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MOOD AND ANXIETY DISORDERS (KL PHAN, SECTION EDITOR)

Current Neural and Behavioral Dimensional Constructs Across Mood Disorders

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Abstract Our understanding of the underlying neurobiology for mood disorders is still limited. We present an integrated model for conceptualizing and understanding mood disorders drawing upon a broad literature. This integrated model of emotion processing and regulation incorporates the linguistic constructs of the Research Domain Criteria (RDoC) initiative. In particular, we focus on the positive valence domain/circuit (PVC), highlighting recent reward research and the negative valence domain/circuit (NVC), highlighting rumination. Furthermore, we also illustrate the Cognitive Control and Problem Solving (CCaPS) circuit, which is heavily involved in emotion regulation, as well as the default mode network (DMN) and interactions between circuits. We conclude by proposing methods for addressing challenges in the developmental study of mood disorders, including using high-risk design that incorporates risk for many disorders.

Keywords Depression · Bipolar · RDoC

Introduction

Neuroimaging and behavioral research in mood disorders is coalescing on a transdiagnostic, heterogeneous framework for understanding risk mechanisms leading to the expression of mental illness. The present review expands upon a conceptual framework for depression and related mood disorders offered by Phillips and colleagues [1, 2], presents our integrative model for salience, valence, and executive networks in mood disorders, and adds detail for valence as well as explicit points of measurement and intervention. In addition to reviewing recent literature highlighting the relevance of positive and negative appraisal systems as they relate to dysfunction in mood disorders, we expand on the fundamental and interactive role of cognitive control in the expression of disease. We also touch upon recent research on the default mode network (DMN) as it relates to our model and circuit-based function.

This model for executive and salience networks in mood disorders (Fig. 1) offers a dynamic account of how multiple risk factors lead to mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD). Similar to current diagnostic systems, individuals who meet criteria for MDD may have fundamentally divergent risk and protective factors leading to the same mood disorder. As a simple example, those with melancholic depression share few symptoms with individuals displaying atypical depression. As such, it is unwise to expect that the neural and behavioral bases supporting these subtypes would be the same or even similar. Our model is based on research denoting the brain circuits involved in emotional processing, cognitive control, and in the mind's "default" state, as well as the interactions between these circuits and burgeoning evidence that the behaviors and supporting circuitry evidenced in mood disorders are disrupted. We incorporate terminology used by the National Institutes of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative, with a primary focus on salience networks (SN) including positive and negative valence circuits (PVC and NVC, respectively), cognitive systems including Cognitive Control and Problem Solving (CCaPS), and the DMN.

