Bipolar disorder: A neural network perspective on a disorder of emotion and motivation

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Abstract. Bipolar disorder (BD) is a severe, chronic disease with a heritability of 60–80%. BD is frequently misdiagnosed due to phenomenological overlap with other psychopathologies, an important issue that calls for the identification of biological and psychological vulnerability and disease markers. Altered structural and functional connectivity, mainly between limbic and prefrontal brain areas, have been proposed to underlie emotional and motivational dysregulation in BD and might represent relevant vulnerability and disease markers. In the present laboratory review we discuss functional and structural neuroimaging findings on emotional and motivational dysregulation from our research group in BD patients and healthy individuals at risk to develop BD. As a main result of our studies, we observed altered orbitofrontal and limbic activity and reduced connectivity between dorsal prefrontal and limbic brain regions, as well as reduced integrity of fiber tracts connecting prefrontal and subcortical brain structures in BD patients and high-risk individuals. Our results provide novel insights into pathophysiological mechanisms of bipolar disorder. The current laboratory review provides a specific view of our group on altered brain connectivity and underlying psychological processes in bipolar disorder based on our own work, integrating relevant findings from others. Thereby we attempt to advance neuropsychobiological models of BD.

Keywords: Vulnerability, behavioral activation system, emotion regulation, amygdala, orbitofrontal cortex, reward, connectivity

1. Introduction

Bipolar disorder is a severe and chronic mental disorder that is one of the leading causes of disability worldwide, whose lifetime costs were estimated to be in excess of $45 billion in the US alone (Wyatt & Henter, 1995). Among the several subtypes of bipolar spectrum disorders, bipolar I disorder is characterized by recurrent prominent mood swings that lead to alternating phases of mania and depression with interspersed periods of euthymia. Key symptoms of mania include euphoric or irritable mood, flight of ideas, pressure of speech, increased energy, and hyperactivity with an emphasis on pleasurable activities, even if they lead to negative consequences. In contrast, during depressive episodes patients report depressed mood, lack of energy and loss of interests, pessimistic thoughts, and reduced perception of and response to positive stimuli.

To date, the diagnosis of bipolar disorder is based on the description of behavioral manifestations. However, due to its overlap with other psychopathological conditions, such as unipolar depression, schizophrenia or

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impulse control disorders (Matza et al., 2005; Meyer & Meyer, 2009; Mitchell et al., 2010), initial misdiagnosis is common. This often leads to detrimental effects on the course of this disease (Findling, 2009; Stensland et al., 2008; Stensland et al., 2010) with a more severe and chronic progression in patients with late or misleading diagnosis. Therefore, research aiming at the identification of vulnerability markers of bipolar disorder that allow an early and valid diagnosis is particularly important. An even more serious condition is that in neither of the previously mentioned psychopathologies causal therapy is available. As an ultimate goal it appears therefore essential to determine biological and psychological markers that are common to different pathologies or specific for a certain illness in order to develop tailored treatments. Further, markers that change during the course of the disease might show potential for improvement under treatment and are therefore important to be identified.

As family and twin studies showed a high heritability of bipolar disorder of 60–80% (McGuffin et al., 2003), biological vulnerability factors seem to be of special importance for this disease. The diathesis-stress model, therefore, poses a good framework to develop etiological models that incorporate biological and psychological factors associated with the development and maintenance of bipolar disorder. In general, such models assume that the interplay of biological vulnerability factors (Greek: diathesis) with environmental factors (stress) determines the onset and course of the disorder (Jones, 2004).

