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Asymmetrical frontal cortical activity associated with differential risk for mood and anxiety disorder symptoms: An RDoC perspective

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ABSTRACT

The recently launched NIMH Research Domain Criteria (RDoC) initiative aims to examine the relationship between core biobehavioral dimensions and symptom profiles that either cut across traditional disorder categories or that are unique to specific clinical phenomenon. A biobehavioral construct that has received considerable attention and that is directly relevant to the Positive Valence Systems domain of the RDoC initiative is approach motivation. One way approach motivation is frequently operationalized is left versus right frontal electroencephalographic (EEG) activity, with greater relative left frontal EEG activity reflecting increased approach motivation and decreased relative left frontal EEG activity reflecting decreased approach motivation or increased withdrawal tendencies. The objective of the present review paper is to examine the relationship between relative left frontal EEG activity and mood and anxiety related symptoms from an RDoC perspective. We first provide an overview of the approach–withdrawal motivational model of frontal EEG asymmetry. Second, we review evidence that relative left frontal EEG activity is associated with a differential risk for unipolar depression versus bipolar disorder. Third, and in line with the mission statement of the RDoC, we move beyond considering mood and anxiety disorders as unitary constructs or homogenous disorders and instead propose that individual differences in relative left frontal EEG activity may be uniquely associated with specific symptom clusters of depression (i.e., anhedonia), hypomania/mania (i.e., symptoms characterized by excessive approach motivation), and anxiety (i.e., anxious apprehension versus anxious arousal). Identifying the relationship between relative left frontal EEG activity and specific mood and anxiety-related symptom clusters has important implications for clinical science, assessment, and treatment.

1. Introduction

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5th ed.; American Psychiatric Association, 2013) is based on clinical observations and self-reported symptoms. The development of this system, however, predates breakthroughs in neurophysiology and neuroscience, and our reliance on this system may have negative implications for both the assessment and treatment of psychiatric illness. For example, epidemiological data indicate that it takes an average of 6 to 10 years for an individual with bipolar disorder to receive a correct diagnosis and appropriate treatment (Ghaemi et al., 1999, 2000). Those who are misdiagnosed consult an average of four physicians prior to receiving an accurate diagnosis, and close to 60% of individuals with bipolar disorder are initially misclassified as having MDD (Hirschfeld et al., 2003; Nusslock and Frank, 2011). Furthermore, sole reliance on DSM may be impeding research into the pathophysiology of psychiatric symptoms given it is unlikely that the mechanisms underlying these symptoms cleanly map onto DSM classifications.

To help address this issue, the National Institute of Mental Health (NIMH) recently launched the Research Domain Criteria (RDoC) initiative, which calls for the development of new ways of classifying psychiatric illness based on core brain-behavior dimensions (Insel et al., 2010). Rather than start with an illness definition based on clinical observations and then seek its neurophysiological or neurobiological underpinnings, RDoC begins with our current understanding of physiological mechanisms and aims to link these mechanisms to clinical phenomena. The intention of RDoC is to eventually generate a classification system for psychiatric illness that is grounded in contemporary neuroscience. It is argued that this classification system may help generate empirically-derived, biological markers of psychiatric illness that can increase the precision and reliability of psychiatric assessment.[1]

In its present form, the RDoC framework involves five domains or dimensions reflecting contemporary knowledge about major systems of

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[1] We use the term 'marker' in the present paper in more of a clinical context to refer to a biological or neurophysiological profile that can help identify individuals at risk for a particular psychiatric disorder or a specific cluster of psychiatric symptoms. We do not use the term marker to imply a one-to-one relationship between psychological (i.e., approach motivation) and biological (i.e., relative left frontal EEG activity) constructs, as suggested by Sarter et al. (1996).

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cognition, motivation, and behavior. These domains are Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Systems for Social Processes, and Arousal/Regulatory Systems. RDoC specifies multiple *Units of Analysis* that can be used to examine these domains, including, but not limited to, genes, circuits, physiology, and behavior. One stated goal of RDoC is to identify pathophysiological mechanisms that cut across, or are common to, multiple psychiatric disorders. As an example, elevated threat processing (Negative Valence Systems) is observed across multiple psychiatric disorders, including unipolar depression (Hamilton et al., 2012), bipolar disorder (Phillips and Vieta, 2007; Almeida et al., 2010), and anxiety disorders (Etkin and Wager, 2007). Thus, elevated threat processing may reflect a risk factor for transdiagnostic symptoms that are common across multiple psychiatric conditions.

Another stated goal of RDoC, however, is to identify mechanisms that are unique to specific psychiatric symptoms, and that reflect biosignatures of differential risk for these distinct symptom profiles. Relevant to this goal is growing evidence that certain psychiatric disorders are characterized by distinct and opposite profiles of activation within the Positive Valence Systems. For example, unipolar depression (without a history of hypo/mania) has been associated with abnormally reduced positive emotion or approach motivation (Forbes, 2009; Pizzagalli et al., 2008; Thibodeau et al., 2006), bipolar disorder has been associated with abnormally elevated positive emotion or approach motivation (Alloy and Abramson, 2010; Johnson, 2005; Nusslock et al., 2012a), and certain anxiety symptoms may be associated with elevated or maintained approach motivation (Heller et al., 1997; Mathersul et al., 2008; Nitschke et al., 2009; Guyer et al., 2006). Thus, if one were to look for mechanisms of differential risk for specific psychiatric symptoms, we argue that the Positive Valance Systems are an appropriate target.

A central construct of the Positive Valence Systems domain within the RDoC framework is approach motivation (Insel et al., 2010). Approach motivation involves mechanisms and processes that regulate the direction and maintenance of approach-related behavior. Approach motivation may simply reflect the impulse to go toward and it may be associated with positive or negative emotions, as we discuss later (e.g., Harmon-Jones et al., 2013). Approach behavior can be directed toward innate or acquired cues (i.e., unconditioned vs. learned stimuli), external (e.g., an opportunity for promotion) or internal (e.g., expectancy of winning an award) stimuli, or toward the removal of goal-obstruction.

To date, one of the most reliable neurophysiological indices of approach motivation involves asymmetrical activity in the alpha frequency band over the frontal cortex (Coan and Allen, 2004; Allen et al., 2004; Davidson, 1995, 1998a,b; Harmon-Jones et al., 2010). Alpha power is typically operationalized as power between 8 and 13 Hz in adults, although lower frequencies have been examined in children, as these lower frequencies in the developing brain are assumed to be equivalent to adult alpha (see Coan and Allen, 2004 for review). A guiding assumption underlying the interpretation of frontal EEG alpha asymmetry is that alpha power is inversely related to cortical activity; such that greater alpha power is indicative of less neuronal activity and reduced alpha power is indicative of elevated neuronal activity (see Allen et al., 2004; Davidson, 1998b for review). In line with this assumption is research documenting that sensory input shows modality-specific blocking of alpha activity at cortical regions involved in processing such input. For example, whereas visual stimuli block alpha over the occipital cortex, a region that is central to processing visual stimuli, auditory stimuli block alpha more so over the auditory cortex (see Allen et al., 2004; Davidson, 1988 for review).[2] Investigators conducting frontal EEG asymmetry research often use a difference score or asymmetry index (ln(right) − ln(left) alpha power) to conveniently summarize the relative activity at homologous right hemisphere and left hemisphere electrodes (Allen et al., 2004). Given the inverse relationship between alpha power and cortical activity (Allen et al., 2004; Larson et al., 1998), this asymmetry index provides a unidimensional scale in which greater values indicate increased relative left hemispheric cortical activity and lower values indicate decreased relative left hemispheric cortical activity.

The approach–withdrawal motivational model of frontal EEG asymmetry posits that increased relative left frontal activity indicates a propensity to approach or engage a stimulus, whereas decreased relative left frontal activity indicates a propensity toward reduced approach-related motivation or increased withdrawal motivation (Coan and Allen, 2004; Davidson, 1995, 1998a,b; Harmon-Jones, 2003a). Furthermore, growing evidence indicates that relative left frontal EEG activity may be associated with differential risk for unipolar depression versus bipolar disorder. Specifically, unipolar depression is associated with reduced approach motivation and decreased relative left frontal activity and bipolar disorder is associated with elevated approach motivation and increased relative left frontal activity (Harmon-Jones et al., 2002, 2008; Nusslock et al., 2011, 2012b; Thibodeau et al., 2006). By contrast, anxiety appears to be characterized by either elevated or reduced relative left frontal activity, depending on the specific symptom cluster (anxious-apprehension versus anxious-arousal) (Heller et al., 1997; Mathersul et al., 2008; Nitschke et al., 2009; Guyer et al., 2006).