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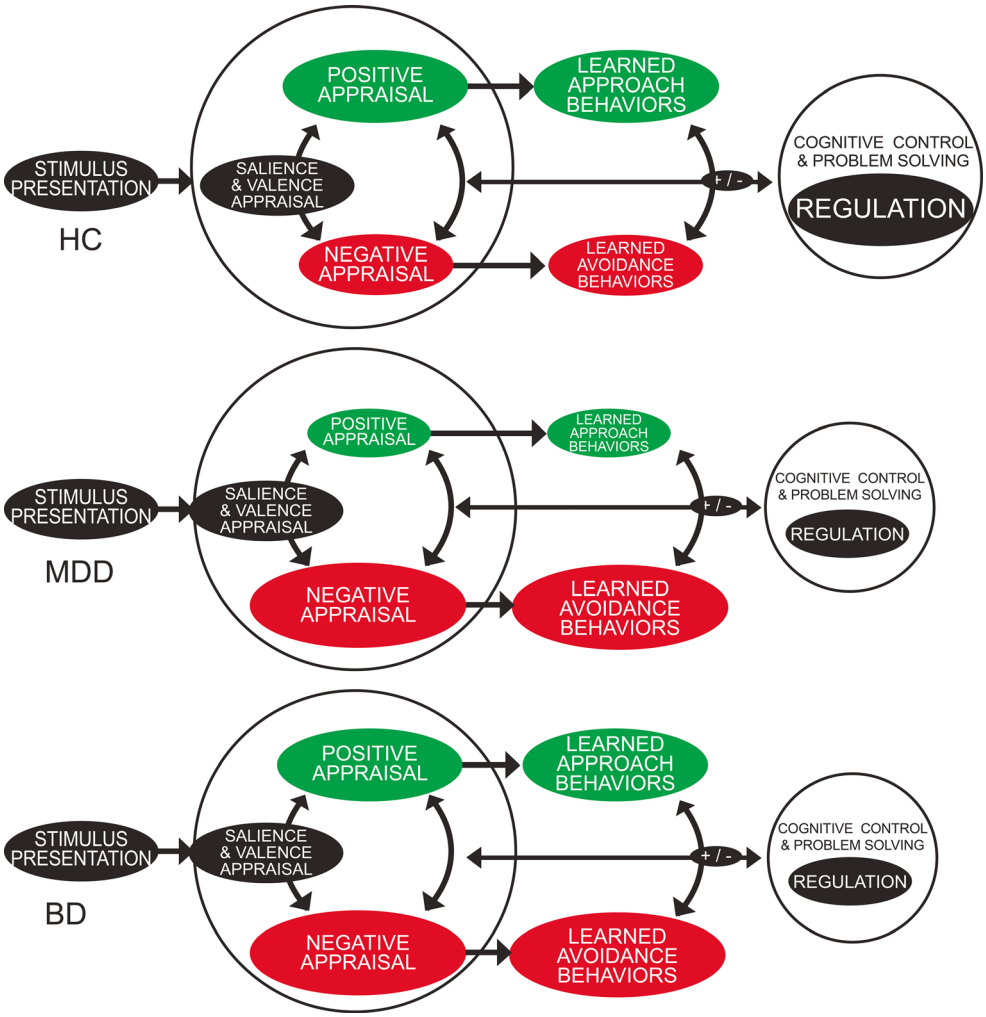

Fig. 1 Model for executive and salience networks in mood disorders illustrating the preferential processing for positive stimuli (positive valence circuit; PVC) in healthy controls (HCs), which leads to a larger available repertoire of approach behaviors and enhanced regulatory capacities [through Cognitive Control and Problem Solving (CCaPS)] for appraisal, reappraisal, and the appropriate selection of alternative responses. In mood disorders, including major depressive disorder (MDD) and bipolar disorder (BD), the preferential strength of the PVC is diminished and so is CCaPS regulatory capacity, whereas the negative valence circuit (NVC) and related avoidance behaviors are strengthened and over-represented. The PVC may be over- or under-utilized in BD and MDD, respectively

The PVC and NVC are rapid, efficient feature detectors that tag emotional, salient, and novel stimuli for further classification and processing [3–5]. These salience and valence processing steps help rapidly filter significant amounts of external and internal stimuli. In contrast, the CCaPS network is a slower, often more deliberate circuit that can engage in the modulation or regulation of emotion [6, 7••, 8]. Moreover, there are intermediate stages of processing and response preparation where learned experience and habits can form prepotent response tendencies to certain types of external and internal stimuli and milieus. From a disease expression standpoint, overlearned response tendencies and emotional regulation need not *all* be dysfunctional. Environmental contributions and interactions between environment and genetic predispositions can vary the risk for and expression of disease dramatically. A mood disordered and healthy individual could have the exact same neural and behavioral profile, yet differ only in environmental stressors. This traditional stress–diathesis model is not well integrated into neuroimaging studies of mood disorders, nor has a multi-risk diathesis stress framework consistently been applied. The model presented here allows for fundamentally different loadings in the neural and behavioral risk factors observed in any mood disorders (AMD) relative to non-disordered groups.

