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Review article

An emotional-response model of bipolar disorders integrating recent findings on amygdala circuits

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ABSTRACT

Because of our classification system limitations for defining psychiatric disorders and understanding their physiopathology, a new research area based on dimensions has emerged. It consists of exploring domains derived from fundamental behavioral components linked to neurobiological systems. Emotional processing is among the most affected dimensions in bipolar disorders (BD), but is excluded from the definition criteria. The purpose of this review is to synthesize the emotional responses disruption during the different phases of BD, using intensity and valence as the two key characteristics of emotions. We integrate those emotional disruptions into an original, emotion-based model contrasting with the current diagnostic frame built on mood. Emotional processing is underpinned by cortico-limbic circuits involving the amygdala. Recent publications showed the crucial role of the amygdala in emotional processes triggered by stimuli of negative, but also positive valence. We show how these neuroscience data can provide physiological basis for emotional disturbances observed in BD. We conclude with translational perspectives to improve the current knowledge about neural substrates underlying altered emotional responses characterizing BD.

1. Introduction

Lifetime prevalence of bipolar disorders (BD) is about 4.5 % in the general population with a high suicide rate and a huge impact on patients functioning (Grande et al., 2016; Merikangas et al., 2007). BD is defined by the recurrence of depressive, manic, and/or mixed episodes, in which manic and depressive symptoms are simultaneously present.

Our current classifications to define psychiatric disorders are based on clinical consensus relying on the observation of signs and symptoms but are questionable from both a clinical and research standpoint and therefore need to be refined (Bauer et al., 2018). We can note many shortcomings common for all psychiatric diagnoses. The clinical heterogeneity of syndromes results in patients with very different symptoms being diagnosed with the same disease. Moreover, these classifications do not provide access to the fundamental mechanisms underlying the syndromes, neither predict response to treatment. Concerning BD specifically, the altered mood is the main criterion to define episodes, with sadness in depressive states and euphoria or irritability in mania (American Psychiatric Association, 2013). Nevertheless, the existence of mixed states associating manic and depressive symptoms challenges the relevance of this model of bipolarity based on mood (Koukopoulos et al., 2013). During mixed states, mood must be both exalted and sad at the same time or within a very short period. However, mood is a persistent and slow-moving feeling and then is not adequate to describe mixed states. This may explain the difficulties in diagnosing mixed states and its wide variations in estimating its prevalence (6–19.6%)(Shim et al., 2015). On the other hand, mood is not sensitive enough to detect sub-threshold or residuals symptoms that persist beyond clinically defined episodes. Then, they are not considered in current definitions despite their strong impact on functioning, while they are particularly difficult to treat (Serra et al., 2019; Dargél et al., 2018). Finally, the subjective assessment of mood is inappropriate for quantitative measurements and so for experimental research.

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To overcome these issues, a dimensional approach has been proposed. The principle is to explore not any more symptoms, but domains or dimensions that are constructs derived from fundamental behavioral components which can be linked to neurobiological systems (such as cognition, motivation, perception, etc.), and range from normal to pathological (Malhi et al., 2018; Cuthbert and Insel, 2013). One of the most impacted domains in BD is emotional processing whose disruptions underlie a large number of symptoms. Research in this area has long been neglected, as emotional processes remained poorly defined and difficult to measure in animal models. Currently, consensual and efficient definitions for research have made possible to carry out clinical and pre-clinical studies allowing us to determine the brain structures involved in emotional processes.

Emotions are brief responses characterized by a physiological arousal that are triggered by a stimulus to drive an adapted behavior (Schachter and Singer, 1962; Russell, 2003; Tye, 2018) and are characterized by two quantifiable features: (i) the intensity of the response and (ii) the valence. Emotional valence is the subjective value assigned to sensory stimuli which determines subsequent behavior. Positive valence leads to approach and consummatory behaviors while negative valence leads to defensive and avoidance behaviors (Pignatelli and Beyeler, 2019). Stimuli can be external via our senses or internal, and the perception of these stimuli will directly influence the behavioral response (Fig. 1). Conversely to mood, emotional response can be studied in real time during brain imaging studies in human and can be inferred in animal models by assessment of approach or avoidance behaviors (Beyeler, 2016a). Based on these two characteristics of emotion and fostered by the recent advent of sophisticated techniques, basic research is revisiting the role of amygdala circuits. Previously considered has the hub of fear, we now know that the amygdala is involved in valence assignment of both positive and negative salient stimuli, where potentially all kind of emotional responses could arise.

The purpose of this review is to synthesize the disruption of emotional responses during the different phases of BD and integrate them into a new model that is based on variations in the intensity and valence of emotional responses. We then propose an overview of recent neuroscience data that could provide a physiological basis for these disturbances. We conclude with translational research perspectives to improve current knowledge about the brain support of emotional responses that characterize BD.

2. Emotional disturbances in BD: from mood to emotional responses

2.1. Clinical data

As brief response following stimuli, emotional response can be assessed in day-to-day practice using self-questionnaires and ecological assessments or during laboratory experiments. We report here variations in emotional response during the different phases of the illness in adult BD patients.