The objective of the present review paper is to examine the relationship between relative left frontal EEG activity and mood and anxiety disorder symptoms from an RDoC perspective. In addition, we also extend previous reviews of frontal EEG asymmetry and psychopathology (e.g., Allen and Reznik, in press; Shankman and Klein, 2003) by examining the relationship between relative left frontal EEG activity and mood disorder symptoms across the entire mood spectrum, from unipolar depression to bipolar disorder. We first provide an overview of the approach–withdrawal motivational model of frontal EEG asymmetry. Second, we review evidence that relative left frontal EEG activity is associated with a differential risk for unipolar depression versus bipolar disorder. Our review of the existing literature on relative left frontal activity in unipolar depression versus bipolar disorder focuses on individuals with a DSM diagnosis given that most of the research to date on this topic has been conducted on diagnosed mood disorder samples. As part of this second aim, we briefly review complimentary neuroimaging research to highlight the fact that at multiple units of analysis, biological indices of approach motivation are associated with differential risk for unipolar depression versus bipolar disorder. Third, we move beyond considering mood and anxiety disorders as unitary constructs or homogenous disorders and instead propose that individual differences in frontal EEG asymmetry may be useful in identifying differential risk for specific clusters of mood and anxiety-related symptoms. This third aim is directly in line with one of the stated goals of the RDoC initiative, which is to identify mechanisms that are uniquely related to specific psychiatric symptoms and that reflect biosignatures of differential risk for these distinct symptom profiles (Insel et al., 2010). Specifically, we predict that a) decreased relative left frontal EEG activity will be most strongly associated with the unipolar depressive symptom of anhedonia; b) elevated relative left frontal EEG activity will be most strongly associated with a cluster of hypomanic/manic symptoms characterized by excessive approach motivation (i.e., elevated energy, increased goal-directed activity, decreased need for sleep, increased confidence, and irritability when goal-pursuit is thwarted); and c) anxious-apprehension and anxious-arousal are characterized by distinct and opposite profiles of relative left frontal EEG activity. Finally, we argue that a motivational based framework organized around whether mechanisms facilitate approach versus withdrawal/inhibitory tendencies may be superior to the valence based framework currently employed by the RDoC initiative, which focuses on whether mechanisms facilitate positive versus negative emotions.

[2] It is difficult to test the assumption that alpha power is inversely related to cortical activity in regions other than primary sensory regions. This is due to the fact that multiple and distributed brain regions are involved in higher order cognitive processing and the lack of clearly defined stimuli to precisely engage these cortical regions. Despite these challenges, however, several studies have provided data consistent with the notion that greater alpha power is indicative of less cortical activity in neural regions subserving higher order task performance (see Allen et al., 2004 for review).

2. Approach–withdrawal motivational model of frontal EEG asymmetry

Two research approaches typify the frontal EEG asymmetry literature. The first examines the relationship between *resting* EEG activity and trait-like phenomena such as measures of motivational style (e.g., Harmon-Jones and Allen, 1997), psychopathology (e.g., Gotlib et al., 1998), or with subsequent state fluctuations in emotional behavior (e.g., Tomarken et al., 1990). This approach treats resting EEG asymmetry as a trait-like individual difference variable, one that may moderate emotional responding or tap risk for the development of emotion-related psychopathology. The second approach involves correlating state fluctuations in frontal EEG asymmetry with changes in emotional or motivational state (e.g., Coan et al., 2001). This approach treats changes in frontal EEG asymmetry as a dependent measure or, in some cases, as a mediator that underlies affective processes.

With respect to resting data, findings from over 40 studies suggest that resting frontal EEG asymmetry may serve as an indicator of a trait-like propensity to respond to emotional situations in a characteristic way. Davidson (1998a,b) has called this propensity "affective style" and proposed that frontal EEG asymmetry indexes a system that may have emotion-specific or valence-specific moderating influences, with implications for risk for affective psychopathology.[3]

As noted, the approach–withdrawal motivational model of frontal EEG asymmetry posits that increased relative left frontal activity indicates a propensity to approach or engage a stimulus, whereas decreased relative left frontal activity indicates a propensity toward reduced approach motivation or increased withdrawal tendencies (Coan and Allen, 2004). In line with this view, multiple studies have found that relatively greater left frontal activity at rest is associated with higher self-reported behavioral approach system (BAS) sensitivity, as indexed by Carver and White's (1994) Behavioral Inhibition System/Behavioral Activation System (BIS/BAS) scales (Coan and Allen, 2003; Harmon-Jones and Allen, 1997; Sutton and Davidson, 1997). According to Carver and White (1994), "greater self-reported BAS sensitivity should be reflected in greater proneness to engage in goal-directed efforts and experience positive feelings when the person is exposed to cues of impending reward" (pp. 319). Greater relative left frontal activity at rest has also been associated with greater trait positive affect (Tomarken et al., 1992), sociability (Schmidt, 1999), and both eudaimonic and hedonic well being (Urry et al., 2004).

With respect to task-related data, more than 30 studies have documented task-dependent changes in frontal EEG asymmetry in response to a diverse array of emotional stimuli (for reviews, see Coan and Allen, 2004; Harmon-Jones et al., 2010). For example, task-dependent changes in relative left frontal activity are responsive to both voluntary (Coan et al., 2001; Ekman and Davidson, 1993; Price, Hortensius, and Harmon-Jones, 2013) and spontaneous (Ekman et al., 1990) facial expressions of emotion. Relative left frontal activity shows approach-related modulation in response to pleasant and unpleasant odors (Kline et al., 2000), emotional film clips (Tomarken et al., 1990), and anger-provoking events (Harmon-Jones and Sigelman, 2001; Harmon-Jones et al., 2006). [As discussed in detail below, anger is considered an approach-oriented emotion despite its negative valence (Carver and Harmon-Jones, 2009).] Even in infants, frontal EEG asymmetry shifts toward relative left frontal activity in response to a desirable flavor (sucrose; Fox and Davidson, 1987). Furthermore, multiple studies with healthy controls report increased relative left frontal activity to reward/monetary cues (Miller and Tomarken, 2001; Sobotka et al., 1992), reflecting the induction of an approach-oriented state toward the desired reward.

2.1. Hemispheric specificity in frontal EEG asymmetry

The research discussed thus far on the approach–withdrawal model of frontal EEG asymmetry has relied largely on the asymmetry index (ln(right) − ln(left) alpha power), reflecting the relative relationship between right and left hemispheric alpha power. Despite the simplicity of this difference score, researchers have been interested in the contribution of activity in each hemisphere. Historically it has been argued that the left prefrontal cortex subserves approach-related motivation and the right prefrontal cortex withdrawal-related tendencies (Davidson, 1995, 1998a,b). This perspective originated from early lesion studies in which post stroke depression was more evident depending on the proximity of the lesion to the left frontal cortex (Robinson, 1985; Robinson et al., 1984). Although there has been some support for the localization of approach and withdrawal tendencies to the left and right prefrontal cortex, respectively (e.g., Pizzagalli et al., 2005b), there have also been numerous conflicting results on this topic (see Allen et al., 2004). This is a notable limitation of the literature on frontal EEG asymmetry given that researchers have not been able to reliably determine whether elevated relative left frontal EEG activity (i.e., the asymmetry index) reflects increased approach motivation, decreased withdrawal motivation, or both. For both simplicity and conceptual reasons, we focus on the construct of approach motivation in the present paper. Accordingly, we discuss greater relative left frontal EEG activity as reflecting increased approach motivation, and decreased relative left frontal EEG activity as reflecting decreased approach motivation. We acknowledge, however, the potential role that withdrawal-related tendencies may play in the frontal asymmetry index and argue that it will be important for future research to use multi-modal techniques (e.g., combined EEG and fMRI) to determine the neuronal generators of frontal EEG asymmetry and dissociate approach from withdrawal related tendencies in the prefrontal cortex.

