

CORTICAL ASYMMETRY AS A POTENTIAL LINK BETWEEN DEPRESSIVE
SYMPTOMS AND CARDIOVASCULAR REACTIVITY

by

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ABSTRACT OF THE THESIS

Cortical Asymmetry as a Potential Link between Depressive Symptoms and Cardiovascular Reactivity

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Although depression appears to be an independent risk factor for cardiovascular morbidity and mortality, the mechanisms by which emotion dysregulation leads to cardiovascular disease (CVD) are largely unclear. One suggestion that has received considerable attention is that depression promotes cardiovascular reactivity, which is hypothesized to contribute to CVD over time (Blascovich & Katkin, 1993; Krantz & Manuck, 1984). There are putative neurobiological pathways by which the brain communicates with the heart during the processing of emotion and stress. Prefrontal cortical asymmetry appears to be an objective physiological index of a depressive affective style that may promote autonomic nervous system dysregulation. In the proposed study, cortical asymmetry was examined as a predictor of cardiovascular reactivity. Sixty-four healthy female undergraduate students completed the Beck Depression Inventory-II (Beck et al., 1996) and a speech stressor task, in which they were asked to recall a personally-relevant event that made them feel depressed. It was hypothesized that greater self-reported depression would be associated with right-lateralized prefrontal cortical asymmetry, and that this asymmetry would be associated with increased systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) at rest and during the speech. Results indicated that greater self-reported depression was neither associated with right-dominant prefrontal cortical asymmetry nor cardiovascular resting activity nor reactivity to the stressor. Although several analyses

also revealed that cortical asymmetry did not moderate the effect of depression on cardiovascular reactivity, right dominant midfrontal cortical activity was a significant predictor of increased DBP reactivity to the speech stressor when electrocortical activity was treated as a categorical variable. Continued investigation of cortical asymmetry as a potential link between clinical depression and increased vascular resistance may be useful in clarifying the utility of EEG measures of depression and for identifying high-risk groups for CVD.

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INTRODUCTION

CVD is a leading cause of morbidity and mortality in the United States, and results in approximately \$400 billion in health-care expenditures each year (American Heart Association, 2008). Depression is one of the most consistent and robust predictors of cardiac events in both healthy individuals (Rugulies, 2003; Wulsin & Singal, 2003) and heart patient populations (Barth et al., 2004; Van Melle et al., 2004). The magnitude of the effects of psychosocial variables such as depression rival or exceed those of more traditional risk factors for myocardial infarction such as diabetes, smoking, hypertension, and obesity (Yusuf et al., 2004). Because psychosocial factors appear to contribute to the pathogenesis of CVD, pathophysiological mechanisms are now being explored. Several behavioral and direct pathophysiological mechanisms may mediate the effects of depression on the manifestation of CVD. Among an extensive list are the hypothalamic-pituitary-adrenal axis, autonomic nervous system activity, hypertension, cardiovascular reactivity, endothelial dysfunction, inflammatory markers, platelet dysfunction, coagulation factors, and glucose metabolism. Three factors that seem to be most strongly implicated in the association between depression and increased CVD risk are abnormalities in the autonomic nervous system, increased activation of the hypothalamic-pituitary-adrenal axis, and abnormalities in platelet function (Schlienger & Meier, 2003).

Sympathetic Nervous System Hyperactivity

There is ample evidence suggesting that depressed individuals show exaggerated sympathetic nervous system (SNS) responses to psychological stressors and enhanced SNS activity at rest (Guinjoan, Bernabo, & Cardinali, 1995; Lehofer, Hoehn-Saric, McLeod, Liebmann, Drnovsek, et al., 1997). One meta-analysis (Kibler &

Ma, 2004) determined that HR reactivity was most strongly related to depressive symptoms compared with other measures of autonomic nervous system activity. Some research has revealed that depressed patients with coronary heart disease have higher 24-hour HRs and higher heart HR responses to physical stressors than nondepressed patients (Carney et al., 1999). Depression is also associated with enhanced cardiovascular reactivity in response to psychological and physiological stressors in medically-well individuals (Lehofer et al., 1997). For example, medically-well depressed individuals demonstrate faster HRs in response to a speech stressor compared with non-depressed individuals (Light, Kothandapani, & Allen, 1998). Several additional studies (Sheffield, Krittayaphong, Cascio, Light, Golden, Finkel, et al., 1998; Thornton & Hallas, 1999; Guinjoan et al., 1995) found similar results, suggesting a link between depressive symptoms and mental stress-induced HR elevations.