In bipolar disorder, neurobiological abnormalities on different levels have been identified, using various methods ranging from techniques examining intracellular and molecular mechanisms to neuroimaging of neural networks (Langan & McDonald, 2009). Neurobiological models of bipolar disorder (Phillips et al., 2008) generally assume a hypoactive dorsal neural system including the dorsolateral prefrontal, ventrolateral prefrontal, and dorsal anterior cingulate cortex as well as the hippocampus. This dorsal system is relevant for selective attention, planning, performance monitoring and voluntary regulation of emotional states in bipolar disorder. It has been hypothesized that the hypoactive dorsal system interacts with a hyperactive ventral brain system comprising amygdala, insula, ventral striatum, ventral anterior cingulate cortex and medial orbitofrontal cortex implicated in the detection of emotionally salient stimuli, mediation of autonomic responses to emotional stimuli and the generation of an emotional state (Keener & Phillips, 2007). It is assumed that an imbalance and decreased connectivity between these two systems, particularly the ventrolateral prefrontal cortex and the amygdala, accounts for mood instability, motivational dysregulation and cognitive deficits observed in patients with bipolar disorder (Cahill et al., 2009; Kurtz & Gerraty, 2009; Strakowski et al., 2012; Wessa & Linke, 2009).

Most recently, it has been proposed that impaired white matter development in early life might precede the onset of bipolar disorder. In more detail, it has been hypothesized that the impaired development of white matter results in 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. Both networks are 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 (Schneider et al., 2012; Strakowski et al., 2012).

Although, the simplicity of this hypothesis is rather intriguing, we would like to point out that it neglects motivational aspects of bipolar symptomatology despite the fact that both emotion and motivation are related. Whereas the focus on emotion implies a certain state of feeling, the emphasis of motivation relates to a certain state of goal pursuit like the achievement of pleasant and the avoidance of unpleasant feelings.

Yet, to date, most of the existing studies in patients with bipolar disorder have focused on the neural correlates of aberrant emotion processing, mainly operationalized by paradigms that use emotionally evocative stimuli (e.g., words, faces) during passive viewing, implicit and explicit labeling tasks and response inhibition tasks (Houenou et al., 2011). However, although tightly linked to emotion processing, the investigation of motivational processes, such as the anticipation of positive (reward) and negative consequences (punishment) and the response to their delivery has received little attention in the field. Yet, the evaluation of stimuli as appetitive (reward) or aversive (punishment) facilitates approach or avoidance motivation and behavior (Alloy & Abramson, 2010). Indeed, motivational dysregulation and altered reward processing have been hypothesized as important

mechanisms of the alternating phases of mania and depression and as an endophenotype of bipolar disorder (Hasler et al., 2006).

In the present laboratory review we will provide a specific view of our group on the structural and functional neural mechanisms underlying emotional and motivational dysregulation in bipolar disorder based on our own work. By additionally integrating relevant findings from other group we attempt to contribute to a further development of neurobiological models of bipolar disorder.

2. Motivational processes

Most of the structures comprised in neurobiological models of bipolar disorder are innervated by dopaminergic projections ascending from the ventral tegmental area to the mesolimbic system, including ventral striatum, amygdala and hippocampus and to the mesocortical system comprising, among others, the dorsolateral prefrontal, anterior cingulate and orbitofrontal cortex (Depue & Iacono, 1989). These dopamine-irrigated structures represent the neural correlate of the behavioral activation system that mediates individual differences in the sensitivity and reactivity to appetitive stimuli. High sensitivity of the behavioral activation system is associated with enhanced appetitive stimulus processing and approach-motivation as well as the diminished processing of aversive stimuli. However, the behavioral activation system might also facilitate active avoidance responses, when safety is perceived as reward, and aggressive behavior, when reward acquisition is blocked (Gray, 1987). In the context of bipolar disorder, dysregulation model of the behavioral activation system suggests a hypersensitive behavioral activation system as vulnerability factor (Alloy & Abramson, 2010; Depue & Iacono, 1989; Urosévic et al., 2008). Extreme fluctuations in activation and deactivation of the behavioral activation system might be reflected in bipolar symptoms like "excessive involvement in pleasurable activities that have a high potential for painful consequences" during mania and "markedly diminished... pleasure in all, or almost all, activities" during depression (American Psychiatric Association, 2000). On a behavioral level, reduced and delayed responses to more frequently rewarded stimuli (Pizzagalli et al., 2008) as well as longer reaction times for decisions that lead to reward or punishment (Gorrindo et al., 2005; McClure et al.,

2005; Rich et al., 2005) were reported, suggesting a general deficit in responding to motivationally relevant stimuli in bipolar disorder patients.

