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Emotional dysfunction as a marker of bipolar disorders

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1. ABSTRACT

Background assessment of emotional reactivity, defined as rapid emotional responses to salient environmental events, has been neglected in mood disorders. This article reviews data showing the relevance of using emotional reactivity to better characterize bipolar mood episodes. Method We reviewed clinical data on emotional reactivity during all phases of bipolar disorders (euthymic, manic, mixed and depressive states) and brain-imaging, neurochemical, genetic studies related to emotional reactivity disturbances. Result Euthymic bipolar patients show mild abnormalities (hypersensitivity to emotional stimuli and higher arousability) in comparison to controls. Both manic and mixed states are characterized by a significant increase in emotional reactivity. Furthermore, emotional reactivity may discriminate between two types of bipolar depression, the first being characterized by emotional hypo-reactivity and global behavioral inhibition, the second by emotional hyper-reactivity. Brain-imaging studies can help to identify the underlying mechanisms involved in disturbances of emotional reactivity. Conclusion Emotional reactivity can be used to refine more homogeneous pathophysiological subtypes of mood episodes. Future research should explore possible correlations between biomarkers, response to treatments and these clinical phenotypes.

2. INTRODUCTION

Little is known about the interaction between mood and emotional reactivity in people who suffer from major affective disorders (major depressive disorder or bipolar disorder). Mood is a diffuse feeling state that lasts hours, days, or longer, while emotions are short-lived responses to stimuli that elicit adaptive responses (1). Emotional reactivity refers to the threshold for, and magnitude of, emotional responses to these salient stimuli. These emotional responses typically involve changes in several response systems, including perception, feelings, expressive behavior, and peripheral and central physiology. Emotional regulation may be part of an individual's coping style, while emotional dysregulation may impair functioning and be associated with a psychiatric disorder. However, the diagnostic criteria for mood disorders only center on sustained mood disturbances i.e., sadness in depressive episodes and elevated, expansive, or irritable mood in manic episodes (2).

Historically, most studies of affective disorders focused on mood characteristics; the study of emotion is only a recent development in this area, fostered by tremendous advances in understanding the basic science of emotion (3). Moreover, the advent of neuroimaging techniques has made it possible to examine the neural

circuitry mediating emotional responses and emotion regulation. An increasing number of studies show that mood disorders are associated with specific structural and functional abnormalities in the neural systems regulating emotion (4). Ironically, then, researchers use fMRI to study the pathophysiology of mood disorders, but to do so they use paradigms that rely on evoking emotional responses, rather than moods, because the time frame of emotions is particularly well-suited for study within the fMRI environment. Therefore, when interpreting the results of functional brain-imaging studies in mood disorders, it is important to understand the links between mood episodes and emotional reactivity. As a corollary, more research is needed on the nature of emotional reactivity in patients with mood disorders.

Moods and emotions appear to be interconnected in that moods may potentiate emotions of a similar type (e.g. sad mood exacerbates emotional reactivity to negative stimuli). However, some data do not support this hypothesis (5), and the relationship between mood and emotional reactivity in bipolar disorder is complex since some episodes are associated with both depressed and elevated mood (mixed states, dysphoric mania).

The purpose of this review is to better understand interactions between mood episodes and emotional reactivity. First, we review the clinical data on emotional reactivity in all phases of bipolar disorder (euthymic, manic, mixed and depressive states) and in major depressive disorder. We have classified data as those obtained using clinical tools (mostly self-reports) and those obtained from mood induction experiments or tasks exploring the interference of emotional information with cognitive processes. Second, we review results from brain-imaging, neurochemical, and genetic studies that can help to elucidate the pathophysiology of the disturbed emotional reactivity in bipolar disorder. Finally, using emotional reactivity as a key dimension, we propose a new model to better define bipolar disorders that could be useful in guiding both pathophysiological and pharmacological studies by providing more homogeneous sub-groups.

3. CLINICAL DATA REGARDING EMOTIONAL REACTIVITY IN BIPOLAR AND MAJOR DEPRESSIVE DISORDERS

3.1. Emotional reactivity in euthymic bipolar patients

Many studies indicate that, even during remission, most bipolar patients continue to display symptoms, including sleep disturbance (6), impulsivity (7), or cognitive impairment (8). Here we review studies demonstrating that emotional dysregulation may also be characteristic of this inter-episodic period.

3.1.1. Self-report studies

In a review, Johnson (9) reported that sensitivity to incentive stimuli measured with the BAS (10) in euthymic bipolar patients is greater than that of healthy controls. He also suggests that emotional reactivity and instability are robust predictors of relapse after life stressor.