Another manifestation of SNS hyperactivity is increased blood pressure (BP). In one study assessing CVD patients (Hallas, Thornton, Fabri, Fox, & Jackson, 2003), depression was the strongest independent predictor of BP prior to coronary artery bypass surgery, compared with anxiety; DBP was most strongly predicted by mood state, compared with other cardiovascular measures. Other research (Southard, Coates, Kolodner, Parker, Padgett, Kennedy 1986), conducted in a natural environment with an adolescent sample, suggested that depressed mood is positively associated with both ambulatory SBP and ambulatory DBP. Additionally, Light and colleagues (1998) found that both SBP and DBP levels were significantly higher among individuals who had the most depressive symptoms during baseline, challenges, and recovery, compared with individuals with low depression scores. An interesting explanation given for these findings is that homeostatic mechanisms in depressed individuals maintain BP at higher and higher set-points. Light and colleagues (1998) noted that, over time, this heightened BP could potentially result in hypertension, hypertension-related morbidity

(Simonsick, Wallace, Berkman, 1995), coronary atherosclerosis, and cardiac arrhythmia (Carney, Saunders, Freedland, Stein, Rich, & Jaffe, 1995; Cameron, 1996). Evidence derived from animal studies suggests that individual behavior characteristics (i.e., social status and aggression), physiologic responses to psychological stress, and instability of the social environment interact to affect atherogenesis among males; among females, aggressiveness that is purportedly linked to ovarian dysfunction may contribute to atherosclerosis (Clarkson, Kaplan, Adams, & Manuck, 1987).

Self-Report Measures of Depression

Observational studies have used a variety of measures of depression. While it is remarkable that a majority of these studies have supported an association between depression and increased risk for CVD, greater standardization of nomenclature and of diagnosis and assessment of depression is necessary (Davidson, Kupfer, Bigger, Califf, Carney, & Coyne 2006). The National Heart, Lung, and Blood Institute (NHLBI) recommends use of the Beck Depression Inventory (BDI; Beck et al., 1961) to measure depressive symptoms. However, even the NHLBI notes that self-report instruments may be limited (Davidson et al., 2006). Specifically, they may lack the ability to differentiate between somatic and cognitive symptoms. They may also be confounded with other negative affective states and psychiatric comorbidity, such as anxiety. Additional potential limitations of self-report measures of depression include inaccurate memory or interpretation of items (Holmes, Krantz, Rogers, Gottdiener, & Contrada, 2006) and social desirability (Edwards, 1957).

Although self-report measures might provide insight into depressive symptomatology, they may be inadequate for capturing core characteristics of affective style. Affective style has been defined as a valence-specific feature of emotional reactivity or emotional responding (Davidson, 2003), although more recent models have

emphasized the motivational features of emotion (Harmon-Jones, 2003). Neurobiological evidence suggests that lesions in critical zones of the left hemisphere play a role in the pathogenesis of depression (Robinson & Price, 1982; Robinson, Kubos, Starr, Rao, & Price, 1984), and might alter an individual's vulnerability to depression by affecting components of their affective style (Davidson, 1998). It is doubtful that an individual can self-assess brain abnormalities or predict their vulnerability to psychopathology, which may partly be to blame for inconsistencies in the literature on depression. One of the "seven sins" in the study of emotion (Davidson, 2003) is viewing emotions as conscious feeling states. Several converging lines of evidence suggest that much of the emotion-related neurobiological activity we generate is likely to be non-conscious (e.g., Damasio, 1998; LeDoux, 1995; Tankard, Waldstein, Siegel, Holder, Lefkowitz, Anstett, et al., 2003). To assess depression adequately, it is necessary to supplement self-report measures with other objective behavioral indices that may reflect aspects of emotion that are not fully represented in conscious experience and not amenable to self-report (Davidson, 1998). A brain measure could potentially tap into a depressive emotional style that might otherwise go unnoticed in studies only using self-report assessments. More specifically, it is of interest to determine whether or not conscious mood correlates with prefrontal function.