The NVC and PVC consist of overlapping fronto-limbic networks supporting the detection of salience and valence processing [9]. The NVC is comprised of the ventral, central, and lateral amygdala, portions of the orbito-frontal cortex (OFC), and the posterior nucleus accumbens, which may also be more responsive to negative stimuli [10]. The NVC responds rapidly with low signal discrimination ability [11–13] and pre-activates learned response contingencies [12, 14, 15]. For example, the well-known fight or flight mechanism as a nearly automatic response contingency set that can be triggered in tens of milliseconds.

In parallel, the PVC comprises subcortical regions such as the nucleus accumbens, ventral pallidum, basal ganglia, and OFC [16, 17]. The PVC responds fairly rapidly, with low signal discrimination, and relies upon and is predicated toward developing learned contingencies. The PVC is somewhat subordinate to the NVC, in that its responses and functioning can be subverted under threat, and it responds more slowly

[18]. Depending on the valence, salience, and intensity of a given stimuli, appropriate response contingencies from short- and long-term memory are recalled and drawn upon [19]. Approach and/or avoidance responses are selected from amongst pre-potent responses, unless CCaPS is substantially engaged [20, 21]. Thus, the PVC and NVC reside in partially overlapping brain regions, but represent distinct processing streams [9, 10, 22], and are thought to work in dynamic opposition.

The NVC and PVC interact with fronto-parietal circuits involved in cognitive control (CCaPS) and working memory (WM), which normally modulate these circuits and assist in selection of the appropriate response. The CCaPS circuit incorporates a number of regions involved in processing, regulating, and developing learning contingencies that can be incorporated into the present repertoire activated by PVC and NVC. In fact, one of the primary functions of this circuit is to minimize the complex processing that is required in the future [23]. The ability to distill complex environmental sets, integrate those with internal needs, and allow for rapid and efficient signal detection and response preparation, can place an individual at significant advantage over peers. Regions of the prefrontal cortex (PFC) organize and select behavior from response contingencies based upon prior knowledge, learning, and experience. Disruptions or damage to connections between the anterior cingulate cortex (ACC), including the dorsal ACC (dACC), and prefrontal regions have been found to be relevant to depression and diminished cognitive control [24]. Expectations and cost–benefit analyses also play a role in decision making, particularly from the medial and lateral OFC [25], providing an integration node between CCaPS and PVC/NVC. Furthermore, CCaPS can be inhibited by elicitation of emotional responses, either positive or negative [26]. One can conceptualize that NVC has hard-wired capabilities that in a moment may interfere with and trump PVC and CCaPS function. A number of studies have investigated emotional interference effects, although these are methodologically complex and often confounded. We highlight interactions between the PVC, NVC, and CCaPS later in this review.

In addition to disruptions in task-related CCaPS and salience (PVC and NVC) circuits in mood disorders, there is also more recent mood disorder literature highlighting disruptions in the DMN, which is a "resting state" network devoted to internal thought and maintenance processes (e.g., memory consolidation). The DMN is a large-scale network of regions implicated in self-oriented thought patterns [27–29], including rumination [30–32]. Other large-scale intrinsic networks that interact with the DMN include the CCaPS (executive) and PVC/NVC (salience) [33]. Disrupted interactions within and between these networks are hypothesized to support the pathophysiology of MDD [34–36].

Current Research on Negative Valence Domain/Circuit (NVC) Disruption in Mood Disorders

Behavioral studies of NVC abnormalities in depression have often focused on mood congruent memory biases [37–39], negative processing biases [40–42], memory priming [43, 44], face emotion processing [45], and interference effects [46]. A majority of these studies indicate that depressed individuals have difficulty in correctly classifying facial stimuli [45, 47, 48], and exhibit negative memory bias, which is one of the largest effect sizes in comparisons between depressed and non-depressed groups [49].