Although considered in remitted phases, BD patients experience more frequent and intense emotions in response to environmental conditions relative to healthy subjects, which leads to mood instability (Henry et al., 2009). Emotional hyper-reactivity and mood instability have a detrimental impact on functioning, relapses, and suicide attempts (Strejilevich et al., 2013; Dargél et al., 2017). In a large cohort of BD patients clinically defined in a remitted phase by classical assessment, we showed that emotional response intensity is predictive of outcome (Dargél et al., 2018). Patients with higher emotional responses made more suicide attempts; had a higher level of C-reactive protein, a marker of inflammation; and had more physiological disturbances such as higher blood pressure and higher fasting glucose level. This pinpoints the relevance of assessing emotional responses to detect patients at risk of suicide, and at risk of developing cardiovascular diseases or cognitive decline linked to chronic inflammatory process, which are among the most important causes of the high mortality/morbidity of BD. Using ecological momentary assessment, specific profiles of emotional reactivity to daily events and mood instability were identified, which allowed us to distinguish BD I relative to patients with BD II, major depressive disorders (MDD), and anxiety (Lamers et al., 2018; Jepsen et al., 2019). Emotional responses could also represent an endophenotype, because subjects at risk for BD, defined by a score on a scale of hypomania, exhibited higher emotional reactivity (Kwapil et al., 2011; Gruber et al., 2008). Some authors suggest that excessive reactivity to positive events might be a core dimension of BD (Johnson, 2005; Gruber, 2011; Kærsgaard et al. (2018)). In this vein, we have reported that neutral pictures are assessed as more pleasant by BD patients relative to control, testifying that the misallocation of valence is in the direction of a positive bias (M'Bailara et al., 2009). However, the corpus of findings suggests that excessive emotional responses concern all kinds of stimuli, possibly depending on residual symptoms.

Compared to remitted phases, mood states are characterized by

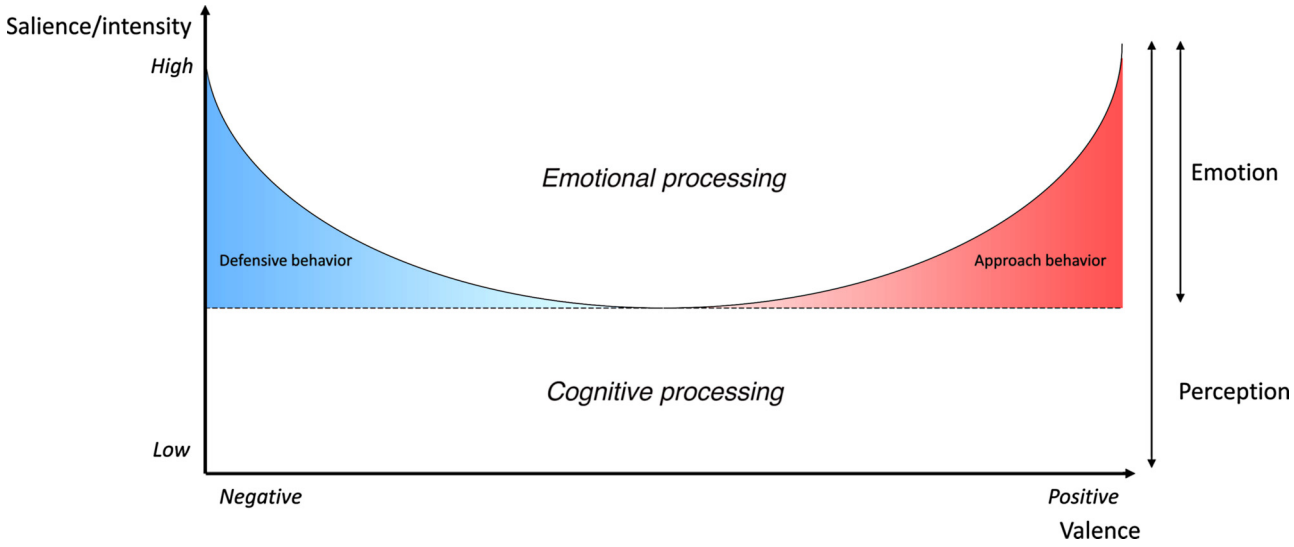

Fig. 1. When a perception is sufficiently salient, it triggers an emotion with a congruent valence (positive or negative). In turn, the emotion will trigger either a defensive (in blue) or an approach behavior (in pink). In animal models, it is possible to measure the valence attribution to various stimuli by measuring behavior and thus to infer the animal's emotional state.