However, our own results show a more differentiated pattern of reward and punishment processing in bipolar disorder. In euthymic bipolar disorder patients, we observed differential learning from positive and negative consequences depending on the last illness phase of the patients (Linke et al., 2011). Interestingly, currently euthymic bipolar patients who last experienced a manic episode showed a bias towards positive consequences, whereas bipolar patients who last experienced a depressive episode showed a bias towards negative consequences. This effect occurred even though patients had been euthymic for up to sixty months. To explain this carry-over effect from symptomatic to euthymic phases, we proposed that affective episodes might represent learning experiences during which patients perceive and experience outcomes (failure vs. success) and consequences (reward vs. punishment) mostly in a mood-congruent manner which shapes their perception of self-efficacy as well as their action-outcome expectancies and outcome-consequence expectancies persisting beyond the symptomatic phases. The influence of action-outcome and outcome-consequence expectancies on personality constructs of generalized self-referential cognitions like control orientations and subjective knowledge (Krampen, 1988) further explains the endurance of these biases, which might only be changed by very powerful learning experiences like the next affective episode or psychotherapy. These results correspond to the theoretical framework of the dysregulation model of the behavioral activation system (Urosévic et al., 2008) suggesting that altered expectancies and beliefs influence the appraisal as well as the creation and selection of events relevant for the behavioral activation system and thus interact with the dysregulation of that system.

Furthermore, there is some evidence on brain function and structure underlying this motivational bias. Altered activity of and changed connectivity between brain regions like the orbitofrontal cortex, rostral cingulate cortex, amygdala and striatum that are involved in motivation (Diekhof et al., 2008; Ernst et al., 2004) have been reported in patients with bipolar disorder (for reviews see Blond et al., 2012; Strakowski et al., 2012) and might constitute the neuronal correlate of differential responses to positive and negative feedback.

Indeed, in a recent study, we observed decreased deactivation in the medial orbitofrontal cortex and greater activation of the amygdala in response to reversal of reward contingencies in euthymic patients with bipolar-I disorder and unaffected first-degree relatives of bipolar I disorder patients (Linke et al., 2012a see Fig. 1). Further, patients and relatives showed greater activation of the medial orbitofrontal cortex in response to reward delivery, whereas only in unaffected first-degree relatives of bipolar patients (Linke et al., 2012a) and in healthy individuals carrying a genetic risk variant (*CACNA1C* rs1006737) for bipolar disorder (Wessa et al., 2010) the amygdala appeared hyperactive in response to reward. However, in euthymic patients with bipolar-I disorder, hyper-activation of amygdala was normalized by psychotropic medication as indicated by a significant negative correlation between medication load and amygdala activation to reward delivery.

Differential activation patterns in medial orbitofrontal cortex during reward delivery and reversal of reward contingencies in BD patients and first-degree relatives of bipolar disorder patients might represent different underlying mechanisms: whereas heightened activation of the medial orbitofrontal cortex (and amygdala) in response to reward is interpreted as heightened reward sensitivity, reduced deactivation of the medial orbitofrontal cortex and hyper-activation of the amygdala during reversal of reward contingencies, observed in both patients with bipolar disorder and healthy relatives of bipolar disorder patients represents an attenuated prediction error signal. Such an attenuated prediction error signal was particularly prominent in unaffected relatives when negative feedback was not followed by a behavioral change, which reminds of clinical symptoms in manic bipolar patients, who continue to pursue immediate rewards despite negative consequences (American Psychiatric Association 2000). Interestingly, in a very recent neuropsychological study (Wessa et al., unpublished manuscript) we observed increased delay aversion scores in healthy first-degree relatives of bipolar disorder patients, which reflect an impulsive behavior, i.e., the inability to delay and inhibit responses in the context of reward-related decision-making. However, no such effect was present in bipolar disorder patients themselves. This even higher sensitivity to immediate rewards and impulsive behavior in healthy individuals at risk to develop bipolar disorder compared to bipolar patients might be related to medication effects.