EEG Measurement of Depressive Affective Style

EEG appears to be a useful tool for examining the neural substrates of individual differences in affective style. Asymmetries in frontal EEG resting activity and state-related activation both have been shown to be involved in emotional responses and changes in emotional state (Coan & Allen, 2003). The prefrontal cortex is thought to be involved in guiding action, organizing motivational behavior, and anticipating rewards and punishments (Davidson, Pizzagalli, Nitschke, & Putnam, 2002). It subsumes the

dorsolateral, ventromedial, and orbitofrontal sectors, all of which are part of a larger overall circuit that involves subcortical structures such as the amygdala and hippocampus. Studies have shown that unilateral left-sided damage is associated with increased depressive symptoms (Gainotti, 1972), and that successful antidepressant treatment is associated with increased activation in the left-sided dorsolateral PFC (Kennedy, Evans, Kruger, Mayberg, Meyer, McCann, et al., 2001). Anatomical studies have also identified decreases in cortical thickness, neuronal size, and neuronal and glial densities in the left prefrontal cortices of patients with major depression (Rajkowska, 2000). Many EEG studies have identified reduced left relative to right activation in anterior scalp regions of depressed or dysphoric individuals (Bell, Schwartz, Hardin, Baldwin, & Kline, 1998; Bruder, Fong, Tenke, Leite, Towey, Stewart, et al., 1997; Debener, Beauducel, Nessler, Brocke, Heilemann, & Kayser, 2000; Pauli, Wiedemann, & Nickola, 1999; Reid, Duke, & Allen, 1998). Taken together, it appears that a depressive emotive style is associated with asymmetrical structure and function in the frontal cortex. Whereas the left frontal cortex is thought to participate in a process that underlies certain forms of positive affect and approach-related appetitive emotion, the right frontal cortex is thought to participate in negative affect and withdrawal-related emotion.

There are three theoretical models of affective style: (1) the valence model, (2) the motivational direction model, and (3) the valenced motivational model. Davidson and Irwin (1999) emphasize the valence model in their work, theorizing that depressive symptoms are increased following left-sided anterior PFC damage because this brain area is involved in processing positive affect, and when damaged, leads to deficits in the capacity to experience positive affect. The valence model thus suggests that individuals with reduced relative left-sided prefrontal activity have a more negative profile (e.g., poorer resiliency, decreased psychological well-being, ineffective coping), whereas

individuals with reduced relative right-sided prefrontal activity have a more positive profile (e.g., greater resiliency, increased psychological well-being, effective coping; Davidson, 2004). However, some theorists use a valenced motivational model to explain earlier work in which there was a confounding of affective valence and motivational direction. This model posits that the left frontal cortical region is involved in the expression and experience of positive and approach-related emotions (e.g., happiness), whereas the right frontal cortical region is involved in negative and withdrawal-related emotions (e.g., depression). Some work has been guided by a motivational direction model, which posits that the left frontal cortical region is involved in the expression and experience of approach-related emotions, whereas the right frontal cortical region is paired with withdrawal-related emotions (Davidson, 2000). It is possible that this model can explain earlier work in which valence and motivation were confounded as well as more recent work on anger. That is, it suggests that relative left dominance would be associated with happiness or anger that is hopeful or outwardly expressive, whereas relative right dominance would be associated with depression or anger that is hopeless or inwardly expressed. Regardless of which model is superior, the present study views depression as a negatively-valenced, withdrawal-related emotion that should theoretically be associated with greater electrocortical activity in the right frontal cortex and relatively less activity in the left frontal cortex.

Cortical Asymmetry as a Predictor of Cardiovascular Reactivity

Although animal studies suggest that there are pathophysiological pathways by which behavioral responses to stress contribute to atherosclerosis and its clinical manifestations (Clarkson et al., 1987), the precise role of frontal asymmetry in physical health is unclear. In order to assess the relationship between asymmetrical cortical activity, cardiovascular reactivity, and CVD, neurophysiological mechanisms by which

emotion relates to cardiovascular reactivity must be examined. There are several hypotheses concerning the way in which asymmetrical cerebral activation influences the heart, two of which are discussed and integrated below.