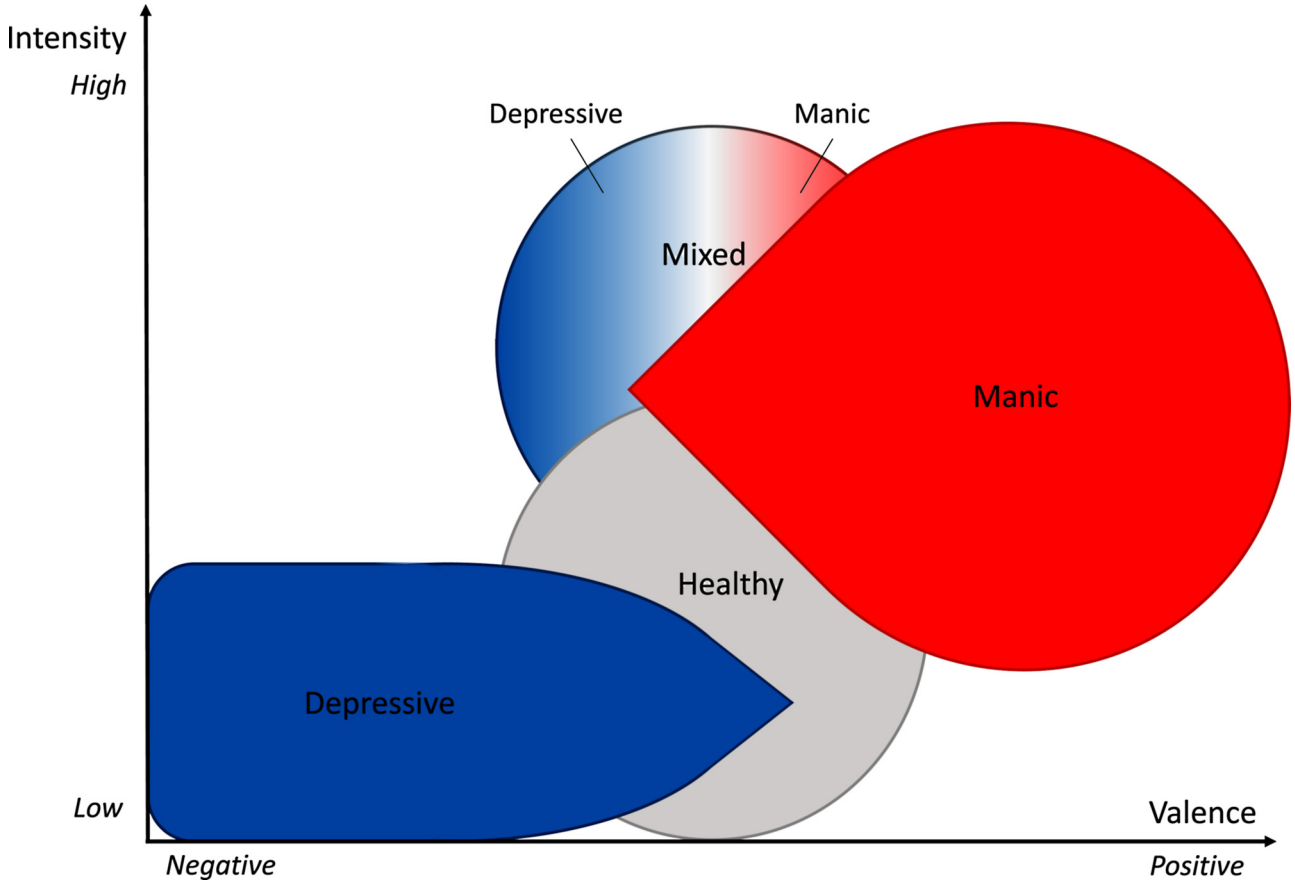

Fig. 2. In this emotional-response model, conversely to those of mood-model, mania and depression are not placed on the extremes of a unidirectional continuum, allowing us to integrate the broad spectrum of mixed and sub-syndromic states. During manic episodes (in red), there is a propensity to assign more positive valences with higher intensity. In mixed states (blue-white-red), the arousal is higher, but the attribution of valence is flexible. In depression (in blue), there is a decreased arousal and a greater weight assigned to negative valences, whereas during the remitted phase, as a function of the type of sub-syndromal symptoms, arousal and valence can slightly change in a chronic manner.

drastic changes in both intensity and valence of emotional responses. We showed that neutral, negative, and positive pictures are more arousing during both manic and mixed states in comparison to patients in remitted phases (M'Bailara et al., 2012). On the basis of the theoretical model of the behavioral approach system (BAS) and the behavioral inhibition system (BIS), bipolar mood states are supposed to result from either an increase or a decrease in the activity of these two systems (Meyer and Hofmann, 2005). Regarding the functioning of these two opposite systems, manic patients present increased reward awareness, whereas depressed patients avoid reward and exhibit higher sensitivity to punishment. In other words, during manic states, a positive emotional bias to reward cues drives a high level of goal-seeking behavior and magnifies and exacerbates sensory perception (Parker, 2014). This is accompanied by poorer perception of dangers leading to high risk-taking behaviors (i.e., lower attribution of negative value).

The intensity of emotional responses during depressive episodes is more complex, as bipolar depression is heterogeneous. In major depressive disorder (MDD), a meta-analysis including data collected by self-questionnaires, behavioral expressions, or physiological measurements has shown that there is a global emotional hypo-reactivity with a reduction of all emotional responses to both positive and negative stimuli, leading to a global insensitivity (Bylsma et al., 2008). In bipolar patients, because of the widespread clinical heterogeneity of depression, emotional responses are not homogeneous. We showed that depressed bipolar patients can be separated depending on the level of intensity of their emotional responses (Henry et al., 2007). One BD depression is characterized by emotional hypo-reactivity associated with overall behavioral inhibition, whereas the other is characterized by emotional hyper-reactivity and mild activation that corresponds to depression with mixed features in the DSM-5 (American Psychiatric Association, 2013). That could explain why bipolar depressed patients as a whole are more reactive to emotional cues than healthy subjects, conversely to those with MDD (Stratta et al., 2014). Concerning valence assignment in depressed patients, there is a well-documented global negative bias (Leppänen, 2006). A human model suggest that the direct effect of successful antidepressant treatment is to modify negative biases in emotional processing and is an early marker of good response to monoaminergic antidepressants (Harmer et al., 2017).