To test the sensitivity of euthymic bipolar patients to daily life-events, we evaluated euthymic bipolar patients (type I and II) and control subjects using two self-rating scales, the Affective Lability Scale (ALS) (11) and the Affect Intensity Measure (AIM) (12). ALS items assess the subject's perception of their ability to shift from what they consider to be their normal (euthymic) mood to affective states such as anger, depression, elation and anxiety over a short time frame (a day, a few hours or even a few minutes). It measures the rapid instability of mood. AIM, more focused on the intensity of emotional responses, assesses individual differences in emotional reactivity regardless of the hedonic tone of the stimuli. Items include statements such as, "When I solve a small personal problem, I feel euphoric" and "When I do feel anxiety, it is normally very strong". The two scales were built to assess affective dimensions as traits independent of clinical status. Although they assess different aspects of emotional responses, these two scales are highly correlated since the higher the reactivity, the higher the lability (13).

We found that affective intensity and lability of emotions in response to daily life events were markedly higher in euthymic bipolar subjects (n=179) than controls (n=86) (respectively $p=0.006$; and $p<0.0001$) (13). Compared to controls, bipolar patients report being more reactive in daily life to both pleasant and unpleasant emotional stimuli.

Using an experience sampling method, Myin-Germeys *et al.* (14) found that bipolar patients differ from those with major depression in their emotional reactivity to daily life stress. Specifically, they found that, compared to controls, patients with history of major depressive episodes had increased negative emotional reactivity and, surprisingly, patients with bipolar disorder had decreased positive affect (14). However, in this study bipolar patients in partial remission were included, meaning that sub-syndromal depressed symptomatology might have influenced the results.

Several studies have assessed the relationship between personality and bipolar disorder. Two personality dimensions, neuroticism and extraversion, have received particular attention. Neuroticism is characterized by proneness to anxiety, emotional instability, and self-consciousness, whereas extraversion involves positive emotionality, energy, and dominance (15). Thus, these two personality traits encompass emotional reactivity, focused on the negative side for neuroticism and on the positive side for extraversion. Taken together, these studies have reported inconsistent findings with bipolar patients having higher, equal or lower neuroticism or extraversion scores than control subjects (16). When compared to unipolar patients, patients with bipolar disorder have had higher, lower, or equal neuroticism scores, and equal or higher extraversion scores (16). These mixed results might be explained in part by the fact that subsyndromal symptoms, which are very common in patients with bipolar disorder, can influence self-reports of personality dimensions. It is possible that examinations of more focused traits, such as emotional reactivity, might yield more consistent results.

3.1.2. Experimental studies

In addition to self-report, emotional responses can be measured with standardized behavioral paradigms. In the experimental setting, emotions may be triggered by emotional induction tasks e.g., those including exposure to images or films with different valences (positive, negative or neutral). Patients' responses to stimuli can be assessed through their self-reported perception of the stimuli (typically, valence and arousal) and through the measurement of autonomic nervous system (ANS) responses. Measures of ANS responses include variations in skin conductance or cardiac vagal tone, and startle eyeblink modulation.

Other tasks, such as the affective go/no go or the emotional Stroop, assess the impact of emotion on cognitive function. During the affective go/no go, an adaptation of classic go/no go paradigms, subjects have to respond as quickly as possible to target stimuli and withhold responses to distracter stimuli. In affective go/no go paradigms, some of the distracter stimuli have emotional content. The emotional Stroop task requires subjects to name, as fast as possible, the printed colors of both neutral and emotional words. In both tasks, differences in response time between trials with neutral vs. emotional stimuli can be used to measure the degree of interference from the emotional stimuli.

Using an emotional induction task, we have shown that euthymic bipolar patients assigned the same valence and arousal to positive and negative pictures as did control subjects. However, bipolar patients perceived neutral images as more pleasant and arousing than did controls. The startle reflex was concordant with self-assessment, as neutral pictures triggered a stronger startle reflex in euthymic bipolar patients than in controls (17). The same responses between bipolar and control subjects, in the case of positive and negative pictures, might represent a ceiling effect.

Using both a classical and an emotional Stroop tasks, attentional deficits and emotional bias were reported in manic, depressed and euthymic bipolar patients when compared to healthy subjects since all patients were slower on neutral, positive and negative conditions (18). These findings suggest that bipolar patients demonstrate impaired performance on emotionally salient attentionally demanding tasks.

These data, though admittedly limited, suggest that, relative to controls, euthymic bipolar patients may exhibit increased reactivity to emotional stimuli, when reactivity is measured by self-report, response to emotion induction, or the impact of emotional stimuli on cognition. More studies are needed, and one challenge for such studies is that, even during euthymic periods, many patients with bipolar disorder experience mild depressive or manic symptoms that may impact on the dependent variables being measured. Moreover, the cross-sectional design of these studies does not allow investigators to test the stability of these measures, and no studies have examined the impact of pharmacological treatment. Studies in unaffected relatives could help to rule out the impact of treatment while also identifying possible risk markers. However, there is a major lack of studies including first-degree relatives or subjects at risk for bipolar disorders to clarify whether a mild emotional hyperreactivity can be considered as a marker of vulnerability.