3. Asymmetrical frontal cortical activity associated with differential risk for unipolar depression versus bipolar disorder

Having introduced the approach-withdrawal motivational model of frontal EEG asymmetry, our objective for the remainder of this review is three-fold. First, we review the literature suggesting that profiles of relative left frontal EEG are associated with differential risk for unipolar depression (without a history of hypo/mania) versus bipolar disorder. As indicated, our review of this literature focuses on individuals with a DSM diagnosis given that most of the existing research on this topic has been conducted on diagnosed mood disorder samples. Complimentary neuroimaging research is briefly reviewed to highlight the fact that at multiple levels of analysis, biological indices of approach-related motivational tendencies are associated with differential risk for unipolar depression versus bipolar disorder. Second, and directly in line with the mission statement of RDoC initiative (Insel et al., 2010), we move beyond examining psychiatric disorders as homogenous disorders or constructs and instead consider the relationship between relative left frontal activity and specific clusters of mood and anxiety-related symptoms. Finally, we argue that a motivational based framework organized around whether mechanisms facilitate approach versus withdrawal/inhibitory tendencies may be optimal for the RDoC initiative.

3.1. Unipolar depression is characterized by reduced approach motivation and decreased relative left frontal EEG activity

Decreased approach motivation and reduced positive affect has long been considered a core feature of unipolar depression (Meehl, 1975; Lewinsohn and Graf, 1973). Individuals with unipolar depression self-

[3] In line with the perspective that resting frontal EEG asymmetry reflects trait-like activation patterns is research indicating that approximately 60% of the variance in frontal asymmetry is due to individual differences on a temporally stable latent trait (Hagemann et al., 2002). This percentage of variance accounted for by trait-related factors is comparable to other trait-related measures of individual differences (e.g., the Big Five personality traits; Roberts and DelVecchio, 2000). These data also highlight, however, the important role that state-related effects have on frontal EEG asymmetry, accounting for approximately 40% of the variance.

report decreased BAS sensitivity (Kasch et al., 2002) and engage less frequently in goal-directed behavior (Forbes, 2009). During gambling or monetary-reward tasks, adults with depression make decisions that are more conservative (Corwin et al., 1990), slower (Kaplan et al., 2006) and less flexible in the face of shifting contingencies (Cella et al., 2010). Depression – and anhedonia in particular – is associated with a failure to exhibit a response bias toward rewarded stimuli in signal detection tasks, in which one set of stimuli is subtly rewarded more frequently than another (Pizzagalli et al., 2005a, 2008). Moreover, reduced approach motivation and blunted positive affect have been concurrently and prospectively linked to depression onset in adult samples (Clark et al., 1994). In children, reduced positive affect at age 3 predicted depressogenic cognitive styles at age 7 (Hayden et al., 2006) and was associated with a maternal history of depressive disorders (Durbin et al., 2005).

In line with the approach–withdrawal model, individuals with unipolar depression show decreased relative left frontal EEG activity at rest (see Thibodeau et al., 2006, for meta-analytic review), reflecting reduced approach system sensitivity and blunted reward-related affect. Individuals with unipolar depression show decreased relative left frontal EEG activity at rest during both depressive (Gotlib et al., 1998; Henriques and Davidson, 1991) and euthymic states (Henriques and Davidson, 1990), suggesting that reduced left frontal activity may be a state-independent correlate of unipolar depression. Decreased left frontal EEG activity has been observed in offspring of depressed individuals who have yet to experience a depressive episode (Dawson et al., 1997), has been observed across the life span (Deslandes et al., 2008), is associated with genetic risk for unipolar depression (Bismark et al., 2010), is predictive of depressive symptoms twelve months following EEG recording (Pössel et al., 2008), is predictive of treatment response (Bruder et al., 2001), and prospectively predicts onset of first unipolar depressive episode (Nusslock et al., 2011).

Although most of the research on relative left frontal activity in depression has measured EEG activity at rest, there is growing evidence that individuals with unipolar depression also display frontal EEG asymmetry during laboratory tasks. Relative to healthy controls, individuals with unipolar depression display decreased relative left frontal activity during facial emotion tasks (Stewart et al., 2011, 2014) and during reward anticipation (Shankman et al., 2013). Furthermore, decreased relative left frontal activity during emotional/reward-based laboratory tasks is associated with depression proneness in children (Feng et al., 2012) and is associated with increased familial risk for depression (Nelson et al., 2013).

We hypothesize that frontal EEG asymmetry in depression occurs in the context of a vulnerability-stress model. Specifically, we propose that individuals with decreased relative left frontal activity are prone to experience an excessive decrease in approach motivation and goal-directed activity in the presence of approach deactivation-relevant life events such as definite failure or loss. In the extreme, this decrease in approach motivation is reflected in depressive symptoms (see Fig. 1). Support for this prediction is two-fold. First, the fact that decreased relative left frontal EEG activity has been observed in the offspring of depressed individuals who have yet to experience a depressive episode (Dawson et al., 1997), is associated with genetic risk for unipolar depression (Bismark et al., 2010), and prospectively predicts the onset of a first unipolar depressive episode (Nusslock et al., 2011), suggests that decreased relative left frontal activity is a pre-existing vulnerability for depression. Second, there is preliminary evidence that frontal EEG asymmetry interacts with stressful life events in the onset of internalizing symptoms among children at familial risk for depression (Lopez-Duran, et al., 2012). Future research, however, is needed to more fully test a vulnerability-stress model of relative left frontal EEG activity and the onset of unipolar depression.

Despite this documented decrease in relative left frontal EEG activity in unipolar depression, there are inconsistencies in this literature, and a handful of studies have failed to observe a relationship between frontal EEG asymmetry and unipolar depression (see Reid et al., 1998; Thibodeau et al., 2006 for review). Although there have been both methodological and conceptual explanations put forth to help explain these inconsistencies (see Davidson, 1998b), we argue that other factors to consider are the heterogeneity of depression and the possibility that different pathophysiological processes may underlie different expressions or symptoms of the depressive illness. The present paper argues that decreased relative left frontal EEG activity may be particularly associated with the symptom of anhedonia, or a diminished interest or pleasure in response to rewarding stimuli (see below for details). If this prediction proves accurate it would suggest that the prevalence of anhedonia in a given sample of depressed participants may modulate the likelihood of observing decreased relative left frontal EEG activity among those participants. Specifically, studies of depressed participants that either by design or chance have high rates of anhedonia should be more likely to observe a relationship between relative left-frontal EEG activity and depression than studies with lower rates of anhedonia. Future research is needed to test this hypothesis. However, we argue that examining the relationship between relative left frontal EEG activity and specific depressive symptoms, as supported by the RDoC initiative, may not only enhance our understanding of the pathophysiology of these symptoms, but may also help us better understand inconsistencies in the literature on frontal EEG asymmetry and depression, more generally.

Complimenting research on relative left frontal EEG activity in depression is neuroimaging research on the fronto-striatal reward neural circuit involving the ventral striatum and orbitofrontal cortex (OFC), among other regions (Haber and Knutson, 2010; Knutson et al., 2005; Kringelbach and Rolls, 2004; Schultz, 2000). The ventral striatum is involved in processing both primary and secondary (e.g., monetary) rewards and plays a particularly important role in incentive motivation, reward anticipation, and reward pursuit (Haber and Knutson, 2010; Knutson et al., 2005). The OFC may be particularly important for encoding reward value and assessing the probability of reward receipt (Haber and Knutson, 2010; Kringelbach and Rolls, 2004; Schultz, 2000). Unipolar depression is associated with decreased ventral striatal activation during reward processing in functional neuroimaging studies. Both adolescents and adults with depression exhibit reduced reactivity in the striatum in response to decision-making, anticipation and outcome involving monetary reward (Forbes, 2009; Forbes et al., 2009; Pizzagalli et al., 2009; Smoski et al., 2009). OFC data are less consistent, with some studies reporting decreased (Osuch et al., 2009), and others increased (Smoski, et al., 2009) OFC activity to reward cues in depressed individuals. These discrepancies may be driven by developmental considerations (i.e., different profiles of reward processing in adolescents versus adults) and differences in how the OFC is anatomically defined across studies. Thus, at multiple units of analysis (relative left frontal EEG activity and fMRI), unipolar depression is characterized by reduced approach motivation and decreased approach/reward-related neural activity.