Functional MRI (fMRI) studies of NVC among individuals with mood disorders have focused heavily on the processing of emotion [50–52], emotionally evocative paradigms related to harsh/negative faces, complex visual scenes and images, films, autobiographical memories, social rejection, and semantic stimuli, some of which may be personally relevant [49, 53–59]. Disruptions to NVC include elevated amygdala, subgenual cingulate, and insula response to threat and diminished capability of those with mood disorders to regulate these responses. This domain is pertinent to our discussion because emotional appraisal and physiological reactivity to emotional stimuli and emotion induction are distinctly different in depressed than in control groups [11, 14, 50]. Furthermore, disruption in neurophysiological response to emotion stimuli is reversible with successful treatment [50, 63, 64]. In fact, the NVC is the most heavily researched in mood disorders and a number of reviews are available that cover these in detail [60–62]. As such, the NVC subdomains are not reviewed exhaustively here, rather we focus on one rapidly emerging aspect of the NVC, rumination.

A recent focus of study within the NVC is the construct of rumination, which falls within the Loss domain of the RDoC framework. Rumination is a perseverative negative thought pattern that involves passively dwelling on negative feelings [65]. The learned behavior and underlying neural signature of rumination represents a maladaptive habit. The development of this response style prior to full maturation of the PFC may result in a tendency to use avoidance strategies rather than the selection of responses requiring executive functioning such as problem-solving and approach-related behaviors. These patterns may result in a recurrent form of chronic depression that derails healthy emergence into adulthood.

Rumination impairs functional behavior by leading an individual to become stuck in thought and blocks the approach of action [66], leading to the proposal that rumination represents a transdiagnostic mechanism in the development of psychopathology [67••]. Rumination remains elevated following remission from depression, is associated with lower levels of treatment response, prospectively predicts severity and duration of depressive episodes (for a review, see [65]), and mediates the

effect of negative life events on subsequent affect [68]. Rumination hinders the reciprocal and dynamic interchange between cognitive and emotional states [69]. For example, rumination interferes with effective problem-solving [70] and instrumental behavior [71]. Preliminary studies have linked rumination to the DMN.

Research specific to the DMN, including studies with resting state fMRI (rs-fMRI) and task-based approaches, have evaluated the neural correlates of rumination among adults with active MDD [30–32]. Task-based fMRI studies have demonstrated correlations between regions of the DMN, particularly the dorsomedial PFC (dmPFC), and self-report rumination [30]. Additional studies have examined the neural correlates of rumination among healthy adults [30], and one study has linked functional connectivity of DMN to self-report rumination among currently depressed adolescents [72•].

Rumination has also been explored in relation to loss anticipation within the NVC using monetary incentive delay (MID) tasks. For example, adults with remitted MDD (rMDD) demonstrated lower superior frontal gyrus (SFG) activation during loss anticipation and less inferior and SFG activation during loss outcomes [73•]. Self-report rumination was negatively correlated with SFG activation during loss outcomes in the rMDD group. The degree of SFG hypoactivation was associated with rumination, suggesting that abnormal prefrontal responses to loss may reflect a trait-like vulnerability to MDD. Prospective research conducted with 200 adolescents enrolled at age 12 or 13 years found that higher levels of baseline rumination were associated with decreases in selective attention and attentional switching at follow-up [74]. As such, rumination processes can detract from, interfere with, or undermine problem solving and control circuit processes.

Current Research on Positive Valence Domain/Circuit (PVC) Disruption in Mood Disorders

Reward and reward anticipation are recent foci areas when studying the PVC. Within this context, one important distinction is between *reward anticipation or appraisal*, that is, the "motivational" aspect (i.e., "wanting") of rewards, and *response to delivered rewards*, that is, the "consummatory" aspect (i.e., "liking") [75••]. Studying the relationship between reward systems and affect dysregulation is very promising, as positive affect is an emotional state elicited by reward and similar processes [76]. In recent years, behavioral studies of PVC disruptions in mood disorders have focused heavily on a deficient PVC model that, for example, conceptualizes anhedonia as disruption in reward consummatory processes, and apathy as disruption in anticipation of reward.