3.2. Emotional reactivity during manic and mixed episodes

Manic episodes are characterized by euphoric or irritable mood, accompanied by symptoms such as distractibility, increased impulsivity and a decreased need for sleep (1). Patients in this acute mood state often engage in behaviors with such an intensity that the potential for harmful consequences is high. These disturbed behaviors can be in part linked to increased emotional reactivity.

3.2.1. Self-report studies

As there was no clinical tool in use for the assessment of emotional reactivity in mood states, we developed and validated the dimensional MATHYS (Multidimensional Assessment of Thymic States) self-rated scale. This scale was built a priori, with five clinically relevant quantitative dimensions (emotional reactivity, cognition, motivation, psychomotor agitation or retardation and sensory perception), which vary from inhibition to activation. Using this scale, all bipolar mood states (manic, hypomanic, mixed and depressive episodes) can be evaluated as a function of a total score measuring global levels of behavioral activation/inhibition and a sub-score assessing emotional reactivity (hyper/hyporeactivity) (19). The scale is a visual analog scale including 20 items related to how the individual felt during the previous week. The English version of the scale can be found at this link: (http://www.biomedcentral.com/content/supplementary/1471-244X-8-82-S1.doc) .

Using the MATHYS, we have observed that manic and mixed episodes are characterized by a high global level of behavioral activation and high emotional hyperreactivity. Patients reported experiencing all emotions with a greater intensity than usual (20). Although no differences in the level of emotional reactivity are reported by manic vs. mixed patients on the MATHYS scale, mixed patients complain more about negative affect (20).

3.2.2. Experimental studies

In an emotion induction study, we compared 33 manic patients with 33 matched euthymic patients and 33 healthy control subjects. Subjects rated the arousal and valence of pictures extracted from the International Affective Picture System. The level of arousal in response to positive, negative, and neutral pictures was higher in manic patients than in euthymic patients and healthy subjects (21). These data suggest that manic episodes may be characterized by emotional hyper-reactivity to variables of all valences, rather than simply as over sensitivity to positive stimuli.

Elliot and al. (22) used an affective go/no go task during a brain-imaging study to assess how affective valence of words can modulate cognitive processing in patients with mania. Manic patients compared with controls showed differential neuronal responses associated with emotional targets relative to neutral targets. This effect was present for both happy and sad stimuli. Second, using a recall task with

emotional words, Lyon *et al* (23) also reported slower responses for both positive and negative words in manic patients, compared to controls. Finally, Besnier *et al* (2010), using an emotional Stroop task, found that manic patients showed more interferences with both negative, as well as positive, valence words (24).

All together, these data support the conclusion that manic patients are hyperresponsive to negative as well as positive stimuli.

3.3. Evaluation of emotional reactivity during depression

Currently, the same criteria are used to diagnose unipolar and bipolar depressions (1). However, depression is not a homogeneous condition and it is important to distinguish sub-groups in order to choose the most appropriate treatment. In this section, we review studies on emotional reactivity in bipolar and unipolar depression to explore whether this criterion might usefully discriminate them.

3.3.1. Identification of two subtypes of bipolar depression: self-report studies

We used the MATHYS scale to characterize bipolar depression on the basis of global levels of behavioral activation/inhibition and emotional reactivity (19). All patients met DSM-IV criteria for bipolar disorder in an acute depressive phase and did not meet criteria for a mixed episode. Using all the MATHYS items, we performed a cluster analysis, which discriminated two types of bipolar depression. Using as a comparison the mean for euthymia, one type is characterized by behavioral inhibition and emotional hypo-reactivity (n=38/60). The second type of bipolar depression is characterized by mild behavioral over-activity and high emotional reactivity (n=22/60). This dimensional analysis indicates that bipolar depression is not a homogeneous group.

Using a Likert scale (never to constantly), the MATHYS scale can also be used to assess the frequency of the emotions reported by the patient (sadness, joy, irritability, panic, anxiety, anger, exaltation) during the last week (25). Compared to depression with emotional hypo-reactivity, depression with emotional hyper-reactivity was associated with higher irritability ($p<0.0001$), panic ($p<0.0001$), anxiety ($p<0.0001$), anger ($p<0.001$), and exaltation ($p<0.0001$). Globally, these patients are more sensitive to their environment and have more affective lability than those with depression with an emotional hyporeactivity. Thus one subtype of bipolar depression is associated with emotional hyporeactivity (patients are less sensitive, whatever the valence of stimuli), and the other with emotional hyper reactivity (patients frequently report negative affects but are still able to react to positive stimuli).