3.2. Bipolar disorder is characterized by elevated approach motivation and increased relative left frontal EEG activity

The DSM defines the bipolar spectrum disorders as encompassing three diagnoses: cyclothymia, bipolar II disorder, and bipolar I disorder. All three diagnoses involve extreme highs (hypomania or mania) and lows (depression) of mood, motivation, cognition, and behavior, but differ in severity level with bipolar I disorder being the most severe and cyclothymia the least severe. Moreover, having a milder form of bipolar disorder (cyclothymia, bipolar II) increases the risk for developing full-blown bipolar I disorder in both children/adolescents (Birmaher et al., 2009; Kochman et al., 2005) and adults (Alloy et al., 2012b), supporting the concept that bipolar disorder involves a spectrum of severity.

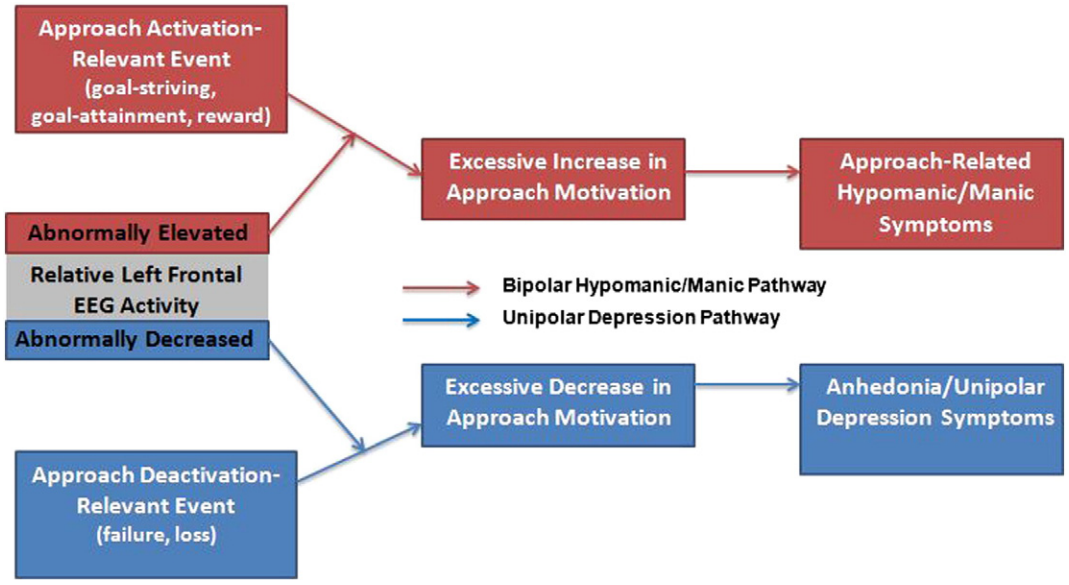

Fig. 1. Frontal EEG asymmetry vulnerability-stress model of mood disorder symptoms. Adapted from Alloy et al. (2015).

Contrary to unipolar depression, evidence suggests that bipolar disorder is characterized by elevated motivation and increased approach-related physiological activity. These data have been conceptualized in the context of the behavioral approach system (BAS)/reward hypersensitivity model of bipolar disorder. This model proposes that risk for bipolar disorder symptoms, in particular hypomanic/manic symptoms, is characterized by a hypersensitivity to goal- and reward-relevant cues (Alloy and Abramson, 2010; Johnson, 2005; Johnson et al., 2012; Urosevic et al., 2010). This hypersensitivity can lead to an excessive increase in approach-related motivation during life events involving rewards or goal striving and attainment. In the extreme, this excessive increase in approach motivation is reflected in hypomanic/manic symptoms, such as elevated or irritable mood, decreased need for sleep, increased psychomotor activation, extreme self-confidence, and pursuit of rewarding activities without attention to risks. Thus, from the perspective of the BAS/reward hypersensitivity model, symptoms of hypomania/mania involve extreme expressions along an underlying core brain-behavior dimension of reward-processing and approach motivation.

In line with the BAS/reward hypersensitivity model, individuals with bipolar disorder self-report a hypersensitivity to reward-relevant cues and a propensity to experience elevated approach motivation. Compared to relevant control groups, individuals with bipolar I disorder (Meyer et al., 2001; Salavert et al., 2007), bipolar II disorder, and cyclothymia (Alloy et al., 2008), and people prone to hypomanic symptoms (Meyer et al., 1999) self-report elevated BAS/reward sensitivity.

Growing evidence indicates that profiles of BAS/reward sensitivity have predictive validity for the course of bipolar spectrum disorders. Elevated self-reported BAS/reward sensitivity is associated with a greater likelihood of having a lifetime bipolar spectrum diagnosis (Alloy et al., 2006), a greater likelihood of developing a first onset of a bipolar spectrum disorder (Alloy et al., 2012a), a shorter time to recurrences of hypomanic/manic episodes (Alloy et al., 2008), an increase in manic symptoms among recovered individuals with bipolar I disorder (Meyer et al., 2001), and a greater likelihood of progressing to a more severe bipolar diagnosis among those with milder bipolar spectrum diagnoses (Alloy et al., 2012b). Furthermore, both reward-striving (Nusslock et al., 2007) and reward-attainment (Johnson et al., 2000) relevant life events have been shown to trigger hypomanic/manic episodes, and self-reported BAS sensitivity interacts with reward-relevant events to prospectively predict increases in hypomanic symptoms (Alloy et al., 2009). Lastly, the relationship between bipolarity and BAS/reward sensitivity appears to be state-independent in that it is not related to current levels of mania (Lozano and Johnson, 2001; Scott et al., 2000), and reward sensitivity continues to be elevated into remission relative to controls (Lam et al., 2004; Meyer et al., 2001).

Research has only recently begun to examine the relationship between bipolar disorder and relative left frontal EEG activity. In line with the BAS hypersensitivity model and the approach–withdrawal model of frontal EEG asymmetry, evidence suggests that bipolar spectrum disorders are characterized by elevated relative left frontal cortical activity. In an earlier study, Harmon-Jones et al. (2002) examined the relationship between proneness to symptoms of hypomania/mania and relative left frontal cortical activity in response to an anger-evoking laboratory event. Anger-evoking events are considered approach-oriented or BAS activating given the appetitive motivational state they typically induce as a person attempts to remedy the anger-provoking situation (Carver and Harmon-Jones, 2009). In line with the link between hypomania/mania and increased reactivity to approach-relevant stimuli (Alloy and Abramson, 2010; Johnson, 2005; Nusslock et al., 2007; Johnson et al., 2000), the research found that proneness toward hypomania/mania was related to increased relative left frontal activity in response to the anger-evoking event. In a follow-up, Harmon-Jones et al. (2008) compared relative left frontal EEG activity in individuals with a bipolar spectrum diagnosis (bipolar II disorder, cyclothymia) and healthy controls during a goal-striving laboratory task in which participants could win money for correctly solving anagrams (an anagram is a group of randomized letters which when placed in the proper order form a word). As expected, bipolar individuals displayed elevated relative left frontal EEG activity, as compared to healthy controls, during the preparation period for solving very challenging anagrams where the likelihood of success and monetary reward was low. This finding is in line with research indicating that individuals with bipolar disorder are prone toward engaging in excessive goal pursuit (Johnson, 2005).

Lastly, among individuals with a bipolar spectrum diagnosis, elevated relative left-frontal activity is a risk factor for a more severe course. Nusslock et al. (2012b) reported that elevated relative left frontal EEG activity was associated with a greater likelihood of converting from cyclothymia or bipolar II disorder to bipolar I disorder (i.e., mania onset) over a five-year follow-up period. This is the first study to identify a neurophysiological risk factor for conversion to a more severe bipolar diagnosis and parallels the previously mentioned research indicating that elevated self-reported BAS/reward sensitivity is associated with a

more severe bipolar course (Alloy et al., 2008, 2012b). Furthermore, in this study by Nusslock and colleagues, elevated relative left frontal cortical activity was associated with a younger age-of-onset of a first bipolar spectrum episode. Research has consistently identified early age-of-onset of a first bipolar spectrum episode as a primary risk factor for heightened impairment and poor outcome among bipolar individuals (Alloy, et al., 2012b; Birmaher et al., 2009; Nusslock and Frank, 2011). Thus, according to multiple indices (conversion to bipolar I disorder and age-of onset), elevated relative left-frontal cortical activity is associated with a more severe course of bipolar disorder.