Patients with MDD tend to show apathy and anhedonia as well as hypoactivation of fronto-striatal circuits. Reward system abnormalities have also been found both in adult [77] and adolescent populations with MDD [78], leading to a characterization of "*hypo-sensitivity to rewards*" in MDD, with hypo-activation in ventral striatum (VS)/PVC [79, 80]. In fact, a recent study with adolescents with MDD found reduced reward-related activity in the right caudal ACC, caudate, and OFC during high-risk/high-gain trials [81]. Similarly, [78] found decreased activation in the caudate and inferior OFC during both reward anticipation and response in 9–17 year olds with MDD. It is noteworthy that this pattern of dysfunction involving decreased striatal activation may be a promising candidate bio-marker for depression as it was found also in 10- to 14-year-old girls with high familial risk for depression, relative to a low-risk group, during anticipation and receipt of reward during an MID task [82]. PVC studies have shown the most progress in potentially predicting BD and distinguishing between MDD and BD [83].

Current Research of Cognitive Control and Problem Solving (CCaPS) Disruption in Mood Disorders

Behavioral studies of CCaPS on executive functioning, working memory (WM), and regulatory abnormalities in depression have focused more heavily on traditional neuropsychological tests of executive functioning. Executive functioning deficits have been reported in MDD and to a greater extent in BD, although not consistently so [45, 84, 85]. Executive functioning measures have also been found to be predictive of treatment response in depressed patients [86–88] and of everyday functioning [89•]. Interestingly, studies of behavioral inhibition (BI) in depression have shown increased inhibition or withdrawal behavior in depressed patients [90, 91, 92]. Some studies suggest that these difficulties exist even in the remitted state [93], including amongst younger remitted individuals with an MDD history [94]. A recent meta-analysis suggests that even in rMDD, effect sizes for performance differences in CCaPS measures may be moderate to large, including the Trail Making Test B ($d=0.48$) and Stroop interference ($d=0.74$) [95••].

Recent fMRI studies have employed the Stroop Color Word Test [96], and variations of what has been called the Emotion Stroop [96–98]. WM paradigms have also been used widely, but they are slightly different than the regulatory difficulties in MDD [99, 100]. Measuring behavioral regulation, including response styles to a difficult cognitive task, may simulate real-life difficulties in behavioral and emotional regulation experienced by depressed patients [101], as evidenced by our and others' recent work [102, 103]. Our work with parametric Go/No-Go tasks [6, 103] suggests that regulatory mechanism may play a key role in the etiology,

maintenance, and resolution of depression. More recently, a study in recurrent MDD demonstrated hypoactive right superior and dorsal medial PFC (dmPFC) for errors of commission relative to healthy comparison subjects [104•]. This hypoactivity was also present when visual negative feedback was given that a response was too slow for correct hits. In addition, more rapid normalization of the hypoactivation in the dACC extending into dmPFC was present in a subset of individuals who did not have recurrence of MDD within one year. A larger recent study with a Stroop task reported fronto-parietal hypoactivation in unmedicated MDD patients relative to healthy controls, in the context of atypically non-different group performance across color and incongruent trials [105•].

Current Research of Circuit Interactions in Mood Disorders

The dynamic interaction of NVC (typically increased in mood disorders) and PVC (decreased in MDD, increased in BD), and CCaPS (decreased in mood disorders) has been difficult to quantify in many studies. For example, if individuals are studied in active states of mood disorder, the circuits are already perturbed to a greater extent than what might or could be observed in the euthymic state, let alone the interactions between them. A shift away from PVC in depression might suggest a change in the regulatory skills in depressed patients [106, 107]. On the contrary, reduced behavioral regulation, associated with altered fronto-striatal activation, has been found in BD and MDD during response inhibition and WM tasks [108, 109, 110]. However, unlike MDD, BD is typically characterized by increased reward-seeking behavior [111]. Yet another pattern of relationship between reward–control systems is the one presented by individuals with "BI" who exhibit increased inhibition but also hypersensitivity of PVC, possibly as part of their hyper-vigilance to novelty and environmental cues [112•].