Data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) indicates that: i) two-thirds of bipolar depressed patients had concomitant manic symptoms; ii) compared to patients who did not experience concomitant manic symptoms during depression, those who did had more severe illness with onset at an early age, more bipolar I subtype, more rapid cycling in the past year, and a more frequent history of suicide attempts;, and iii) bipolar depression with concomitant manic symptoms is associated with antidepressant treatment-emergent mania or hypomania (26,27). These findings highlight the clinical need for improved assessment of the differences between pure bipolar depression and that associated with manic symptoms, which may help in predicting short-term prognosis and in selecting appropriate medications. To compare our results with those of the STEP-BD, we categorized bipolar depression according to the presence or absence of manic symptoms and assessed these two sub-groups with the MATHYS (28). Depressive episodes with manic symptoms had higher levels of activation and showed emotional hyper reactivity, whereas major depressive episodes without manic symptoms showed emotional hypo-reactivity (28). Thus, both our dimensional approach and the categorical model of STP-BD find that bipolar depressions are not homogeneous.

3.3.2. Emotional reactivity in major depressive disorder: self report and experimental studies

Rottenberg's Emotion Context Insensitivity (ECI) model states that depressed individuals show reduced reactivity to all emotional cues, regardless of valence (5). The ECI model is derived from the evolutionary hypothesis that describes depression as a defensive motivational state which fosters environmental disengagement (29). According to this hypothesis, depressed mood states evolved as internal signals to bias organisms against action in adverse situations where continued activity was potentially dangerous.

In a meta-analysis of 19 studies, Byslma *et al.* (30), evaluated the emotional reactivity of healthy individuals and individuals with major depressive disorder. This meta-analysis only included studies that used DSM criteria for major depressive disorder (MDD) and elicited emotion in a well-controlled manner. The meta-analysis included studies that assessed positive and negative emotional reactivity using self-reported experience, expressive behavior, and/or peripheral physiology. The authors found that MDD was characterized by reduced emotional reactivity to both positively and negatively valenced stimuli, although this reduction was larger for positive stimuli. The authors concluded that the findings of the meta-analysis did not support the concept of mood-congruent processing bias, in which depression would tend to bias stimulus processing towards negative information (31).

4. SUMMARY OF CLINICAL DATA ON EMOTIONAL REACTIVITY DURING MOOD DISORDERS

Mild emotional hyperactivity may be characteristic of bipolar patients during euthymia and could be considered as a marker of vulnerability, although data regarding the latter are limited. During manic and mixed states, there is consistent emotional hyper-reactivity and patients experience all emotions with a greater intensity than in the euthymic state. Intuitively, it makes sense that emotional reactions are stronger when they are congruent with a pre-existing mood. However, contrary to this intuitive idea, even during euphoric mania, patients can become irritable and even violently aggressive. This is contrary to the idea of mood-congruent processing bias and instead supports the notion of global emotional dysregulation during mania. In bipolar depression, the characterization of patients according to emotional reactivity allows the identification of two subtypes:

one associated with emotional hyporeactivity and the other with emotional hyper reactivity, the latter probably belonging to a broad spectrum of mixed states.

5. BRAIN IMAGING AND ABNORMAL EMOTIONAL REACTIVITY IN MOOD DISORDERS

Most functional imaging studies in bipolar disorder have used behavioral paradigms that study emotional processing. In particular, the most frequently used designs in brain-imaging studies involve either facial affect recognition tasks (32) or response to emotional stimuli. Neuroanatomic investigations implicate a network of both cortical and subcortical anterior limbic structures in emotion processing. These include the amygdala, ventral striatum, subgenual (ventral) cingulate, ventromedial prefrontal cortex, anterior hippocampus, and anterior insula (33). The prefrontal cortex and amygdala, are two major components of emotion regulatory networks; the former negatively modulates the amygdala response when subjects identify emotional facial expression.

Functional brain-imaging studies in euthymic bipolar disorder patients demonstrate abnormal responses to emotional stimuli and dysfunction in emotional processing circuitry, especially the anterior limbic regions (32). However, neural responses to emotional challenges in euthymic bipolar patients as a function of stimulus valence have been examined in only a few studies. Lawrence *et al* (34) investigated neural activation in response to emotionally salient stimuli in bipolar and MDD patients, and healthy control subjects. Euthymic bipolar patients had elevated subcortical (ventral striatal, thalamic, hippocampal) and ventral prefrontal cortical responses, particularly in response to mild and intense fear, mild happy, and mild sad expressions. Thus, compared with healthy controls and MDD patients, euthymic bipolar patients had increased subcortical and ventral prefrontal cortical responses to both positive and negative emotional expressions. The authors concluded that these results might indicate an enhanced salience of both positive and negative emotional stimuli in euthymic bipolar patients, which may be associated with the increased mood lability observed in these patients. However, there is no study that explores directly the link between emotional reactivity and brain imaging patterns.

To examine the interference of emotional information with cognitive processes, euthymic bipolar patients and healthy comparison subjects underwent functional magnetic resonance imaging (MRI) while performing an emotional go/nogo task. Bipolar disorder patients, compared to healthy controls, exhibited an over activation in ventral-limbic, temporal and dorsal brain structures when they have to inhibited responses to emotional stimuli compared with neutral stimuli (35) However, there was no behavioral difference between groups.