From a clinical point of view, characterizing mood episodes with emotional responses is of clear interest for discriminating subgroups of patients pooled within the same diagnosis by current classifications (Henry et al., 2007). This strategy could help to understand various responses to pharmacological treatments for bipolar depressions and propose more personalized treatment. Currently, recommendations propose treatments with very different and sometimes opposed mechanisms of action, such as antipsychotics with an antidopaminergic action, molecules acting on other monoamines such as serotonin, but also dopaminergic agonists. For remitted patients, it could allow us to develop preventive strategies. Dialectical behavioral therapy would be particularly appropriate for patients with chronic emotional hyper-reactivity, whereas those with a hypo-reactivity may better benefit from interventions focused on behavioral activation (Dimidjian et al., 2011; Eisner et al., 2017). Regarding our results on patients during the remitted period, measuring emotional reactivity opens a new avenue to understanding the links between inflammatory processes and BD. Importantly, disruption in emotional responses is a transnosographic

dimension, which can also affect patients with personality disorders, attention deficit hyperactivity disorders, or substance users (Henry et al., 2001; Patel et al., 2015; Richard-Lepouriel et al., 2016). Therefore, assessment of emotional responses can also help to better understand links between these highly comorbid conditions or reduce misdiagnosis between them.

2.2. A new model based on emotional response in bipolar disorders

To guide research perspectives, we propose to deconstruct the mood-based model of BD and replace it with an emotional response-based model that can serve as a conceptual framework. Using the two-dimensional theory of emotion and the main results in clinical reports on emotional responses in BD, we propose here a model to characterize the variations of emotional responses during BD mood states using their two main features, intensity and valence (Fig. 2). The mood-based model is constructed from a unidimensional scale ranging from euphoria to sadness, circumscribing BD to two poles that does not allow us for a correct integration of mixed states and sub-threshold symptoms. Our model, by including two parameters, enables us to better account for the complexity of the emotional processing. During manic episodes, there is a positive emotional bias leading to assign more positive valences with higher intensity. Thus, neutral stimuli become positive, negative stimuli lose their negative value (e.g. a danger becoming less scary), and positive stimuli have a stronger rewarding value. In mixed states, the arousal is higher, but the attribution of valence will determine whether it is a depressive or manic episode with mixed features. In depression, there is a decreased arousal and a negative emotional bias, whereas during the remitted phase, as a function of the type of sub-syndromal symptoms, arousal and valence can slightly change in a chronic way.

This model can explain many of the symptoms such as frenetic pleasure seeking, risk-taking behaviors, emotional lability and disproportionate emotional responses in manic patients. On the contrary, loss of emotional responses associated with a negative bias may explain the apathy and anhedonia of depressed patients.

Obviously, mood disorders cannot be defined just by emotional responses and it is necessary to add other relevant dimensions that refer to different sets of symptoms. Recently, we highlighted the major interest in better studying motor activity (Scott et al., 2017). Other authors, using Kraepelin's model to explain mixed states, proposed a scheme with three dimensions: emotions, cognition and motor activity (Malhi et al., 2018). However, in this model, emotions are considered only for their valence. We believe that integrating intensity of emotion is essential to placing all domain on a continuum from inhibition to activation (Henry et al., 2010), as proposed in our emotional response model.

An important point to disentangle is whether those emotional disturbances are due to an alteration in emotional processing, involving brain limbic structures, or an alteration of the perception and sensory processing of the stimuli, relying on modifications in sensory areas. In a large sample of BD patients in remitted period, we performed a cluster analysis using five dimensions which are emotional reactivity, sensory perception, psychomotor activity, motivation and cognition that lead to discriminate four clusters. In all the clusters, emotional reactivity and sensory perception co-varied in the same direction (Dargél et al., 2019). Indeed, with a behavioral evaluation, it is very difficult to disentangle the sensory from the emotional contribution to the intensity and valence attribution to a particular stimulus. To completely distinguish both effects, a parallel evaluation of sensory system functioning is required, assessing several aspects of sensory perception including detection, identification and discrimination of stimuli, among other parameters. Alterations in sensory cortices activity, structure and connectivity have been recently reported (Shaffer et al., 2018; Thomas et al., 2019), but further research on this question is necessary to demonstrate the role of sensory processing in the pathophysiology of BD, independently of the altered emotional processing. Concerning this emotional processing, limbic areas including the amygdala, have been consistently observed as disrupted in BD patients compared to healthy subjects (Chen et al., 2011).

3. The amygdala: a key structure for emotional processing involved in the pathophysiological model of bipolar disorders

The amygdala has for a long time been identified as a key structure for emotional response. However, during the last decades, because of the tremendous work highlighting its role in fear mainly based on the very robust fear-conditioning model, it resulted in the amygdala being considered as the hub of fear (Rogan et al., 1997; Rodrigues et al., 2004; LeDoux, 2017). These pre-clinical data have been reinforced by data in patients with post-traumatic stress disorders, social phobia, and specific phobias for whom functional neuroimaging showed an over-activation of the amygdala triggered by negative emotional stimuli in comparison to control subjects (Rauch et al., 2006; Etkin and Wager, 2007). Moreover, fear conditioning in healthy subjects reproduced the same pattern of activation. Altogether, these data focused attention on the role of amygdala as a key component in fear and anxiety disorders.