However, with respect to the prediction error signal and delay aversion we did not observe significant correlations with medication load, which of course does not rule out that medication has some effect or that it has a more specific effect than we were able to detect with a rather global measure like the composite medication load score. Another explanation refers to the fact that bipolar disorder patients in our study were chronic patients with a history of multiple manic and depressive episodes and ideally, during psychotherapy, they already acquired some strategies to regulate their initially increased sensitivity to immediate reward and impulsivity.

The convergent results in patients with bipolar disorder, unaffected first-degree relatives of patients with bipolar disorder (Linke et al., 2012a) and carriers of a genome-wide supported genetic risk variant for bipolar disorder (*CACNA1C* rs1006737, Wessa et al., 2010) strongly suggest that alterations in the medial orbitofrontal cortex and amygdala represent a trait marker for bipolar disorder. On a cautious note, these abnormalities might also contribute to increased illness vulnerability, a proposition that is in line with the above-mentioned dysregulation theory of the behavioral activation system (Alloy & Abramson, 2010). This theory suggests that a hypersensitive behavioral activation system, which regulates approach motivation and goal-directed behavior and depends (amongst other structures) on the orbitofrontal cortex (Depue and Iacono, 1989), mediates vulnerability for bipolar disorder. Indeed, further analyses of our data revealed moderate and significantly positive correlations between the score on the behavioral activation system scale (Carver & White, 1994) and neural activation in the medial orbitofrontal cortex in response to reward and reversal of reward contingencies in bipolar disorder patients and their relatives. The behavior activation system scale measures dispositional sensitivity to the behavioral activation system (Carver & White, 1994) and is calculated from questionnaire items loading high on the dimensions 'Drive', 'Reward Responsiveness' and 'Fun Seeking'.

Despite the evidence from our studies, the question whether alterations in the medial orbitofrontal cortex and amygdala in response to reward delivery and reversal of reward contingencies represent a vulnerability marker for bipolar disorder has to be further evaluated in longitudinal studies considering conversion rates in high-risk individuals, particularly at young age, to bipolar disorder or other psychopathologies.

In addition to these potential vulnerability markers for bipolar disorder, we also identified increased activity in the ventral putamen and lateral orbitofrontal cortex during reversal of reward contingencies. As described earlier, these structures have been subsumed under an external emotional control network in a recently published neurobiological consensus model of bipolar disorder (Strakowski et al., 2012). Furthermore, increased activity in lateral orbitofrontal cortex seems to signal punishment and could thus represent a compensatory mechanism in bipolar patients that aides to suppress previously rewarded responses (Cools et al., 2002) and potentially enables adequate performance during euthymia. Such compensatory recruitment of orbitofrontal structures was previously reported by our group for euthymic bipolar disorder patients during the inhibition of responses to emotional compared to neutral faces (Wessa et al., 2007).

Taken as a whole, our results support neurobiological models of bipolar disorder, highlighting the role of the ventral prefrontal cortex and the amygdala as key structures in the development and maintenance of bipolar disorder (Blond et al., 2012; Strakowski et al., 2012). Our findings add to the existing models in identifying abnormal amygdala and ventral prefrontal cortex functioning in response to reward as potential vulnerability marker for bipolar disorder. Furthermore, our data extend previous results by showing that heightened emotional reactivity in bipolar disorder is not limited to primary emotional cues but also occurs for positive and negative feedback probably leading to motivational dysregulation.

3. Emotional processing

As pointed out, the majority of neuroimaging studies in bipolar disorder investigated the recognition of or reaction to emotional stimuli, such as emotional faces or words. In line with the clinical observation of an emotional instability and emotional hyper-reactivity in patients with bipolar disorder, an emotion-specific hyperactivity of ventral-limbic brain structures such as the amygdala, the insula, the anterior cingulate cortex and the orbitofrontal cortex has been repeatedly reported in adult depressed and euthymic bipolar disorder patients (Altshuler et al., 2005; Lawrence et al., 2004; Malhi et al., 2004; Wessa et al., 2007; Yurgelun-Todd et al., 2000). During mania, results are more conflicting with a number of studies

reporting decreased rather than increased amygdala activity (Chen et al., 2010; Hulvershorn et al., 2012; Lennox, 2004).