All these results are consistent with the conclusion that increased emotional reactivity is characteristic of euthymia patients with bipolar disorder.

Studies during mood states in bipolar disorder patients have also demonstrated increased subcortical limbic activity to emotional stimuli. Chen *et al.* (36) report that depressed and manic patients overactivate brain regions in response to facial expressions of happiness and sadness, and both groups showed increased neural responses to facial expressions of fear. The pattern of increased subcortical limbic activity to positive emotional stimuli may distinguish bipolar from unipolar depressed patients. Indeed, abnormal amydala-prefrontal effective connectivity to happy faces may distinguish bipolar depression from MDD (37). However, since, as noted above, bipolar depression is unlikely to be a homogenous group, there is a need to better characterize which kind of bipolar depressed patients were included in the study in order to be able to properly compare them.

Future studies should subtype individuals with bipolar depression, as described above, in an effort to ascertain whether these two subtypes of bipolar depression are associated with different neural activation patterns in response to emotional stimuli.

6. NEUROCHEMICAL SYSTEMS, GENES AND EMOTIONAL REACTIVITY

A number of abnormalities within the amine neurotransmitter systems have been identified in bipolar disorder. However, little is known about relationships between these abnormalities and emotional reactivity, since this feature has not typically been characterized. Nonetheless, potential clues may be derived from data concerning anhedonia and the dopaminergic system. Anhedonia is defined as loss of interest and pleasure, with lack of reactivity to positively valenced emotional stimuli. Anhedonia might be considered to be a component of emotional hypo reactivity, in that the latter involves globally blunted responsiveness. Studies show associations between anhedonia and dysfunction in the brain reward system, which is mediated primarily by dopaminergic mechanisms (38). Thus, reduced ventral striatum activity during performance of a reward task is associated with anhedonia in depression (39,40).

Conversely, the post-partum blues may be a potential model to explore transient emotional hyper-reactivity. This specific period is characterized by minor mood disturbances affecting many women a few days after delivery (41). The pattern of symptoms and their time course, peaking between the third and fifth post-partum days, suggest that the underlying causes include biological determinants. Although the post-partum blues have often been considered to be a mild depressive state, it is better defined as a transient period characterized by emotional hyper-reactivity and affective lability (42). We performed a study designed to evaluate the possible role of the serotonin system during this period by assessing brain tryptophan availability. Post-partum blues were associated with a decrease in brain tryptophan availability, and the intensity of symptoms correlated significantly ($p<0.05$) with tryptophan availability (43).

Turning to genetic data, the association of the serotonin transporter (5-HTT) gene with bipolar disorder has been investigated in a series of studies because the initial studies showed a positive association between the short allele

and the disorder. However, recent meta-analyses have shown no or only a small association between bipolar disorder and this polymorphism (44,45,46). However, three recent independent meta-analyses have demonstrated a significant association between the short allele of the gene and neuroticism or harm avoidance (47,48,49). The 5-HTT gene therefore may be more strongly linked to affective instability rather than to a specific disorder.

Many others genes can be involved in emotional regulation and the purpose of this section is not to be exhaustive. The findings on 5-HTT illustrate the possible evolution in genetic studies, showing first an association between a gene and a disease that turn out to be likelihood an association with a trait.

7. CONCLUSION

In this review, we have highlighted the importance of emotional reactivity in the characterization of all phases of bipolar disorder. Self-report and brain imaging studies suggest that euthymia may be characterized by hypersensitivity to emotional stimuli. Major increases of emotional reactivity are a key component of manic and mixed mood states, as patients are more likely than controls to respond with exaggerated intensity to emotional stimuli of all valences.

Hasler *et al.* (50) have tried to explain the limited success of studies on mechanisms underlying major depression and have raised questions concerning the definition of relevant phenotypes. They propose a dissection of the depressive phenotype into key components to allow the more precise definitions of putative psychopathological intermediate phenotypes. They also suggest the development of a new classification system to reduce the heterogeneity of depression, as this has been a major barrier to understanding the mechanisms of the disease. Our model of assessing emotional reactivity together with a global level of behavioural activation is a step in this direction. When developing a new classification system, it is important to avoid including criteria with opposing states (e.g. insomnia and hypersomnia, psychomotor agitation and retardation, or decrease and increase in appetite) under the same definition because doing so increases the probability that research studies will include patients with heterogeneous clinical features that are mediated by diverse mechanisms, leading to false negative results.

Thus, pathophysiological research and clinical trials have to take into account the heterogeneity of depression, and bipolar depression can no longer be considered to be a single entity. In terms of research on mechanisms, one important issue is to know if both phenotypes are stable across episodes in patients. Currently there are no data available. Large longitudinal data sets are needed to address this question.