However, structural and functional abnormalities of the amygdala are also found in other psychiatric disorders, in particular in BD. The current consensual model of BD assumes that a dysfunction in prefrontal cortex regulation of the amygdala is the main pathophysiological cause of the disease. Hence, one of the most reproducible results using fMRI studies is an amygdala over-activation when facing emotional tasks in bipolar patients compared to controls (Strakowski et al., 2012; Phillips and Swartz (2014)). Some authors propose a state-dependent amygdala activation, with an over-activation during mania and hypo-activation during depression (Altshuler et al., 2005; Vizueta et al., 2012). However, a meta-analysis of fMRI found an over-activation of limbic structures, most consistently in the amygdala and hippocampus, triggered by emotional stimuli in BD adult patients whatever the phases (i.e., remitted, manic, or depressive) in comparison to control subjects (Chen et al., 2011). Some authors have also shown that different patterns of amygdala activation may distinguish unipolar depressed patients from bipolar depressed patients (Almeida and Phillips, 2013). Moreover, it is worth mentioning that lithium intake, the gold standard treatment of BD, has been associated with modifications on amygdala in patients treated with lithium (Hartberg et al., 2015; Strakowski et al., 2016). Given the major role of amygdala in emotional processing, structural and functional changes in this area could underlie emotional disturbances both in depressive and manic episodes and explain the lithium effect.

3.1. New robust data from basic science: the amygdala, a hub for positive and negative valence encoding

The development of optogenetics over the past decade has provided novel opportunities to explore the role of neural circuits in behavior, particularly regarding amygdala functioning (Tye and Deisseroth, 2012). Optogenetics relies on the combined use of genetic and optical methods to control spatially and temporally specific neuronal activity. Neurons are first genetically engineered to express a given opsin, proteins sensitive to light, allowing control of their activity by light pulses. Under illumination, these neurons are transiently activated or inhibited, depending on the nature of the opsin that is chosen. The temporal properties of the optogenetic tool allow reshaping the style of the experimental design, and the activity of specific neurons can be controlled in free-moving animals, allowing to assess their behavior. Another way to link specific cell population activity to behavioral outputs relies on chemogenetic technology, which combines the use of chemogenetically engineered proteins (designer receptors exclusively activated by designer drugs, or DREADDs) with chemical reagents to activate or inhibit specific neurons (Roth, 2016). Using the

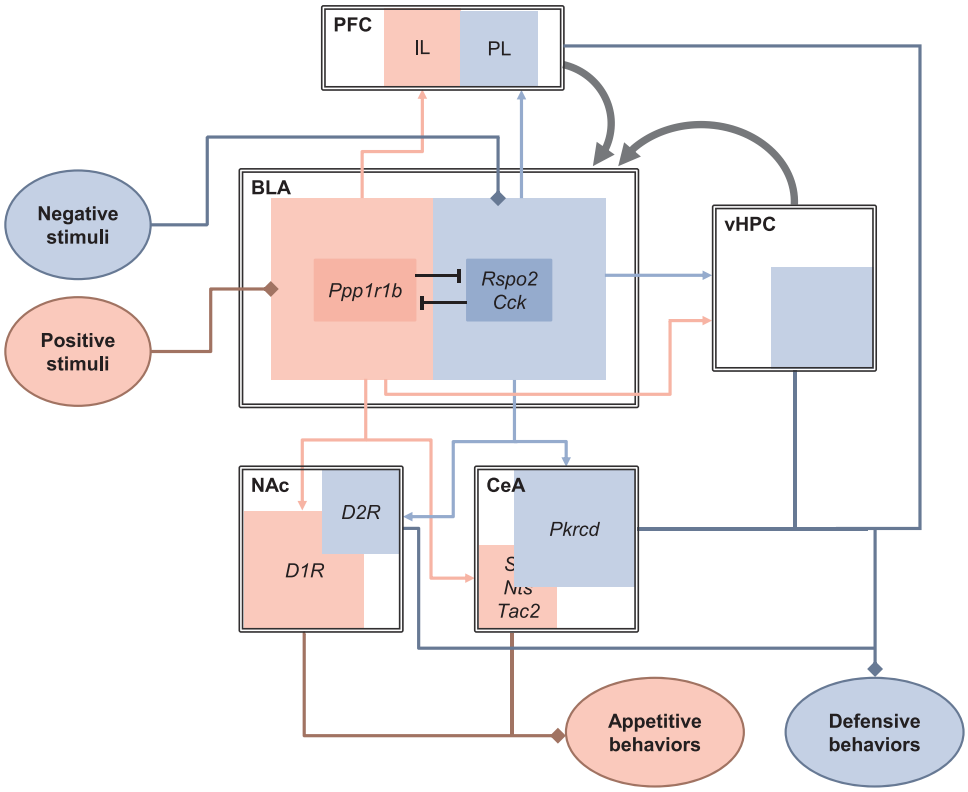

Fig. 3. Anatomical connectivity and genetic identity of positive and negative value-coding BLA neurons and related structures. The BLA is an important structure for valence processing, as demonstrated through recent pre-clinical studies. Distinct neuronal subpopulations encode preferentially either positive or negative values and antagonize the activity of the opposing neurons (Kim et al., 2016). Other studies also found that positive and negative valence-encoding BLA neurons are intermingled throughout BLA (Beyeler et al., 2018) and valence encoding in the BLA is mediated via activity of neural populations defined by their projections (Namburi et al., 2015; Beyeler et al., 2016b). The positive-encoding neurons responds to positively valenced sensory stimuli (in pink). These neurons project mainly to the NAc (Kim et al., 2016; Beyeler et al., 2016b, 2018), but also to the CeA (Kim et al., 2016, 2017), vHPC (Beyeler et al., 2016b) and the IL part of the PFC (Kim et al., 2016; Senn et al., 2014). Negative stimuli activate the negative-encoding neurons, which a subgroup expresses Rspo2 and Cck RNA (in blue; Kim et al., 2016; Shen et al., 2019), and are connected to the CeA (Kim et al., 2016; Beyeler et al., 2016b), NAc (Beyeler et al., 2016b; Shen et al., 2019), vHPC (Beyeler et al., 2016b) and the PL part of the PFC (Kim et al., 2016; Burgos-Robles et al., 2017).