In general, hyper-activation in ventral-limbic brain areas in bipolar disorder patients has been related to diminished top-down control, which is supported by studies showing reduced negative or even increased functional connectivity between the ventrolateral prefrontal cortex/anterior cingulate cortex and the amygdala in manic (Cerullo et al., 2012; Foland et al., 2008), euthymic (Wang et al., 2009) and depressed patients (Versace et al., 2010b). In addition to these task-related abnormal connectivity patterns, a relatively reduced negative correlation and decreased low frequency BOLD fluctuations between ventral prefrontal/anterior cingulate cortex and amygdala activity at rest was reported in bipolar disorder patients as compared to healthy controls (Anand et al., 2009; Chepenik et al., 2010). Among other regions (e.g. medial prefrontal cortex, parietal cortex), the dorsal, anterior cingulate and ventrolateral prefrontal cortices have been found to underlie voluntary emotion regulation through attentional control (e.g. distraction) or cognitive change (e.g. reappraisal) (Kanske et al., 2011; McRae et al., 2010). In bipolar disorder patients, hypo-activation of prefrontal structures and reduced negative functional connectivity between ventral prefrontal and limbic brain areas might therefore lead to a deficit in voluntarily down-regulating exaggerated emotional responses.

Until now, however, very few studies have investigated neural correlates of voluntary emotion regulation in bipolar disorder although theoretical models, empirical data and clinical observations strongly suggest such regulation deficits (Phillips et al., 2008). One major problem in emotion regulation research in bipolar disorder is a very heterogeneous conceptualization of emotion regulation, and consequently diverse operationalization in experimental research. Emotion regulation is part of a broader concept of emotional processing, including 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 (Wessa & Linke, 2009). 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 in psychopathology.

According to Gross & Thompson (2007) regulation of emotions 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, Gross & Thompson (2007), 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, a focus has been placed on the investigation of a few strategies, particularly on distraction as an example for attentional deployment, reappraisal as an example for cognitive change and suppression as an example for response modulation. Whereas distraction refers to directing attention away from the emotional features of the situation to different, potentially non-emotional aspects of the situation, reappraisal means to change the connotation of a situation or how we think about a situation in order to alter its emotional significance.

Previous studies in bipolar disorder employed experimental paradigms that included cognitive tasks (e.g., response inhibition, n-back task) with concurrently presented emotional stimuli (e.g., Bertocci et al., 2012; Deckersbach et al., 2008; Elliott et al., 2004; Wessa et al., 2007). To assure successful task performance, study participants had to direct their attention away from the concurrently presented emotional stimulus and to focus on the cognitive task. Likewise, these studies might also be seen as investigating attentional deployment as one emotion regulation strategy. However, in their analyses the authors mainly investigated the distracting influence of emotion on cognitive processes, for example by contrasting brain activity associated with the task during the presentation of distracting emotional stimuli versus neutral stimuli. Yet, to determine the neural correlates of the influence of cognitive task performance on emotional responses, and thus emotion regulation, a comparison between the 'task + emotion' condition and 'emotion-only' condition would be necessary.

Previously, two studies investigated the impact of disturbing emotional information on response inhibition in manic and euthymic bipolar disorder patients, revealing increased ventral prefrontal activity in bipolar patients when trying to inhibit responses to emotional faces compared to the inhibition of responses to neutral faces (Elliott et al., 2004; Wessa et al., 2007). Two more recent studies investigated working memory performance during either mood induction (Deckersbach et al., 2008) or concurrently presented emotional faces (Bertocci et al., 2012). In depressed bipolar disorder patients, Deckersbach et al. (2008) reported increased activation in dorsal anterior cingulate and dorsolateral prefrontal cortices while performing the working memory task under sad mood as compared to no mood induction. This might be interpreted as a greater demand for executive control to perform the cognitive task when being in a sad mood. Whereas Bertocci et al. (2012) did not find such compensatory activity in bipolar disorder patients, but reported elevated activity in the dorsal anterior cingulate cortex during high working memory-load and concurrently presented neutral faces in depressed patients with unipolar depression, suggesting compensational recruitment of brain regions belonging to the attentional control network.