Improved clinical characterisation through the definition of more homogeneous groups could help identify the most effective class of pharmacological treatment for each subtype. Current guidelines for treatment of bipolar depression propose, without any specification, a mood stabilizer, antidepressant or antipsychotic (51,52). It is unlikely that these different medications have the same efficacy in all types of depression. To go further, we need to assess if different clinical phenotypes respond differently to specific treatments. Currently, there is no study using clinical characteristics as potential predictor of response to the various pharmacological treatments. One can hypothesized that pure depression, close to the characteristics of unipolar depression might respond to an association of a mood stabilizer plus an antidepressant. Conversely, hyperreactive depressions might be worsened by antidepressant because they belong to a broad spectrum of mixed states and have a better response to atypical antipsychotics. This point is purely speculative and need to be explored.

Finally, there is also a need to study the impact of medicine on the level of emotional reactivity. Patients under mood stabilizer often complain to become less sensitive. Is it the price they should pay to avoid relapses? Conversely, what are the links between long prescription of antidepressant in bipolar patients, emotional reactivity and rapid cycling or chronic major emotional instability?

As suggested by the research agenda for DSM-V, there is a clear need to translate basic and clinical research findings into a new classification system for psychiatric disorders based upon etiological processes (53). For this reason, we need to: a) define clinically relevant homogeneous groups; b) have appropriate clinical tools to assess these groups; c) establish correlations between biomarkers and the clinical measures for reclassifying the current DSM-IV categories of mood disorders across a continuous spectrum of affective pathology; and d) use these biomarkers and their clinical correlates to guide personalized treatments for individuals across the spectrum of affective disorders.

Our dimensional model for defining mood episodes based on the assessment of emotional reactivity and behavioural activation/inhibition level can help improving characterization of bipolar mood states. We now need to further explore the mechanisms involved in such disturbances using this model.

8. REFERENCES

1. Morris BH, Bylsma LM, Rottenberg J. Does emotion predict the course of major depressive disorder? A review of prospective studies. *Br J Clin Psychol* 48, 255-73 (2009)

2. American Psychiatry Association. Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1994)

3. Debiec J, Díaz-Mataix L, Bush DE, Doyère V, Ledoux JE. The amygdala encodes specific sensory features of an aversive reinforcer. *Nat Neurosci* 13(5), 536-7 (2010)

4. Phillips ML, Ladouceur CD, Drevets WC. A neural model of voluntary and automatic emotion regulation: implications for understanding the pathophysiology and neurodevelopment of bipolar disorder. *Mol Psychiatry* 13 (9), 833-57 (2008)

5. Rottenberg J, Gross JJ, Gotlib IH. Emotion context insensitivity in major depressive disorder. *J Abnorm Psychol* 114 (4), 627-39 (2005)

6. Harvey AG, Schmidt DA, Scarnà A, Semler CN, Goodwin GM. Sleep-related functioning in euthymic patients with bipolar disorder, patients with insomnia, and subjects without sleep problems. *American Journal of Psychiatry* 162 (1), 50–57 (2005)

7. Swann AC, Lijffijt M, Lane SD, Steinberg JL, Moeller FG. Increased trait-like impulsivity and course of illness in bipolar disorder. *Bipolar Disorders* 11 (3), 280-288 (2009)

8. Martinez-Aran A, Vieta E, Colom F, Torrent C, Sanchez-Moreno J, Reinares M, Benabarre A, Goikolea JM, Brugue A, Daban C, Salamero M. Cognitive impairment in euthymic bipolar patients; implications for clinical and functional outcome. *Bipolar Disorders* 6 (3), 224-232 (2004)

9. Johnson SL. Mania and dysregulation in goal pursuit: A review. *Clinical Psychology Review* 25 (2), 241–262 (2005)

10. Carver, C. S., & White, T. L. Behavioral inhibition, behavioral activation, and affective responses to impending reward and punishment: The BIS/BAS scales. *Journal of Personality and Social Psychology* 67, 319–333 (1994)

11. Harvey, PD., Greenberg, BR., Serper, MR. The affective lability scale: development, reliability and validity. *Journal of Clinical Psychology* 45 (5), 786-793 (1989)

12. Larsen, RJ., Diener, E., Emmons, RA. Affect intensity and reactions to daily life events. *Journal of Personality and Social Psychology* 51, 803-814 (1986)

13. Henry C, Van den Bulke D., Bellivier F., Roy I, Swendsen J, M'Baïlara K, Siever L., Leboyer M. Affective lability and affect intensity as core dimensions of bipolar disorders during euthymic period. *Psychiatry Research* 159 (1-2), 1-6 (2008)

14. Myin-Germeys I, Peeters F, Havermans R, Nicolson NA, DeVries MW, Delespaul P, Van Os J. Emotional reactivity to daily life stress in psychosis and affective disorder: an experience sampling study. *Acta Psychiatr Scand* 107 (2), 124-31 (2003)