Brain-laterality hypothesis. The brain-heart laterality hypothesis (Lane & Jennings, 1995; Lane & Schwartz, 1987) posits that “asymmetrical cerebral activation is transmitted through the autonomic nervous system to cause a lateralized imbalance in sympathetic input to the heart, and a significantly lateralized induction could increase cardiovascular reactivity” (Harmon-Jones, 2003, p. 842). In other words, lateralized central autonomic drive is the putative neurological basis for cardiac arrhythmic vulnerability. Early animal research suggests that unilateral stimulation of sympathetic nerves induces repolarization inhomogeneity (Lown, Verrier, & Rabinowitz, 1977), increased risk for ventricular fibrillation (Schwartz, 1984), and increased HR (Henry & Calaresu, 1974). More recent human neuroimaging studies suggest that lateralized cerebral activity during stress elicits autonomic cardiovascular arousal (Critchley, Corfield, Chandler, Mathias & Dolan 2000), and that stress-induced brain asymmetry is exaggerated in coronary patients at risk of arrhythmia (Soufer, Bremner, Arrighi, Cohen, Zaret, & Burg, 1998). One particularly suggestive study reported that lateralized asymmetry in midbrain activity was positively associated with proarrhythmic abnormalities of cardiac repolarization in coronary patients during stress (Critchley, Taggart, Sutton, Holdright, Batchvarov, Hnatkova, et al., 2005). In sum, emotional arousal, stress, and/or asymmetrical cerebral activation have the potential to cause cardiovascular problems in vulnerable individuals.

Lovallo's model. Lovallo (2005) provides a comprehensive, hierarchical model of the mechanisms and pathways to CVD in relation to stress reactivity. The top level

consists of frontal-limbic¹ interactions, where particular events may be identified as requiring affect-related processes (e.g., feelings of fear). The middle level consists of the hypothalamus and brain stem areas, where specific physiological and behavioral responses are organized and appropriate outputs to the body are formed (e.g., onset of arousal). The lower level consists of peripheral effectors that may enhance cardiovascular reactivity and mediate cardiovascular reactivity. Specifically, autonomic and endocrine outflow is initiated and behavioral responses (e.g., increasing heart rate) are executed. In sum, this model describes a process by which emotions, cognitions, and motivations begin in the central nervous system circuits and culminate in peripheral organ reactivity. This enhanced reactivity, in turn, may contribute to the onset of CVD.

Integrated model. The brain-heart laterality model is most relevant to research concerning rhythmic cardiovascular activity, whereas Lovallo's (2005) model better suits research concerning the amplitude of BP and HR elevations. Because the proposed study examines the link between cortical asymmetry and the amplitude of cardiovascular reactivity, Lovallo's (2005) model will be applied while accounting for the lateralization component of the brain-heart laterality hypothesis (Lane & Jennings, 1995; Lane & Schwartz, 1987). Specifically, it is hypothesized that lateralized frontal cortex activation leads to abnormal interactions with the hypothalamus, brain stem areas, peripheral effectors, thereby resulting in enhanced cardiovascular reactivity. On a more microphysiological level, lateralized cerebral activity may descend contralaterally or ipsilaterally, stimulating the left and/or the right stellate ganglion in the heart. Since stimulation of the left and right stellate ganglion has been associated with increased mean arterial BP and HR, respectively (Lane & Schwartz, 1987), depressed individuals

¹ Although the limbic system concept is widely used to describe the brain circuitry that handles emotion, newer notions of emotion suggest that it may rest on inadequate theory (LeDoux, 2000). For purposes of this paper, the limbic system will be viewed as described by Lovallo (2005), in order to characterize his model, while acknowledging that it may require modification in light of emerging evidence.

with right lateralized cerebral activity could conceivably exhibit elevated BP and/or HR. Moreover, given that the right cerebral hemisphere is purportedly dominant for the elicitation of autonomic responses (Wittling, 1990), it is hypothesized that depressed individuals will exhibit autonomic hyperactivity, increased sympathetic outflow, and increased BP and/or HR compared with nondepressed individuals.