Interestingly, our group could show a similar effect in patients with unipolar depression not only for distraction but also for reappraisal (Kanske et al., 2012). Activity in the regulating control-network including anterior cingulate cortex and lateral orbitofrontal cortex was increased during both distraction and reappraisal. In contrast, patients with unipolar depression showed a selective deficit in down-regulating amygdala responses to negative emotional stimuli using reappraisal. This down-regulation of amygdala activity was strongest in participants with high habitual use of reappraisal measured with the Cognitive Emotion Regulation Questionnaire (CERQ; Garnefski & Kraaij, 2007) that assesses the regular use of reappraisal or suppression as emotion regulation strategy during every-day life. These data are in line with previous studies on cognitive control of emotions in patients with unipolar depression, suggesting a deficit in the ability to down-regulate amygdala activity to negative emotional stimuli (Beauregard et al., 2006), and altered connectivity between the amygdala and prefrontal control regions (Erk et al., 2010; Johnstone et al., 2007).

To overcome the described gap in voluntary emotion regulation research in bipolar disorder patients, we recently completed a study on the neural correlates of two different voluntary emotion regulation strategies, i.e., distraction and reappraisal, in patients with
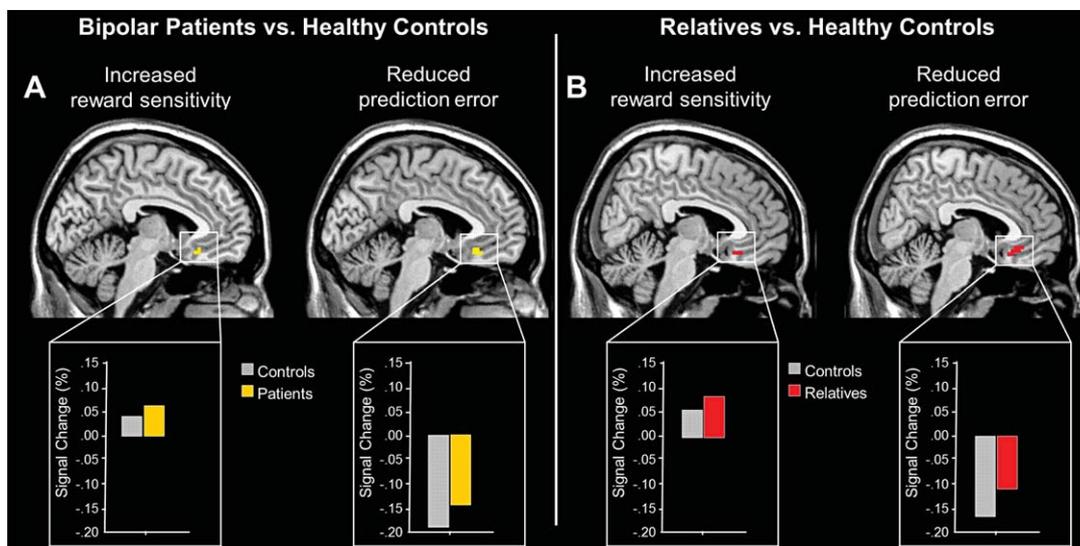
Fig. 1. Illustration of heightened reward sensitivity and reduced prediction error signal in the medial orbitofrontal cortex as observed in Linke et al., 2012a. (A) Depiction of significant greater activation in patients with bipolar-I disorder ($n = 19$) compared to healthy controls ($n = 19$) and (B) of significant greater activation in relatives of bipolar-I patients ($n = 22$) compared to healthy controls ($n = 22$). Sagittal slices are overlaid on the MRIcron ch2 template. Activation is thresholded at $p < 0.05$ corrected for family-wise error rates within the orbitofrontal cortex as defined by the aal template.

bipolar-I disorder and their unaffected first-degree relatives (Kanske et al., in press). Bipolar disorder patients and their first-degree relatives when compared to healthy controls showed impaired down-regulation of amygdala activity in response to positive and negative stimuli during reappraisal, 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 in bipolar disorder patients and their relatives compared to healthy controls. These results suggest that deficits in emotion regulation through reappraisal are a vulnerability factor 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 (Schneider et al., 2012; Strakowski et al., 2012).