15. Pervin LA, Cervone D, John OP. Personality, theory and research. John Wiley et Sons. Inc.

16. Goodwin F, Jamison K. Manic-Depressive Illness: Bipolar Disorders and Recurrent Depression. Oxford: Oxford University Press Inc (2nd Revised edition), (2007)

17. M'bailara K, Demotes-Mainard J, Swendsen J, Mathieu F, Leboyer M, Henry C. Emotional hyper-reactivity in normothymic bipolar patients. *Bipolar Disord* 11 (1), 63-9 (2009)

18. Kerr N, Scott J, Phillips ML. Patterns of attentional deficits and emotional bias in bipolar and major depressive disorder. *Br J Clin Psychol* 44, 343-56 (2005)

19. Henry C, M'Bailara K, Mathieu F, Poinsot R, Falissard B. Construction and validation of a dimensional scale exploring mood disorders: MAThyS (Multidimensional Assessment of Thymic States) *BMC Psychiatry* 8:82 (2008)

20. Henry C, M'Baïlara K, Desage A, Gard S, Misdrahi D, Vieta E. Towards a reconceptualization of mixed states, based on an emotional-reactivity dimensional model. *J Affect Disord* 101 (1-3), 35-41 (2007)

21. M'Bailara K, Demotes-Mainard J, Colom F, Swendsen J, Cretu L, Henry C. Emotional hyperreactivity as a core dimension of manic and mixed states. *Psychiatr Res*. In press

22. Elliott R, Ogilvie A, Rubinsztein JS, Calderon G, Dolan RJ, Sahakian BJ. Abnormal ventral frontal response during performance of an affective go/no go task in patients with mania. *Biol Psychiatry* 12, 1163-70 (2004)

23. Lyon HM, Startup M, Bentall RP. Social cognition and the manic defense: attributions, selective attention, and self-schema in bipolar affective disorder. *J Abnorm Psychol* 108 (2), 273-82 (1999)

24. Besnier N, Kaladjian A, Mazzola-Pomietto P, Adida M, Fakra E, Jeanningros R, Azorin JM. Differential response to emotional interference in paranoid schizophrenia and bipolar mania. *Psychopathology* 44 (1), 1-11 (2010)

25. Henry C, M'Baïlara K, Poinsot R, Casteret AA, Sorbara F, Leboyer M, Vieta E. Evidence for two types of bipolar depression using a dimensional approach. *Psychother Psychosom* 76 (6), 325-31 (2007)

26. Goldberg JF, Perlis RH, Bowden CL, Thase ME, Miklowitz DJ, Marangell LB, Calabrese JR, Nierenberg AA, Sachs GS. Manic symptoms during depressive episodes in 1,380 patients with bipolar disorder: findings from the STEP-BD. *Am J Psychiatry* 166, 173-81 (2009)

27. Frye MA, Helleman G, McElroy SL, Altshuler LL, Black DO, Keck PE Jr, Nolen WA, Kupka R, Leverich GS, Grunze H, Mintz J, Post RM, Suppes T. Correlates of treatment-emergent mania associated with antidepressant treatment in bipolar depression. *Am J Psychiatry*166, 164-72 (2009)

28. Henry C, M'Bailara K, Jean-Pierre Lepine JP, Lajnef M, Leboyer M. Defining bipolar mood states with quantitative measurement of inhibition /activation and emotional reactivity. *J Affect Disord* 127 (1-3), 300-4 (2010)

29. Nesse RM. Is depression an adaptation? *Arch Gen Psychiatry* 57 (1), 14-20 (2000)

30. Bylsma LM, Morris BH, Rottenberg J. A meta-analysis of emotional reactivity in major depressive disorder. *Clin Psychol Rev* 28 (4), 676-91 (2008)

31. Elliott R, Rubinsztein JS, Sahakian BJ, Dolan RJ. The neural basis of mood-congruent processing biases in depression. *Arch Gen Psychiatry* 59 (7), 597-604 (2002)

32. Keener MT, Phillips ML. Neuroimaging in bipolar disorder: a critical review of current findings. *Curr Psychiatry Rep* 9 (6), 512-20 (2007)

33. Phillips ML, Drevets WC, Rauch SL, Lane R. Neurobiology of emotion perception II: Implications for major psychiatric disorders. *Biol Psychiatry* 54 (5), 515-28 (2003)

34. Lawrence NS, Williams AM, Surguladze S, Giampietro V, Brammer MJ, Andrew C, Frangou S, Ecker C, Phillips ML. Subcortical and ventral prefrontal cortical neural responses to facial expressions distinguish patients with bipolar disorder and major depression. *Biol Psychiatry* 55 (6), 78-87 (2004)

35. Wessa M, Houenou J, Paillère-Martinot ML, Berthoz S, Artiges E, Leboyer M, Martinot JL. Fronto-striatal overactivation in euthymic bipolar patients during an emotional go/nogo task. *Am J Psychiatry* 164 (4), 638-46 (2007)