Artificial activation of the BLA-to-NAc pathway mainly lead to appetitive behaviors (Stuber et al., 2011; Namburi et al., 2015), even if specific inhibition or activation the negative subpopulation of the BLA projecting to the NAc bidirectionally regulate defensive behaviors (Shen et al., 2019). In the same way, global activation of the BLA-to-CeA neurons generates defensive behaviors, although activating BLA neurons that project to specific neuronal types of the CeA (Sst+, Nts+, Tac2+) induces opposite behaviors (Kim et al., 2017). In contrary, inhibition of BLA-to-CeA projections impairs defensive behaviors and enhance appetitive ones (Namburi et al., 2015).

Enhancing BLA-to-vHPC neuronal activity triggers defensive behaviors (Felix-Ortiz et al., 2013; Felix-Ortiz and Tye, 2014), as well as BLA to PFC (Burgos-Robles et al., 2017). Finally, reciprocal connections from the PFC and vHPC would regulate BLA activity, as suggested by McGarry and Carter, 2017 and Sotres-Bayon and Quirk, 2010.

Pink: positive pathways. Blue: negative pathways. Grey: regulatory pathways. BLA: basolateral amygdala. CeA: central amygdala. IL: infralimbic part of the PFC. NAc: nucleus accumbens. PFC: prefrontal cortex. PL: prelimbic part of the PFC. vHPC: ventral hippocampus; D1R: dopamine receptor type 1; D2R: dopamine receptor type 2; Sst: somatostatin; Nts: neurotensin; Tac2: tachykinin 2; Pkrcd: protein kinase C-d; Ppp1r1b: protein phosphatase 1 regulatory subunit 1B+; DARPP-32: Dopamine and c-AMP-regulated phosphoprotein; Rspo2: R-spondin 2+; Cck: Cholecystokinin.

aforementioned techniques, the role of the amygdala and its multiple nuclei has been studied, deconstructing the complex whole-amygdala circuits involved in various behavioral responses (Janak and Tye, 2015; Tye, 2018; O'Neill et al., 2018). The amygdala consists of multiple interconnected nuclei located in the deeper region of the temporal lobe. Its structure and functions have been well-conserved across evolution, and findings from mice provide a good approximation of amygdala functioning in humans (Janak and Tye, 2015). The two main structures of the amygdala include the basolateral (BLA) and the central nucleus (CeA) of the amygdala (Fig. 3). The BLA receives information originating from all sensory modalities via the thalamus or sensory cortex. The main outputs of the BLA are the ventral striatum (mainly the nucleus accumbens, NAc) and the CeA. The BLA is also reciprocally connected to the ventral hippocampus (vHPC) and the medial prefrontal cortex (mPFC) (Janak and Tye, 2015).

3.1.1. Molecular-defined valence populations: Rspo2 & Ppp1r1b

Using immunohistostaining for the immediate early gene cFos, it was recently shown that two genetically distinct, spatially segregated populations of neurons within the BLA are differentially activated by positive or negative stimuli. Specifically, aversive stimuli such as foot shocks preferentially activates neurons expressing Rspo2 (R-spondin2), which correspond to magnocellular pyramidal neurons, whereas exposition to a reward (female mouse presentation to the tested male), preferentially activates the neurons expressing Ppp1r1b (protein phosphatase 1 regulatory inhibitor subunit 1B, also known as DARPP-32), which correspond to parvocellular pyramidal neurons (Kim et al., 2016). The differential activation of these neurons was confirmed by other valence-specific stimuli, namely pleasant or unpleasant odorants and gustatory stimuli. To confirm the role of these two neuronal populations in valence-specific behaviors, these authors used optogenetics to alternatively inhibit these two populations during fear-conditioning and reward-motivated learning. Inhibition of Rspo2-expressing neurons reduced the freezing in response to foot shocks, whereas inhibition of Ppp1r1b-expressing neurons decreased the reward-conditioning performance. The reverse was true when activating the same populations. Interestingly, activation of one population of neurons antagonized the activity of the other one (Kim et al., 2016). Another recent study using single cell calcium imaging showed that BLA neurons encoding negative affective valence of pain largely overlap with those encoding for other sensory-aversive cues (Corder et al., 2019). It is interesting to note that the protein Ppp1r1b is also known as DARPP-32 that plays a critical role in dopaminergic and glutamatergic signaling and is potentially implicated in schizophrenia and BD pathophysiology (Kunii et al., 2014).