4. Structural connectivity

The brain regions related to disturbed motivational and emotional processes in bipolar disorder are connected through white matter, which is composed of axons and was shown to be under strong genetic control (Kochunov et al., 2010). Deviation from normal axonal organization can be investigated by means of diffusion tensor imaging. This technique allows the visualization of white matter tracts in the brain and the quantification of diffusion characteristics of water in white matter (e.g., fractional anisotropy) which gives an estimate of the directionality and coherence of white matter bundles (Basser et al., 1994). Children and adolescents with bipolar disorder show decreased fractional anisotropy in the corpus callosum, the cingulate-paracingulate white matter, the fornix, and the superior longitudinal fasciculus (Schneider et al., 2012). In adult patients with bipolar disorder, a loss of white matter integrity in fronto-limbic and cortical-striatal-thalamic circuits has been relatively consistently observed and has been proposed to represent a biological vulnerability factor for bipolar disorder (Heng et al., 2010).

In a recent study, we found decreased white matter integrity, as indicated by decreased fractional anisotropy in the anterior limb of the internal capsule in patients with bipolar-I disorder and in healthy first-degree relatives of patients with bipolar-I disorder (Linke et al., in press) as well as in a healthy sample of carriers of a genetic risk variant of bipolar
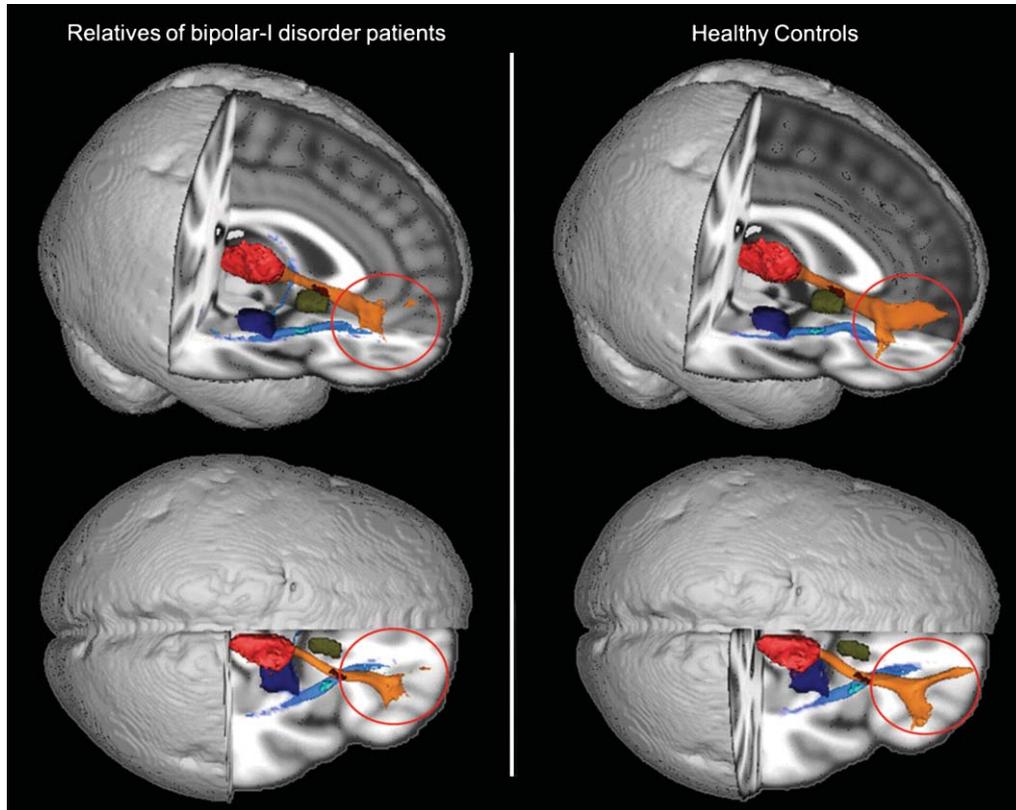
Fig. 2. Illustration of the anterior thalamic radiation (orange) and the uncinate fasciulus (light blue) in healthy relatives of bipoar-I patients compared to controls. Results of probabilistic tractography show fiber pathways that connect thalamus (pink), amygdala (blue) or nucleus accumbens (yellow) with the prefrontal cortex via clusters showing significant group differences in the anterior limb of the internal capsule (brown) and the uncinate fasciulus (turquoise). These connections are thresholded to include at least 70 % of the persons in each group (*n* = 22). Connections between subcortical seed regions and prefrontal cortex are overlapped. Masks and fiber pathways are overlaid on the MNI template in radiological convention.