Speech Provocation of Cardiovascular Reactivity

Cardiovascular reactivity to psychological stress is a proposed mechanism by which depression may lead to CVD (Blascovich & Katkin, 1993; Krantz & Manuck, 1984). Laboratory mental challenges designed to emulate prolonged real-life stress are used to provoke enhanced cardiovascular reactivity through autonomic effects (Blascovich & Katkin, 1993; Krantz & Manuck, 1984). Kibler and Ma (2004) performed a meta-analysis to examine whether elevated symptoms of depression relate reliably to exaggerated cardiovascular reactivity, whether the depression-reactivity relation is stronger for some cardiovascular variables than others, and whether specific population characteristics or types of stress tasks are related to effect size. Studies in the meta-analysis included medically-well participants or patients with CVD, all of whom completed various depression self-report questionnaires (e.g., BDI, Center for Epidemiological Studies-Depression [CES-D], Depression Questionnaire [QD]) and performed stressful tasks (e.g., mental arithmetic, speech task, Stroop Color-Word Test). Results indicated that HR reactivity was moderately related to depressive symptoms, and was more strongly related to depressive symptoms than SBP and DBP reactivity. In moderator analyses, Kibler and Ma's (2004) findings suggested that gender, race, and stress task did not significantly influence the effect sizes for the relation of depressive symptoms to DBP or HR.

Upon closer inspection of studies using various stressors, it is apparent that speech tasks are amenable to simultaneously inducing a depressed mood and provoking cardiovascular reactivity. In one study, Hamer and colleagues (2007) had participants complete two separate speech tasks where they were asked to recall life events that made them feel angry or depressed. In response to the stressful negative mood induction, subclinically depressed individuals had significantly higher 3-methoxyphenylglycol (MHPG, the major metabolite of norepinephrine, a catecholamine) levels compared with less depressed individuals. These findings suggest that reactions to stress in individuals with subclinical levels of depressive symptoms reflect altered central adrenergic activation, and may be most detrimental when stress is relevant to their symptoms. In concordance with the integrated descending pathway model discussed above, stress might provoke lateralized cerebral activity in depressed individuals, which in turn, could lead to abnormal interactions with brain structures and ultimately enhance sympathetic output. Additionally, Light and colleagues (1998) found that subclinically depressed women had significantly higher HRs in response to an anger-arousing speech task compared with less depressed women, accounting for baseline cardiac activity. There are several hypotheses as to why a speech stressor may be selectively provocative of cardiovascular reactivity in depressed individuals. First, executive dysfunction may require depressed individuals to engage in more active coping and put forth more cognitive effort (Beblo & Herrmann, 2000). Second, negative self-reference and self-appraisal involved in giving a speech may activate negative cognitive schemas, which are salient features of depression (Brewin, Smith, Power, & Furnham, 1992). Third, autonomic dysfunction in depression may accompany physiological alterations, such as increased catecholamine secretion and/or receptor sensitivity (Barnes, Veith, Borson, Verhey, Raskind, & Halter, 1983; Lake, Pickar, Ziegler, Lipper, Slater, & Murphy, 1982) as well as increased hypothalamic-pituitary-adrenal activation (Nemeroff,

Widerlov, Bissette, Walleus, Karlsson, Eklund, et al., 1984). As stated above, lateralized frontal cortical activity associated with a depressive emotive style may provoke lateralized CNS projections to peripheral effectors that innervate the heart; in turn, dysfunction of the stellate ganglia in the heart might lead to enhanced cardiovascular reactivity.