3.1.2. Valence-defined topography: antero-posterior or dorso-ventral gradient?

There is no consensus regarding the spatial organization of the positive and negative valence encoding neurons. Kim et al. (2016)

showed, still using *ex vivo* cFos immunohistolabelling, preferential activation of neurons located in the anterior part of the BLA upon presentation of aversive contextual, olfactory and gustatory stimuli, whereas the neurons belonging to the BLA posterior part preferentially responded to pleasant stimuli of these same sensory modalities. In a recent study, more than 1000 neurons were recorded *in vivo* during a Pavlovian task to map their spatial location in the BLA (Beyeler et al., 2018). The data support the notion that although positive and negative neurons are intermingled through the antero-posterior axis, a gradient of valence responses could be seen within a dorso-ventral axis.

3.1.3. Projection-defined valence populations: BLA-vHPC, BLA-CeA, BLA-NAc

The idea that positive and negative valence encoding neuronal projections reach distinct brain areas seems more consistent across studies (Fig. 3). Work from the laboratory of Kay Tye successively explored BLA projections to the vHPC, the CeA, and the NAc in anxiety- and valence-related behaviors. Felix-Ortiz et al., 2013, 2014 showed that optogenetic stimulation of glutamatergic neurons projections from the BLA to the vHPC induces anxiety-like behavior and reduces social interactions, whereas inhibition leads to anxiolytic-like states and increased such interactions.

BLA-to-CeA projecting neurons activation induces real time place aversion, whereas its inhibition impairs fear conditioning and enhances reward conditioning (Namburi et al., 2015). Either BLA-to-NAc neurons projections stimulation (Stuber et al., 2011) or cell bodies activation of these same neurons (Namburi et al., 2015) induces intracranial self-stimulation (ICSS), suggesting a role for this specific circuit in reward-seeking behavior. Conversely, optical inhibition of the same BLA-to NAc neurons fibers decreased response to sucrose reward (Stuber et al., 2011). Finally, other findings employed optogenetic-mediated "photo-tagging" in combination with large-scale *in vivo* electrophysiological recordings to reveal the specific neural code of BLA neurons that synapse in the NAc, CeA or vHPC, in response to the presentation of cues associated with either rewarding or aversive outcomes. They demonstrate that during the retrieval of positive or negative associative memories, the valence encoding in the BLA is at least partially mediated via divergent activity of anatomically defined neural populations (Beyeler et al., 2016b).

Finally, recent articles demonstrated that chronic stress in mice specifically enhances synaptic connections and signal transmission from the BLA to the vHPC (Zhang et al., 2019a, b).

3.1.4. Projection- and molecular-defined valence population: BLA-to-NAc CCK+/-

At a molecular level, Shen et al., 2019 showed that cholecystokinin (CCK) gene expression could be a marker to subdivide the BLA-to-NAc subpopulation into positive (CCK-) and negative (CCK+) valence encoding neurons (Fig. 3). These two types of neurons co-express respectively Ppp1r1b and Rspo2, consistently with their role in positive and negative valence encoding. Furthermore, CCK + and CCK- neurons are respectively connected to D1R- or D2R-expressing neurons, mediating either appetitive or defensive behavior. Therefore, the BLA appears able to transmit information about the positive or negative valence of a stimulus to structures involved in motivational processes.

3.1.5. The amygdala, a central area for valence coding

Altogether, these studies suggest that specific populations of neurons within the BLA are key components to encode valence as they exhibit neural coding bias, meaning they respond preferentially either to positive or negative valence stimulus (Pignatelli and Beyeler, 2019). They attribute valence for different kinds of sensory stimuli and directly impact emotional responses and behavior. In other words, the amygdala circuit orchestrates behaviors by encoding and transmitting information about the external and internal environment. Thus, amygdala has a central position in the circuits controlling emotional processing to trigger rapid and adapted behaviors.

Importantly, which algorithmic models are used by the amygdala to process valence is still debated (Tye, 2018). Is the predominant model based on the specificities of neurons, specific connectivity, or connectivity that can code for both types of valences but modulated according to the context, or does the modulation of these systems depend on specific receptors that can amplify or reverse a signal? An important issue is to know the impact of psychotropic medications on this valence-coding system. What is certain is that BLA circuits are a dynamic system likely to be adjusted over short or long periods of time depending on the context or the internal state.

3.2. Convergent data in human healthy subjects

Preclinical studies are congruent with data from human brain imaging showing an activation of the amygdala in response to both positive and negative stimuli. For instance, a meta-analysis revealed that negative as well as positive stimuli were likely to stimulate the amygdala (Costafreda et al., 2008). First studies in humans suggested that the amygdala is highly activated by negative stimuli and more specifically during fear response (Davis and Whalen, 2001). This may explain why the field primarily focused on the prominent role of this structure in threatening situations. These early studies were probably biased as it is hard to match the arousing properties of stimuli with negative and positive valence. Moreover, in some studies only the response to the fearful stimuli were analyzed in patients with amygdala lesions (Adolphs et al., 1994). However, when positive stimuli are arousing enough, such as humor or erotic pictures, activation of the amygdala is as important as for negative stimuli. In agreement, Pichon et al. (2015) show a larger activation of the amygdala in response to positive emotional movies, compared with negative ones. In the meta-analysis by Costafreda et al. (2008), it was also reported that all kinds of sensory stimuli can switch on the amygdala, but gustatory and olfactory stimuli have the strongest effect. Moreover, it was recently shown that the human amygdala responds to both pleasant and unpleasant odorant stimuli, covering the complete spectrum of valences (Jin et al., 2015). Conversely, autobiographic recalls are not efficient at activating the amygdala (Costafreda et al., 2008). Task instructions might have an impact, as attentional processing tends to decrease amygdala activity, maybe to ensure maintenance of performance of high-level cognitive function in the presence of disrupting emotional stimuli. The more complex the task is, the more it involves regulatory systems such as the pre-frontal cortex. In addition, some evidence pinpoints hemispheric specialization with a left-lateralization for stimuli involving language and a right-lateralization for masked stimuli (Costafreda et al., 2008).