36. Chen CH, Lennox B, Jacob R, Calder A, Lupson V, Bisbrown-Chippendale R, Suckling J, Bullmore E. Explicit and implicit facial affect recognition in manic and depressed States of bipolar disorder: a functional magnetic resonance imaging study. *Biol Psychiatry* 59 (1), 31-9 (2006)

37. Almeida JR, Versace A, Mechelli A, Hassel S, Quevedo K, Kupfer DJ, Phillips ML. Abnormal Amygdala-Prefrontal Effective Connectivity to Happy Faces differentiates Bipolar from Major Depression. *Biol Psychiatry* 66 (5), 451-9 (2009)

38. Nestler EJ, Carlezon WA Jr. The mesolimbic dopamine reward circuit in depression. *Biol Psychiatry* 59 (12), 1151-1159 (2006)

39. Pizzagalli DA, Holmes AJ, Dillon DG, Goetz EL, Birk JL, Bogdan R. Reduced caudate and nucleus accumbens response to rewards in unmediated individuals with major depressive disorder. *Am J Psychiatry* 166, 702–710 (2009)

40. Wacker J, Dillon DG, Pizzagalli DA. The role of the nucleus accumbens and rostral anterior cingulated cortex in anhedonia: Integration of resting EEG, fMRI, and volumetric techniques. *Neuroimage* 46, 327–337 (2009)

41. Hapgood CC, Elkind GS, Wright JJ. Maternity blues: phenomena and relationship to later post partum depression. *Aust N Z J Psychiatry* 22 (3), 299-306 (1988)

42. M'baïlara K, Swendsen J, Glatigny-Dallay E, Dallay D, Roux D, Sutter AL, Demotes-Mainard J, Henry C. Baby blues: characterization and influence of psycho-social factors. Encephale 3, 331-6 (2005)

43 . M'Baïlara K, Henry C, Lestage J, Launay JM, Parrot F, Swendsen J, Sutter AL, Roux D, Dallay D, Demotes-Mainard J. Decreased brain tryptophan availability as a partial determinant of post-partum blues. *Psychoneuroendocrinology* 31 (3), 407-13 (2006)

44. Lotrich FE, Pollock BG. Meta-analysis of serotonin transporter polymorphisms and affective disorders. *Psychiatr Genet* 14 (3), 121-9 (2004)

45. Cho HJ, Meira-Lima I, Cordeiro Q, Michelon L, Sham P, Vallada H, Collier DA. Population-based and family-based studies on the serotonin transporter gene polymorphisms and bipolar disorder: a systematic review and meta-analysis. *Mol Psychiatry*;10 (8), 771-81 (2005)

46. Lasky-Su JA, Faraone SV, Glatt SJ, Tsuang MT. Meta-analysis of the association between two polymorphisms in the serotonin transporter gene and affective disorders. *Am J Med Genet B Neuropsychiatr Genet*. 133B (1), 110-5 (2005)

47. Schinka JA, Busch RM, Robichaux-Keene N. A meta-analysis of the association between the serotonin transporter gene polymorphism (5-HTTLPR) and trait anxiety. *Mol Psychiatry* 9 (2), 197-202 (2004)

48. Sen S, Burmeister M, Ghosh D. Meta-analysis of the association between a serotonin transporter promoter polymorphism (5-HTTLPR) and anxiety-related personality traits. *Am J Med Genet B Neuropsychiatr Genet* 127B (1), 85-9 (2004)

49. Munafo MR, Clark T, Flint J. Does measurement instrument moderate the association between the serotonin transporter gene and anxiety-related personality traits? A meta-analysis. *Mol Psychiatry* 10 (4), 415-9 (2005)

50. Hasler G, Drevets WC, Manji HK, Charney DS. Discovering endophenotypes for major depression. *Neuropsychopharmacology*. 29 (10), 1765-81 (2004)

51. Yatham LN, Kennedy SH, Schaffer A, Parikh SV, Beaulieu S, O'Donovan C, MacQueen G, McIntyre RS, Sharma V, Ravindran A, Young LT, Young AH, Alda M, Milev R, Vieta E, Calabrese JR, Berk M, Ha K, Kapczinski F. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD) collaborative update of CANMAT guidelines for the management of patients with bipolar disorder: update 2009. *Bipolar Disord* 11 (3), 225-55 (2009)

52. Malhi GS, Adams D, Lampe L, Paton M, O'Connor N, Newton LA, Walter G, Taylor A, Porter R, Mulder RT, Berk M; Northern Sydney Central Coast Mental Health Drug & Alcohol; NSW Health Clinical Redesign Program; CADE Clinic, University of Sydney. Clinical practice recommendations for bipolar disorder. *Acta Psychiatr Scand Suppl* 439, 27-46 (2009)

53. Vieta E, Phillips ML. Deconstructing bipolar disorder: a critical review of its diagnostic validity and a proposal for DSM-V and ICD-11. *Schizophr Bull* 33 (4), 886-92 (2007)

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