Neuroimaging research compliments the work on relative left frontal EEG activity in bipolar disorder and provides additional support for the BAS hypersensitivity model of bipolar disorder. Individuals with bipolar disorder display elevated fronto-striatal activation during established fMRI reward paradigms involving the anticipation and receipt of monetary reward. Bipolar I individuals in remission (Nusslock et al., 2012a) and in a manic episode (Bermpohl et al., 2010; Abler et al., 2008) display elevated ventral striatal and left lateral OFC (BA 47) activation during reward processing compared to healthy controls. Abnormally elevated ventral striatal and left lateral OFC activation has also been observed in bipolar II individuals in remission (Caseras et al., 2013) and individuals with a hyperthymic temperament who have not yet developed the illness but who are at elevated risk (Harada et al., 2013). This latter finding suggests that elevated functional reward-related neural activation may reflect a preexisting risk factor for bipolar disorder, as opposed to a consequence of the illness. Lastly, although not displaying elevated ventral striatal activation, bipolar I individuals in a major depressive episode at the time of scanning displayed elevated left lateral OFC activation during reward processing compared to both healthy controls and individuals with unipolar depression in a current depressive episode (Chase et al., 2013). Thus, even during depression, individuals with bipolar I disorder may maintain heightened reward-related neural activation (although see Redlich et al., 2015 for alternative findings).

Several researchers have proposed that a propensity to experience an excessive increase in approach-related neurophysiological or neural activation is a central mechanism through which individuals with bipolar disorder are at risk for developing hypomanic/manic symptoms in the presence of reward-relevant life events (e.g., Alloy and Abramson, 2010; Johnson, et al., 2012). Specifically, it is proposed that individuals with bipolar disorder experience an excessive increase in approach-related neurophysiological activation to reward-relevant life events, which is reflected in an excessive increase in approach motivation. In the extreme, this increase in approach–motivation is reflected in hypomanic/manic symptoms (see Fig. 1). Collectively, this work indicates that risk for unipolar depressive symptoms and hypomanic/manic symptoms is characterized by distinct and opposite profiles of the approach motivation construct within the RDoC Positive Valence Systems domain. Specifically, risk for unipolar depression is characterized by reduced approach motivation and decreased approach-related neural activation, whereas risk for hypomania/mania is associated with elevated approach motivation and increased approach-related neural activation. These findings have important implications for understanding the pathophysiology of unipolar depression and bipolar disorder. As indicated, both these disorders are characterized by deficits in threat-related processes (RDoC Negative Valence Systems) (Hamilton, et al., 2012; Phillips and Vieta, 2007; Almeida, et al., 2010). We argue that deficits in RDoC Negative Valence Systems likely reflect a risk factor for transdiagnostic symptoms that are common to depression and bipolar disorder. These mechanisms, however, may not be particularly informative in distinguishing what puts an individual at risk for symptoms of unipolar depression versus bipolar disorder. We further argue, however, that RDoC Positive Valence Systems, and, in particular, the Approach Motivation Construct within the Positive Valence Systems, is highly relevant for understanding differential risk for symptoms of unipolar depression versus bipolar disorder. Specifically, we propose that what differentiates risk for bipolar disorder versus unipolar depression is risk for mania, and one of the primary risk factors for mania involves a propensity to experience abnormally elevated approach motivation to rewarding cues in the environment. Thus, approach-related neurophysiological and neurobiological processes are clearly important for understanding what distinguishes bipolar disorder from unipolar depression, whereas threat processes may be more informative in understanding what is common or transdiagnostic across these illnesses. Finally, however, we suggest that this logic can only take us so far and, in line with the RDoC initiative, we argue that it is important to move beyond considering mood disorders as homogenous disorders or unitary constructs and instead examine the relationship between individual differences in frontal EEG asymmetry and specific mood-related symptom clusters. We address this objective in detail in the next section of the paper.

There is a convergence between research on frontal EEG asymmetry and fMRI reward-related neural activation in highlighting the importance of abnormalities in the left prefrontal cortex during approach-relevant tasks in the pathophysiology of bipolar disorder. As summarized, individuals prone to hypomania (Harmon-Jones, et al., 2002) and individuals with a bipolar spectrum diagnosis (Harmon-Jones et al., 2008) display abnormally elevated relative left frontal EEG activity during approach-relevant laboratory tasks, and, among individuals with a bipolar spectrum disorder, elevated relative left frontal EEG activity predicts conversion to bipolar I disorder (Nusslock et al., 2012b). In studies that have employed fMRI reward paradigms, the most reliable finding is that bipolar individuals display an abnormal increase in left lateral OFC activation during reward processing. This has been observed across the entire bipolar spectrum and among individuals at risk for bipolar disorder (Nusslock et al., 2012a; Bermpohl, et al., 2010; Chase et al., 2013; Caseras, et al., 2013; Harada, et al., 2013). Elevated left lateral OFC activation during reward processing in fMRI studies has also been observed across all phases of bipolar disorder, including mania (Bermpohl et al., 2010), euthymia (Nusslock et al., 2012a), and depression (Chase et al., 2013). Collectively, these findings suggest that there may be a trait-like, and perhaps endophenotypic, abnormality in left prefrontal activation in individuals with bipolar disorder during reward processing.

The lateral OFC is a complicated area of neuronal real estate, and the precise function of this region is still debated.[4] This region has been implicated in many cognitive and affective processes, including the regulation of affect (Wager et al., 2008), the effect of emotion on memory (Murty et al., 2010), and the flexible control of task performance (Hampshire, and Owen, 2006). The lateral OFC in the context of reward processing has been implicated more in arousal (Schmidt, et al., 2009) and salience (Lewis, et al., 2007), as opposed to positive hedonic evaluation. Thus, in line with the BAS/reward hypersensitivity model, this suggests that bipolar disorder is likely characterized by abnormalities in regulating arousal and behavioral activation during reward processing and goal pursuit.

An important topic for future research is examining the extent to which the neuronal source underlying elevated relative left frontal EEG activity in bipolar disorder corresponds to the location of elevated left lateral OFC activation observed during fMRI reward studies in bipolar individuals. Future research utilizing source localization techniques with EEG data and combining EEG and functional neuroimaging (fMRI, PET) will be useful in locating the neuronal source of abnormally elevated relative left frontal EEG activity in bipolar disorder and the proximity of this source to the left lateral OFC. This work will have important implications for understanding the mechanism underlying elevated approach motivation in bipolar disorder.

Although frontal EEG research and functional neuroimaging converge in highlighting decreased approach-related neural activation in

[4] In many areas of cognitive neuroscience, BA 47 is discussed as being a part of the ventrolateral prefrontal cortex (vlPFC; Badre and Wagner, 2007) or the inferior frontal gyrus (Kensinger and Corkin, 2004), as opposed to the OFC.

unipolar depression, they do not converge in the left prefrontal cortex. Indeed, the majority of prefrontal abnormalities observed in unipolar depression during fMRI reward tasks are in medial regions of the prefrontal cortex (Osuch et al., 2009; Smoski et al., 2009). Like bipolar disorder, however, it will be important to utilize source localization techniques and combined EEG and functional neuroimaging to identify the neuronal source of decreased relative left frontal EEG in unipolar depression to better understand the mechanisms underlying decreased relative left frontal EEG activity and reduced approach motivation in unipolar depression.