An important concept is that in internalizing disorders, disrupted appraisal of positive or negative contingencies may directly affect functioning of the CCaPS circuit. A promising way to look at the altered relationship between PVC and control processes is *cognitive flexibility* in the presence of reward contingencies. This is conceptually captured in the feedback arrows from CCaPS to PVC and approach behavior contingencies (Fig. 1). A probabilistic reversal learning study found that 6- to 17-year-old adolescents with BD showed worse accuracy than healthy controls. This occurred while learning the association between a reward and a stimulus within a pair of stimuli that were presented repeatedly, and while reversing their learned responses after the new reward object had been switched [113]. Similar results were found in adults with BD [114], suggesting developmental continuity in these deficits. Importantly, these dysfunction patterns seem specific to BD [115], in that impaired probabilistic reversal learning was found specifically in BD adolescents, while adolescents with MDD, severe mood dysregulation (SMD), and anxiety did not differ significantly from healthy adolescents.

Interesting results have also been obtained when looking at reward-related processes at the interface with decision-making in terms of a *bias for immediate rewards*. Studies with healthy adults found that hyperactivation of VS and reduced PFC activation correlated with preference for immediate rewards [116]. Developmental studies found that increased fronto-striatal activation with development correlates with decreased delay discounting [117, 118]. Recent studies found that both adult patients with MDD [119] and with BD [120] exhibit steeper discounting during a delay discounting task relative to healthy controls. Altogether, these results suggest altered appraisal of future rewards in MDD and BD that may have implications for treatment approaches. Of course, it is possible that the neural mechanisms of discounting may be different across MDD and BD, and during different developmental stages.

These findings illustrate conceptual and practical interactions between PVC and CCaPS circuits, in addition to the more well-known NVC and CCaPS links described in prior studies. Parameterized designs that captured presence/absence of PVC/NVC priming and variable degrees of CCaPS may help toward understanding interactions between the circuits, and the dynamic irregularities that more closely approximate experiences of those with mood disorders. This would be particularly relevant to test in both active and remitted states.

Developmental Considerations in the Study of Mood Disorders

About 50 % of adults with mental disorders have illness onset by age 14 years [121], suggesting that developmental models of mental illness are important in the evolution of psychiatric illness. The PFC and associative areas of the brain keep maturing until late adolescence [122] and are therefore more vulnerable to trauma and delayed or otherwise abnormal development. It is possible that there are developmental differences in the emergence of these circuits. Are there circuit-based strengths and in/efficiencies? If so, what are the interactions between these circuits? If there is developmental

consistency in the aberrant functioning or interactions between these circuits, this neurophysiological consistency may help in the identification of predictors of illness or early onset. For instance, developmental studies show earlier development and more prominent influence of NVC and PVC in early adolescence and that through late-adolescence, as the PFC matures, CCaPS also improves and PVC decreases [123, 124]. In contrast, the NVC matures relatively early in development. Modulation of NVC and PVC by CCaPS may mature well into adulthood. Researchers have yet to fully understand the mechanisms functioning to derail healthy cognitive development in emerging internalizing disorders, specifically the interactions between NVC, PVC, CCaPS, and DMN circuits. We believe it is clear that these circuits and their interactions as they function in the development of mood disorders remain critical areas for future inquiry.