disorder (*ANK3* rs10994336; Linke et al., 2012b). The anterior limb of the internal capsule contains fibers that interconnect thalamus, striatum, amygdala, hippocampus, anterior cingulate cortex, orbitofrontal cortex, and dorsolateral prefrontal cortex (Livingston & Escobar 1971; Papez, 1995). In our study, probabilistic fiber tracking from the cluster of significant group differences in the anterior limb of the internal capsule were carried out to specify which bundles are predominantly affected (see Fig. 2). We showed that direct connections between the thalamus as well as the nucleus accumbens and orbitofrontal cortex were altered in bipolar patients, healthy first degree relatives of bipolar patients (Linke et al., in press) and risk-allele carriers of ANK3 rs10994336 (Linke et al., 2012b). Consistent with previous studies (Zarei et al., 2010), we observed connections from the amygdala to anterior

and posterior thalamus, but no direct connections to the orbitofrontal cortex passing through the anterior limb of the internal capsule. Our results are in line with previous reports, consistently showing reduced white matter integrity in the anterior limb of the internal capsule in bipolar patients (Haznedar et al., 2005, McIntosh et al., 2005, Sussmann et al., 2009) and first-degree relatives of bipolar disorder patients (Chaddock et al., 2009, Sprooten et al., 2011).

In our study, bipolar-I disorder patients and their healthy first-degree relatives additionally showed reduced white matter integrity in the uncinate fasciculus (Linke et al., in press), which interconnects the amygdala with the orbitofrontal and anterior cingulate cortex (Petrides & Pandya, 2007). This finding is also in line with other reports of reduced fractional anisotropy in the uncinate fasciculus in bipolar disor-

der patients (Lin et al., 2011; McIntosh et al., 2008; Sui et al., 2011; Sussmann et al., 2009; Versace et al., 2008; 2010a). Importantly, the integrity of the uncinate fasciculus was shown to influence functional coupling between the anterior cingulate cortex and the amygdala (Wang et al., 2009).

In conclusion, our own data and previous results support the assumption that altered structural connectivity in networks associated with motivational and emotional processes contributes to functional abnormalities in these networks. However, studies integrating findings from functional and anatomical connectivity measures will have to confirm this notion.

5. Conclusion

Results from our own laboratory as well as empirical data from other research groups provide evidence that bipolar disorder is a disorder of emotion and motivation. Interestingly disturbances in these tightly related psychological processes appear to ground on impairments in overlapping neural networks with the orbitofrontal cortex and the amygdala playing a particularly important role. Based on our own and previous data we further propose that functional and anatomical alterations in orbitofrontal cortex and amygdala as well as the connection between these two regions represents a biological vulnerability marker of bipolar disorder.

It is noteworthy that in reviewing our own data and results from other groups, it appears that neural networks involved in the pathophysiology of bipolar disorder are not either uniformly hypoactive or uniformly hyperactive but that a) the ongoing psychological processes and b) current mood state of the patients crucially interact with neural activation patterns.

Acknowledgments

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