4. Asymmetrical frontal cortical activity and specific symptom clusters of mood and anxiety: an RDoC perspective

Thus far our review of relative left frontal EEG activity in unipolar depression versus bipolar disorder has focused primarily on individuals with DSM diagnoses. This is due to the fact that most of the research on this topic has been conducted on mood disorder samples. As stated, however, a goal of RDoC is to move beyond considering psychiatric disorders as unitary constructs and to instead examine the relationship between core–brain behavior dimensions and specific symptom profiles (Insel et al., 2010). The hypothesis is that a given psychiatric disorder, as currently defined, may involve symptom clusters characterized by distinct pathophysiological mechanisms. Some of these symptom clusters may be transdiagnostic, that is, common across multiple diagnostic disorders. Identifying pathophysiological mechanisms underlying transdiagnostic symptom clusters can help break down potentially arbitrary distinctions between categorically defined psychiatric disorders. Other symptom clusters may be more relevant to unpacking symptom heterogeneity within a particular classification or disorder. Identifying these symptom clusters has important implications for understanding the mechanisms underlying differential risk for specific symptoms. In this next section, and directly in line with the mission of the RDoC initiative, we examine possible relationships between relative left frontal EEG activity and specific symptoms or symptom clusters of unipolar depression, hypomania/mania, and anxiety. As discussed, we argue that indices within the Positive Valence Systems of the RDoC initiative, such as frontal EEG asymmetry, may be particularly relevant for identifying mechanisms of differential risk for specific psychiatric symptoms or symptom clusters.

4.1. Decreased relative left frontal EEG activity and anhedonia

To the best of our knowledge, no studies have directly examined the relationship between asymmetrical frontal cortical activity and specific symptom clusters of unipolar depression. We predict that decreased relative left frontal EEG activity will be most strongly associated with the depressive symptom of anhedonia. Anhedonia involves diminished interest or pleasure in response to stimuli that were previously perceived as rewarding during a premorbid state (Treadway and Zald, 2011). Anhedonia is a core feature of MDD, one of two required symptoms for the diagnosis of MDD, and experienced by approximately 40% of individuals with MDD (American Psychiatric Association, 2013; Pelizza and Ferrari, 2009). We predict that decreased relative left frontal EEG activity will be most strongly associated with anhedonia for both conceptual and empirical reasons. Conceptually, there is a strong convergence between the clinical characteristics of anhedonia and the approach–withdrawal model of frontal EEG asymmetry. The approach–withdrawal model argues that decreased relative left frontal activity is associated reduced approach motivation, decreased reward sensitivity, and a disengagement from goal pursuit (Coan and Allen, 2004). All of these characteristics are consistent with recent motivational models of anhedonia (Treadway and Zald, 2011). Empirically, self-report and behavioral evidence suggest that decreased approach motivation and reward hyporesponsivity in depression reflects anhedonia (see Treadway and Zald, 2011 for review; Clark and Watson, 1991; McFarland and Klein, 2009). Neuroimaging studies indicate that decreased reward-related neural activation in the fronto-striatal circuit, a circuit that is critical to facilitating approach-related motivation, is most strongly associated with anhedonia. For example, Epstein et al. (2006) reported that depressed subjects were characterized by reduced ventral striatal responses to positive pictures, and the strength of these responses was negatively correlated with self-reported anhedonia. Similarly, in a sample of patients with MDD, Keedwell et al. (2005) found a negative correlation between anhedonia (but not depression severity) and ventral striatal responses to positive stimuli. Furthermore, dopamine, the neurotransmitter most directly involved in facilitating approach-related behavior and encoding the motivational aspects of reward processing, has been implicated in anhedonia in animals and humans (Bragulat et al., 2007; Martinot et al., 2001; Sarchiapone et al., 2006). Studies have reported alterations of L-DOPA, a dopamine precursor, in the striatum in depressed individuals with flat affect or psychomotor slowing (Bragulat et al., 2007; Martinot et al., 2001). Additionally, one study that restricted its MDD patient sample to individuals with anhedonic symptoms reported decreased binding in the dopamine transporter gene (Sarchiapone et al., 2006). Importantly, we are not implying that the fronto-striatal circuit or dopamine transmission is necessarily the neuronal generators of frontal EEG asymmetry. We are stating, however, that frontal EEG asymmetry, fronto-striatal neural activation, and dopamine transmission are implicated in approach motivation. Given that decreased fronto-striatal neural activation and dopaminergic abnormalities are associated with anhedonia in depressed patients, it is reasonable to predict that decreased relative left frontal EEG activity also reflects anhedonia. Future research is needed to test this prediction. It will also be important to examine the extent to which decreased relative left frontal EEG activity relates to the motivational deficits and behavioral disengagement embedded in other depressive symptoms, such as sadness, fatigue or loss of energy, and psychomotor slowing.

4.2. Elevated relative left frontal EEG activity and approach-related hypomanic/manic symptoms

With respect to hypomania/mania, we predict that elevated relative left frontal EEG activity will be most strongly associated with a cluster of symptoms characterized by excessive approach motivation. The specific hypomanic/manic symptoms we predict will be a part of this cluster are elevated energy, increased goal-directed activity, decreased need for sleep, increased confidence, and irritability when goal-pursuit is thwarted. We base this prediction on the strong convergence between the clinical characteristics of these symptoms and elevated relative left frontal EEG activity, which is characterized by increased approach motivation, increased reward sensitivity, and elevated goal pursuit. Reward processing and approach motivation have not been directly implicated in cognitive activity (Johnson, et al., 2012), and thus, hypomanic/manic symptoms of elation and expansiveness, as well as cognitive symptoms involving distractibility and flight of ideas, should be less related to relative left frontal activity than the proposed cluster of approach-related hypomanic/manic symptoms. Decreased need for sleep is included in this cluster of approach-related hypomanic/manic symptoms given the coupling of reward processing and approach motivation with sleep variables (Holm et al., 2009; Murray et al., 2009), circadian influences (Murray et al., 2009; Hasler et al., 2010) and circadian genes (Forbes et al., 2011). Increased confidence is included in this cluster given that elevated reward sensitivity, approach motivation, and bipolar spectrum disorders are linked with elevated confidence following goal-attainment (Eisner et al., 2008; Johnson and Jones, 2009; Meyer, et al., 2010). Irritability is included given the neurophysiological overlap between anger and approach motivation (Harmon-Jones, 2003a,b; Carver and Harmon-Jones, 2009) and the increase in approach-related neural activity if goal-pursuit is thwarted (Harmon-Jones, 2007; Harmon-Jones and Sigelman, 2001). Lastly, we propose that approach-related hypomanic/manic symptoms may be etiologically distinct

from hyperactivity symptoms observed in attention deficit hyperactivity disorder (ADHD) given that ADHD has been associated with blunted reward processing and reward-related brain function (Volkow et al., 2009). However, ADHD is characterized by significant heterogeneity and there are high levels of comorbidity between ADHD and bipolar disorder (Wingo and Ghaemi, 2007). Thus, there may be symptom dimensions that cut across both ADHD and bipolar disorder that are characterized by enhanced approach motivation. Future research is needed to test these hypotheses.

Collectively, we have proposed that decreased relative left frontal EEG activity should be most strongly associated with the unipolar depressive symptom of anhedonia, and that elevated relative left frontal activity should be most strongly associated with a cluster of approach-related hypomanic/manic symptoms. This raises the obvious and important question of what mechanisms underlie bipolar depression, and in particular, anhedonia among individuals with bipolar disorder. In its original conceptualization, the BAS/reward hypersensitivity model proposed that reward hypersensitivity underlies risk for both hypomanic/manic and bipolar depression symptoms (e.g., Depue and Collins, 1999). The logic of this original conceptualization was that reward hypersensitivity should make individuals hypersensitive to both cues signaling the possible attainment and loss of reward, and that in the face of loss, individuals with reward hypersensitivity should be at increased risk for depression given the high value they place on rewards. From this perspective, reward hypersensitivity is viewed as a risk for excessive lability in approach motivation, with excessive increases in approach motivation (i.e., hypomania) occurring in the context of reward attainment and excessive decreases in approach motivation (i.e., depression) occurring in the context of reward loss. To date, however, there is rather limited support this lability perspective (Alloy and Abramson, 2010; Johnson, 2005; Johnson, et al., 2012), as the data indicate that reward hypersensitivity is more strongly related to risk for hypomanic/manic symptoms than bipolar depression symptoms. This suggests two possibilities. The first is that there is a relationship between reward hypersensitivity and bipolar depression that researchers have yet to identify. For example, by considering bipolar depression as a homogenous or unitary construct, researchers may have missed or masked the relationship between reward hypersensitivity and anhedonia among bipolar individuals. The prediction from this perspective is that individuals with reward hypersensitivity (i.e., individuals at risk for bipolar disorder) are at particular risk for anhedonia in the face of loss or the failure to obtain a desired reward. The second possibility, however, is that reward hypersensitivity is not related to bipolar depression and different etiological mechanisms (e.g., threat processing) may underlie the symptom of anhedonia among individuals with bipolar disorder compared to unipolar depression. Future research is needed to test these competing hypotheses.