A bias in the attribution of stimuli valence may explain emotional disturbances during depressive and manic states. An imbalance in the activation of neurons encoding positive and negative valence of the amygdala could represent a mechanism for perception modifications of the environment, changes in emotional responses and their associated inhibited or activated behavior in BD.

4. Suggested lines of research

To guide research perspectives, we propose to deconstruct the mood-based model of BD, characterized by a unidimensional scale ranging from sadness to euphoria, and replace it with an emotional response-based model that can serve as a conceptual framework. This new model we present here relies on the two main features of emotions, intensity and valence. It characterizes the variations of emotional responses during BD mood states using clinical data and allows us to better describe the complexity of emotional processing. Our model is based on a dimensional and translational approach, on a major domain which is emotional processing, as suggested by the RDoC programme to better understand the physiopathology of mental illnesses (Insel, 2014).

Measuring emotional responses in connection with amygdala

activity seems to be crucial to better understand the pathophysiology of BD. In pre-clinical studies, animal models of depression and mania could help to assess the existence of perceptual biases and to understand their mechanisms.

Concerning clinical assessment, it would be worth developing research on variations in emotional responses in patients considering intensity and valence in a longitudinal way, potentially with digital monitoring, and evaluate them during the different mood episodes.

Until now, the strongest data on emotional bias existing in BD patients rely on facial emotional expression recognition. However, this remains a complex task that requires complex cognitive treatment, potentially activating the amygdala to a lower level. Studying the valence attribution to simpler stimuli could be a good way to understand how congruent emotions are generated.

About imaging experiments, it would be relevant to distinguish the activation of the different amygdala nuclei to see if human studies are consistent with animal data. Recent developments in high-resolution and high-field MRI allow for a reliable delineation and functional recording of amygdala sub-nuclei in humans, but it has not yet been applied to BD (Saygin et al., 2017). Finally, even if a systematic review synthetizes data on resting-state functional connectivity in BD patients during remission, we lack knowledge on functional connectivity between the amygdala and its projection areas involved in valence processing during acute episodes (Li et al., 2015; Man et al., 2019).

This research field provides new avenues to explore the pathophysiology of mood disorders (depression and BD) but also treatment responses. Lithium, which is the gold standard of BD treatment, modifies the amygdala structurally and functionally (Hartberg et al., 2015; Strakowski et al., 2016). However, some patients do not respond to lithium and others have side effects that require its discontinuation (Licht, 2012). On the other hand, a large proportion of depressed patients (30 %) do not respond to monoaminergic antidepressants (AD). Interestingly, it has been shown that AD may act to restore the balance between positive and negative emotional processing early in treatment, prior to mood improvement (Harmer et al., 2017). For example, 7 days of AD or even an acute dose were found to increase the perception of ambiguous faces as happy and the recall of positive self-referent words in both healthy volunteers and depressed patients compared to placebo (Harmer et al., 2009). This raises the question whether the restoration of emotional bias is a final pathway to all AD for the restauration of mood, and if early emotional bias restoration could predict it delayed response.

If the mechanisms explored are crucial in the pathophysiology of BD and its recovery, it will become essential to test new molecules on their ability to change valence attribution in very early phases (pre-clinical) of the development and phase I in human. The slow onset, unclear biological markers, and variable clinical efficacy even of approved psychiatric drugs makes the potential efficacy of candidate drugs difficult to measure and has led many pharmaceutical companies to withdraw from drug development. Biomarkers that capture how effective drugs modulate the brain's functional anatomy could prioritize candidate compounds for large clinical trials, thus improving the productivity and cost-effectiveness of drug development.

5. Conclusion

Recent literature, with extremely converging data, highlights the essential role of the amygdala in attributing the stimuli's valence, influencing emotional and behavioral responses. These data lead us to question the limits of current bipolar models in which the amygdala is involved as a whole, without considering its diversity and complexity. An imbalance in the activation of neurons preferentially encoding either positive or negative valence could have a great impact in the global perception of the environment, thus change dramatically emotional responses and their associated inhibited or activated behaviors.

We propose an original, emotion-based model to better describe the different mood episodes that could be completed with assessment of other dimensions like sensory perception or motricity, to help classify BD patients within homogeneous groups, probably sharing the same pathophysiology. A better understanding of the fundamental dimensions of BD should allow us to propose more personalized treatments. For now, the genetically identified neurons in the rodent amygdala could be the starting point to develop specific drugs targeting the emotional dimension.

Exploring the mechanisms of altered emotional processing would be of great help to understand the global outcome of BD. Many patients have progressive disappearance of manic phases with more depressive episodes that become longer and more resistant to treatments, suggesting a progressive loss of neuronal activity encoding positive valence.

Emotional bias is a major component of BD and valence assignment can be assessed both in humans and animal models. Thus, it represents a tremendous opportunity to better understand the pathophysiology of BD and the response to treatment.

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Declaration of Competing Interest

Authors have no conflict of interest for this review.

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