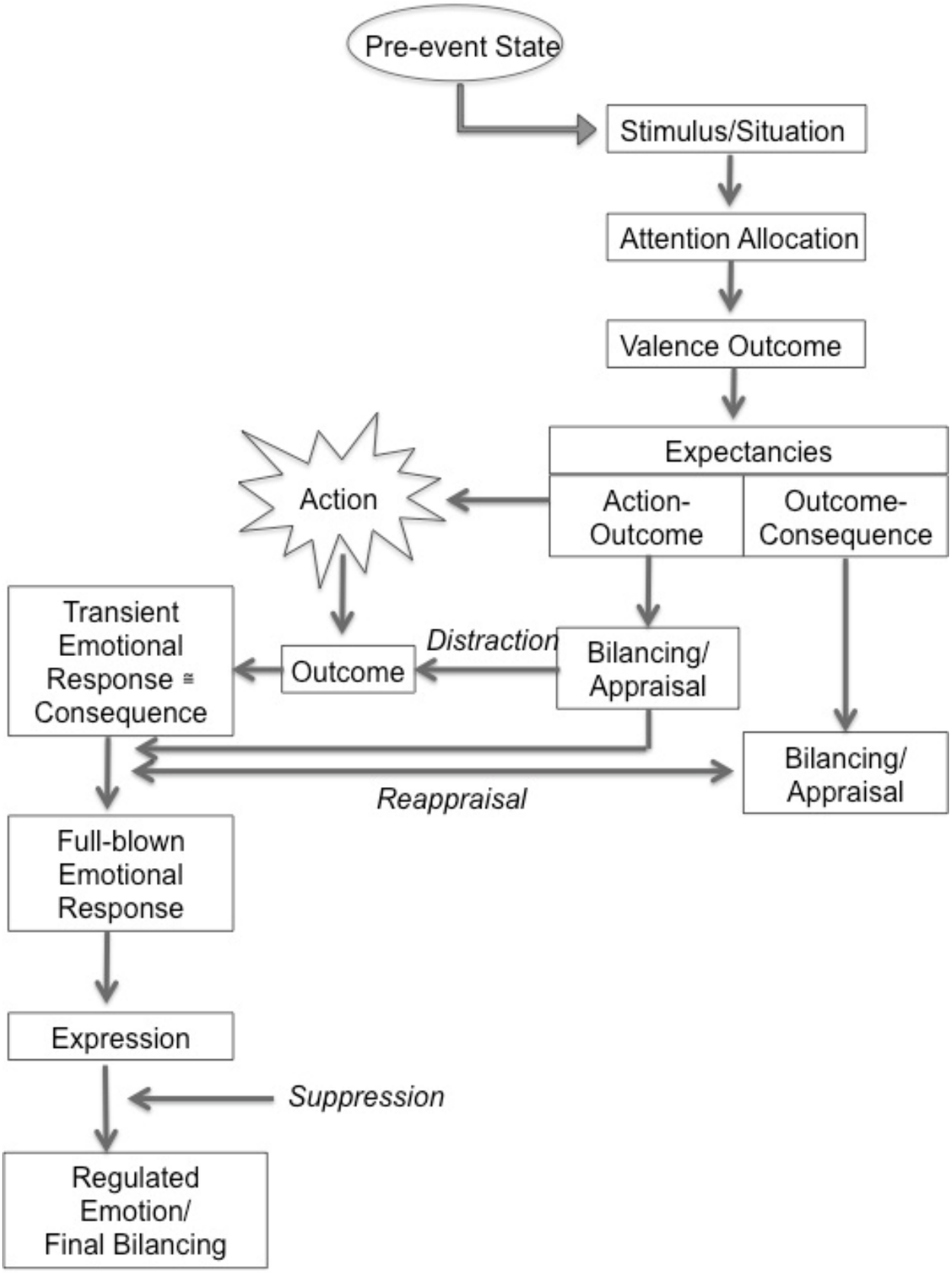

Figure 3. Schematic outline of emotion-motivation interaction

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7. References

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