4.3. Anxious apprehension and anxious arousal characterized by distinct profiles of relative left frontal EEG activity

Research on asymmetrical frontal cortical activity and anxiety disorder symptoms serves as an exemplar for how frontal EEG asymmetry might be used to identify distinct physiological mechanisms underlying specific symptom clusters. These analyses were spearheaded in an attempt to understand inconsistencies in the literature on frontal EEG asymmetry and anxiety disorders (see Thibodeau et al., 2006 for review). While some studies suggest that anxiety is associated with elevated relative left EEG frontal activity (Heller et al., 1997; Mathersul et al., 2008), other research has linked anxiety with reduced relative left frontal activity (e.g., Petruzzello and Landers, 1994; Tomarken and Davidson, 1994; Wiedemann et al., 1999), and a third group of studies suggest that anxiety is associated with symmetrical frontal alpha activity (i.e., neither elevated nor reduced frontal activity; Kentgen et al., 2000; Nitschke et al., 1999).

To reconcile these inconsistencies, Heller and Nitscke (1998) proposed subdividing anxiety into anxious arousal and anxious apprehension, two subtypes hypothesized to be associated with contrasting patterns of frontal brain activation. Anxious arousal (Watson et al., 1995), sometimes referred to as somatic anxiety (e.g., Lehrer and Woolfolk, 1982), is the predominant type of anxiety present in panic. It is characterized by a set of somatic symptoms, including shortness of breath, pounding of the heart, dizziness, sweating, and a feeling of choking. Consistent with the prototypic pattern observed in depression, anxious arousal is associated with reduced relative left (or increased relative right) frontal EEG activity (Wiedemann et al., 1999; Nitschke et al., 1999). In accord with Barlow (1991), anxious apprehension is characterized by a concern for the future and verbal rumination about negative expectations and fears. It is often accompanied by muscle tension, restlessness, and fatigue, and is frequently referred to as worry (e.g., Borkovec et al., 1983), cognitive anxiety (e.g., Lehrer and Woolfolk, 1982), or anticipatory anxiety (e.g., Klein, 1981). Several studies indicate that participants high in anxious apprehension display elevated relative left frontal EEG activity (Heller et al., 1997; Mathersul et al., 2008; Nitschke et al., 1999). Furthermore, individuals with elevated symptoms of both depression and anxious-apprehension do not display decreased relative left frontal EEG activity as typically observed in depression (Nitschke et al., 1999), suggesting that co-occurring anxious-apprehension may 'mask' or cancel out the relationship between depression and frontal EEG asymmetry.

The obvious question is what is driving elevated relative left frontal EEG activity in anxious-apprehension? Here we put forth two competing hypotheses, recognizing that there may be other factors involved as well. The first hypothesis argues that elevated relative left frontal EEG activity in anxious-apprehension reflects sustained, or perhaps even elevated, approach motivation. There is preliminary support for this hypothesis. First, if elevated relative left frontal EEG activity reflects elevated approach motivation, as summarized in the present paper, then it is reasonable to predict that elevated relative left frontal activity in the context of anxious-apprehension also reflects elevated approach motivation. Second, an initial study found that high levels of state anxiety correlate positively with a hypersensitive behavioral response to rewards (Hardin et al., 2006). Third, recent research demonstrates that asking individuals to recall autobiographical memories characterized by high levels of anxious-apprehension elevates self-report and neurophysiological (i.e., midline theta activity) indices of approach motivation (Walden et al., 2015). Finally, two fMRI studies report that individuals high in behavioral inhibition display elevated ventral striatal activation during reward processing, reflecting elevated approach motivation (Bar-Haim et al., 2009; Guyer et al., 2006). These findings are balanced, however, by an fMRI study reporting that social phobia, a disorder aligned with anxious-arousal, was associated with elevated reward-related neural activation, whereas generalized anxiety disorder (GAD), a disorder aligned with anxious-apprehension, did not show elevated reward-related neural activation (Guyer et al., 2012). Future research is needed to examine the hypothesis that elevated relative left frontal EEG activity in anxious-apprehension reflects elevated approach motivation. If results support this hypothesis, subsequent research may wish to examine whether elevated relative left frontal EEG activity and enhanced approach motivation may partially explain the high rates of comorbidity between anxious-apprehension disorders (e.g., GAD) and bipolar disorder.

A competing hypothesis, put forth by Heller and colleagues (Nitschke et al., 1999; Heller et al., 1997) is that elevated relative left frontal EEG activity in anxious-apprehension reflects elevated verbal mental chatter, cognitive activity, or rumination typically associated with anxious-apprehension. From this perspective, elevated verbal mental chatter or rumination may recruit Broca's area, a speech production region partially localized in the left prefrontal cortex, thus elevating relative left frontal EEG activity. Future research testing these competing hypotheses could help us better understand whether motivational

or cognitive processes underlie elevated relative left frontal EEG activity in anxious apprehension. Lastly, it will also be important to consider whether the observed reduction in relative left frontal EEG activity in anxious-arousal is driven by reduced approach motivation or other mechanisms.

Another implication of research on frontal EEG asymmetry and anxious-apprehension is that it may help resolve inconsistencies in the literature on frontal EEG asymmetry and depression. Studies that either by design or chance have a higher percentage of depressed individuals with co-occurring anxious-apprehension should observe a weaker relationship between relative left-frontal activity and depression given anxious-apprehension may mask or attenuate this relationship. Future research on frontal EEG asymmetry and depression should take into consideration the possible moderating influence of co-occurring anxious-apprehension.

5. Approach motivation, anger, and the RDoC Positive Valence Systems

The final topic we wish to discuss is the label ascribed to the Positive Valence Systems domain in the RDoC initiative. Valence-based frameworks are organized along a dimension of positive to negative emotions. Motivational frameworks, by contrast, organize emotions based on whether they facilitate approach versus withdrawal/inhibitory tendencies, irrespective of their valence. We argue that it would be optimal for the RDoC initiative to take more of a motivational, as opposed to a valence, perspective toward positive affect, emphasizing approach motivation tendencies over positive emotionality. Indeed, a more optimal title for the Positive Valence Systems domain might be 'Approach Motivation and Reward Systems'. From our perspective, this is not merely a cosmetic point but has important implications for how research on abnormalities in positive emotion, reward processing, and approach motivation in psychiatric disorders is conceptualized.

The first area of research that poses a challenge to a valence-based framework of emotion is the study of anger. Evidence indicates that anger is an approach-oriented emotion despite its negative valance. Theoretical models argue that anger often arises when movement toward a desired goal is blocked (Berkowitz, 1993; Depue and Zald, 1993), and that anger instantiates approach tendencies aimed at removing the impediment to goal pursuit (Carver and Harmon-Jones, 2009; Fischer and Roseman, 2007). Furthermore, individuals prone to anger are also prone to approach-oriented emotions. High self-reported trait anger and physical aggression have been found to correlate with self-reported BAS sensitivity (Harmon-Jones, 2003b). In an extension of this research, Smits and Kuppens (2005) showed that the tendency to express anger outwardly was associated with elevated BAS sensitivity whereas expressing anger inwardly was related to sensitivity of the Behavioral Inhibition System (BIS), which facilitates avoidance of threats in the environment. Taken together, studies using a variety of self-report measures support the idea that anger is an approach-oriented emotion particularly when expressed outwardly.

Critically, greater relative left frontal EEG activity is associated with increased trait and state-related anger. In an early study, Harmon-Jones and Allen (1998) found that participants who reported high trait levels of physical and verbal aggression, hostility, and the subjective experience of anger, exhibited elevated relative left frontal EEG activity at rest. Stewart et al. (2008) later replicated this link between trait anger and frontal EEG asymmetry (see Harmon-Jones et al., 2010, for a review of other replications). In line with an approach-motivational perspective, elevated relative left frontal activity is positively associated with 'anger-out', or the expression of angry feelings toward other people or objects (Hewig et al., 2004). Furthermore, laboratory tasks designed to elicit anger or thwart goal pursuit elevate relative left frontal EEG activity (Harmon-Jones, 2007; Harmon-Jones et al., 2003). Thus, despite its negative valence, anger is characterized by approach-related tendencies and approach-related neurophysiological activity.