Along with potential developmental delays or dysfunctional interactions, there is other evidence that stable temperament patterns from early childhood related to NVC carry over with development and affect CCaPS by means of interacting with PVC. Some of the more informative developmental studies are with individuals with "BI", which denotes NVC hypersensitivity. These children present with vigilance to novelty, sensitivity to approach–withdrawal cues, and social withdrawal. Independent studies link reward hyper-responsivity to BI, adolescent anxiety, and dopamine gene variants [125]. Moreover, BI participants who had been assessed since infancy on measures of BI showed, relative to non-inhibited adolescents, increased striatal response patterns to social cues, such as during anticipation and receipt of positive and negative feedback from novel peers that were classified as being of high or low interest [112•]. This pattern suggests NVC over-reactivity to salient social cues in BI. Similar patterns in BI were also found in a study with monetary rewards [126], possibly suggesting overactive PVC also. Overactive PVC, but only in response to gain versus loss, was also found in a pediatric population with generalized anxiety disorder; however, they did not show the BI profile of NVC over-reactivity to salient social cues [127]. These studies, while preliminary, suggest the need for additional longitudinal studies that may capture more precisely how early-life temperament can predict altered NVC and PVC responses in both social and non-social contexts, and in different populations such as inhibited versus disinhibited individuals.

Summary, Integration, and Future Steps

The present review highlights critical crossroads and future directions for mood disorders research. We highlight conceptual challenges toward understanding the dynamic role of PVC and NVC, their interactions with CCaPS circuits, and the relationship of these circuits with the DMN. These circuits have a basis in the psychological, theoretical, and animal literature, and are borne out in brain imaging, lesion, and related studies, including functional connectivity analyses. Finally, these circuits are encapsulated within the RDoC framework of the NIMH, the goal of which is to provide dimensional targets for treatment and measurement of post-treatment change.

These circuits also provide an opportunity to conceptualize variations within disorders such as MDD, as well as phases of BD, and potential differences between MDD and BD. A substantial number of studies suggest increased NVC activation in MDD and BD groups. A potentially non-overlapping set within each group also exhibits diminished CCaPS function, which is related to treatment outcome, potential for relapse, and degree of life functioning. In contrast to these relative similarities in NVC and CCaPS dysfunction, initial studies suggest some amount of dissociation in the PVC system across mood disorder groups. A substantial proportion of those with BD exhibit PVC hypersensitivity, whereas a substantial number of those with MDD exhibit hypoactivation.

An important challenge for consideration is the development of these systems through childhood, adolescence, and young adulthood. Evaluating these circuits, the interactions between them, and the impact upon behavior requires careful designs that incorporate parametric evaluations of the presence/absence of NVC/PVC challenge and with and without significant involvement of the CCaPS. To do so, future models must incorporate substantial variability in the amount and degree of development of these circuits. For example, there is evidence that normative adolescent development results in relative dominance of NVC and PVC over CCaPS in childhood that is reversed for most as they transition into mid to late adolescence and adulthood. A delay in this transition may be difficult to characterize and quantify, and to some extent may overlap substantially in ill, at-risk, and no-risk groups. This critical window is an optimal area for study focus and primary and secondary prevention.

Finally, high-risk designs are one key area of continued study that can be successfully pursued using the proposed model. We can optimize the identifiable and measurable neural markers that can differentiate between different illnesses, and subsequently predict the illness progression. For example, one novel study [128••] identified a neurophysiological marker (i.e., elevated at-rest activity in left mid-frontal EEG) that prospectively predicted conversion from cyclothymia or BD Type II to BD Type I over a 4.7-year follow-up. It will also be fruitful to consider the extent to which neural and behavioral markers are shared across a number of illnesses. There is reason to suspect that high-risk studies for substance abuse and for MDD and BD might recruit from the same high-risk populations, allowing for pooling of resources and enhanced power. Such multi-risk group designs fit well into the RDoC

framework and the highlighted circuits within our model of CCaPS, NVC, and PVC dysfunction in mood disorders.

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Compliance with Ethics Guidelines

Conflict of Interest Scott Langenecker, Rachel Jacobs and Alessandra Passarotti declare no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the authors.

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- • Of importance
- •• Of major importance

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