Clinical research also poses a challenge to a valence-based framework of positive versus negative emotions. As outlined in the present paper, there is considerable evidence that mood disorders, to which the Positive Valence Systems are most applicable, are not simply characterized by the dysregulation of positive emotion, but rather by deficits in approach and reward motivational tendencies (Alloy and Abramson, 2010; Johnson, 2005; Nusslock et al., 2014; Treadway and Zald, 2011). Indeed, the BAS hypersensitivity model of bipolar disorder is fundamentally a motivational model of bipolarity, and does not focus on positive emotions per se. At the phenomenological level, there is clear evidence that mood disorder symptoms do not cleanly map onto a positive versus negative valence framework. Take for example mania, the prototypic expression of a hyperactive Positive Valence System. Although mania is frequently characterized by abnormally elevated or expansive moods, it is also frequently characterized by extreme irritability, anger, and negative affect when goal pursuit in thwarted. Irritability is a Criterion A manic symptom in DSM 5 (American Psychiatric Association, 2013) and, 51–75% of individuals with bipolar disorder report experiencing clinically significant levels of irritability during manic episodes (Cassidy et al., 1998). Furthermore, abnormally elevated approach motivation is a central symptom of both irritable and non-irritable manic states and increased goal-directed activity is one of the two most common behavioral prodromes or early warning signs of mania (Lam et al., 2001). Recognizing this literature, the DSM 5 was modified to place an added emphasis on changes in approach motivation, activity, and energy in the diagnosis of mania. With respect to unipolar depression, recent models of anhedonia, the prototypic expression of a hypoactive Positive Valence System, argue that anhedonia does not necessarily involve the absence of positive emotion or an inability to experience pleasure, but rather deficits in the recruitment of motivational resources to pursue rewards in the environment (Treadway and Zald, 2011). Take for example the "sweet taste test" which assesses hedonic capacity by having individuals rate the pleasantness of different sucrose concentrations. In four separate studies, individuals with depression and matched controls reported no differences in their ratings of the sucrose, suggesting that there is no deficit in the hedonic capacity to experience a natural reinforcer in depression (Amsterdam et al., 1987; Berlin et al., 1998; Dichter et al., 2010; Kazes et al., 1994). By contrast, a self-reported reduction in motivation or drive to pursue goals has the second highest odds-ratio in predicting a diagnosis of depression (50.1), ranking only below sad mood (61.2) (McGlinchey et al., 2006). Thus, collectively, there is growing evidence that abnormalities in motivational processes, irrespective of their valence, are central to the pathophysiology of mood disorders.

Lastly, both animal and human based research indicates that the dopaminergic fronto-striatal neural circuit is primarily involved in the motivational aspects of reward processing and relatively uninvolved in the generation of positive emotions or pleasurable hedonic experiences (Haber and Knutson, 2010). The fronto-striatal circuit is central to the Positive Valence Systems domain of the RDoC initiative, and implicated in the pathophysiology of unipolar depression (Forbes et al., 2009; Heller et al., 2009; Smoski et al., 2009), bipolar disorder (Bermpohl et al., 2010; Caseras et al., 2013; Nusslock et al., 2012a, 2014), schizophrenia (Grimm et al., 2014), ADHD (Volkow et al., 2009), and addiction (Volkow et al., 2012). Initially, dopaminergic activity in this circuit was thought to mediate an organism's experience of pleasure, or "yumminess", in response to rewarding stimuli (Wise, 1980). This perspective has largely been abandoned over the past thirty years, and the fronto-striatal circuit is now viewed as the engine that facilitates approach or goal-directed behavior to obtain rewards, as opposed to the mechanism by which an organism enjoys or savors a reward [the primary neurochemical involved in pleasurable hedonic experiences are endogenous opioids (see Treadway and Zald, 2011 for review)]. For

example, lesions to dopamine synapses in the ventral striatum do not impair hedonic liking expressions in rats (Berridge and Robinson, 1998), dopamine depleted mice still favor sucrose-water over regular water and demonstrate a morphine-induced conditioned pace preference (Cannon and Palmiter, 2003), and increasing dopamine shows no effect on liking or pleasure related behavior (Peciña et al., 1997). By contrast, altering dopaminergic functioning has a robust effect of an organism's motivation to pursue and work for rewarding stimuli (Salamone et al., 2007).

Collectively, this work poses a challenge to the Positive Valence Systems versus Negative Valence Systems framework put forth by the RDoC initiative. It suggests that neurophysiological (frontal EEG asymmetry) and neural (fronto-striatal circuitry) units of analysis that are central to the RDoC Positive Valence Systems are not uniquely involved in generating hedonically positive emotions, but rather in facilitating approach and reward-related motivation. Frontal EEG asymmetry is particularly informative to this topic given that elevated relative left frontal activity is associated with both positive and negative (i.e., anger) emotions. A goal of the RDoC initiative is to "capture fundamental underlying mechanisms of dysfunction" (Insel, et al., 2010). We argue that the first order of business in capturing these mechanisms is accurately defining them. Thus, precisely distinguishing between motivational and hedonic states will be critical in elucidating the biological mechanisms underlying psychiatric symptoms, developing a neuroscience informed classification system for psychiatric symptoms, a stated goal of the RDoC initiative, and developing targeted treatment protocols.

6. Conclusion

A goal of the RDoC initiative is to identify pathophysiological mechanisms that are common to multiple psychiatric disorders, as well as mechanisms that are unique to specific psychiatric symptoms or disorders, and that reflect biosignatures of differential risk for these distinct symptom profiles (Insel et al., 2010). We argue that the Positive Valence Systems domain of the RDoC initiative may be particularly relevant for identifying mechanisms of differential risk for specific psychiatric symptoms. The present paper began with a review of the literature indicating that risk for unipolar depression and bipolar disorder is characterized by distinct and opposite profiles of relative left frontal EEG activity, a neurophysiological index of approach motivation (Coan and Allen, 2004). Specifically, risk for unipolar depression is characterized by reduced approach motivation and decreased relative left frontal EEG activity (e.g., Thibodeau et al., 2006), whereas risk for bipolar disorder is associated with increased approach motivation and elevated relative left frontal EEG activity (e.g., Harmon-Jones et al., 2008; Nusslock et al., 2012b). In line with the RDoC initiative, however, we move beyond considering psychiatric disorders as unitary constructs and examine the relationship between frontal EEG asymmetry and specific symptom clusters of unipolar depression, hypomania/mania, and anxiety. For both conceptual and empirical reasons, we hypothesize that decreased relative left frontal EEG activity will be most strongly associated with the symptom of anhedonia. By contrast, we predict that elevated relative left frontal EEG activity will be most strongly associated with a symptom cluster of hypomanic/manic symptoms characterized by excessive approach motivation (i.e., elevated energy, increased goal-directed activity, decreased need for sleep, increased confidence, and irritability when goal pursuit is thwarted). Future research is needed to test these predictions as well as the relationship between reward hypersensitivity and bipolar depression/anhedonia. Research on asymmetrical frontal cortical activity and anxiety disorder symptoms serves as an exemplar for how frontal EEG asymmetry might be used to identify distinct physiological mechanisms underlying specific symptom clusters. Whereas anxious arousal is associated with reduced relative left frontal EEG activity (Wiedemann et al., 1999; Nitschke et al., 1999), anxious apprehension is associated with elevated relative left frontal activity (Heller et al., 1997; Mathersul et al., 2008; Nitschke et al., 1999). Future research is required to determine whether elevated relative left frontal activity in anxious apprehension reflects elevated or maintained approach motivation or other, perhaps non-affective mechanisms (e.g., Broca's area activation secondary to cognitive activity/rumination). Lastly, we argue that a motivational, as opposed to a valence, based framework organized around whether mechanisms facilitate approach versus withdrawal/inhibitory tendencies may be optimal for the RDoC initiative.

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