STATEMENT OF THE PROBLEM

The mechanisms by which emotion dysregulation may lead to CVD are largely unclear. There are also some inconsistencies in relevant findings, which may be due to different methodologies and, especially, a preference for studying depression with self-report measures. To clarify this relationship, several literatures warrant integration. First, depression has repeatedly been associated with an increased risk of cardiovascular morbidity and mortality. Second, it appears that abnormalities in the structure and function of particular brain regions underlie depression; right-dominant prefrontal cortical activity appears to be an objective physiological index of a depressive affective style that may be implicated in abnormal autonomic activity. Third, there are putative mechanisms by which the brain communicates with the heart during the processing of emotion; it is therefore neurobiologically plausible that cortical asymmetry plays a role in abnormal cardiac activity at rest and in response to mood-related psychological stressors. Fourth, enhanced cardiovascular activity at rest and exaggerated cardiovascular responses to stress are both linked to increased risk of CVD.

In the proposed study, a psychophysiological approach was used to address gaps in this research. Cortical asymmetry appears to be an objective physiological index of depressive affective style and was therefore examined as a mechanism linking depression to cardiovascular reactivity. It was anticipated that investigation of this

descending pathway may contribute to clarification of the role of depression in the pathophysiology of CVD. A better understanding of risk factors such as depression may also aid in the prevention and control of CVD, such that prevalence rates, mortality frequency, and economic costs decline.

HYPOTHESES

Several hypotheses were tested concerning the relationship between depression and cardiovascular reactivity. It was hypothesized that:

- (1) Individuals who have higher self-reported depression will exhibit greater right than left frontal cortex EEG activity compared with less depressed individuals.
- (2) Individuals who have higher self-reported depression will exhibit significantly elevated resting HR, SBP, and DBP compared with less depressed individuals.
- (3) Individuals with higher self-reported depression will demonstrate exaggerated HR, SBP, and DBP responses to the stressor compared with less depressed individuals.
- (4) Individuals with right lateralized frontal EEG activity will exhibit elevated resting HR, SBP, and DBP compared with individuals without right lateralized frontal EEG activity
- (5) Individuals with right lateralized frontal EEG activity will demonstrate exaggerated HR, SBP, and DBP responses to the stressor compared to individuals without right lateralized frontal EEG activity.
- (6) Right lateralized frontal EEG resting levels of activity will moderate the effect of depression on HR, SBP, and DBP responses to the stressor. In other words, it is predicted that depressed individuals who possess a greater trait

tendency toward greater right frontal resting EEG activity will be more vulnerable to HR, SBP, and DBP reactivity compared with depressed individuals who possess a lesser trait tendency toward right lateralized resting EEG activity.

METHODS

Participants

Participants were 64 undergraduate females (45.3% White; 7.8% African-American; 25% Asian/Pacific Islander; 1.6% American Indian/Alaskan Native; 20.3% Other) at Rutgers. The State University of New Jersey, who chose to enroll as part of their undergraduate psychology course requirement. All participants were ages 18 and over, proficient in English, and right-handed, who had no self-reported history of CVD or neurological condition. Sample size was based on a power analysis assuming large effect sizes (Cohen's $d = .82$ and over) derived from well-conducted relevant empirical studies (e.g. Light et al., 1998) and Kibler and Ma's (2004) meta-analysis.

Procedure

A script was used by experimenters to standardize procedures. On arrival, a brief introduction to the study was presented to participants, and informed consent was obtained. Participants then sat alone in a room and completed a battery of questionnaires, including the Beck Depression Inventory-II (BDI-II; Beck et al., 1996) and various other psychological assessments and demographic forms.

Next, participants were fitted with a blood pressure cuff on their left arm as well as an electrode cap and electroculogram (EOG) electrodes on their head. Eight minutes of baseline EEGs was continuously recorded during alternating 60s eyes-open and 60s eyes-closed resting periods. Computer programming software prompted participants

and enabled precise time intervals for standardized measurement. During this period, HR, SBP, and DBP were also recorded in 60s increments.

After baseline recordings were completed, participants were informed that they would be expected to give a speech. They were instructed to speak about a life event that occurred within the past 6 months and caused them to feel depressed. Some examples of such life events (e.g., difficulty with school, problems with a relationship, illness of a close family member, being a victim of a crime) were presented. Participants were told that they have 2 minutes to prepare the speech, after which the 3-minute speech would begin. Lang's (1979) theory of emotional imagery was applied to maximize the likelihood of participants reliving an intense depressing experience. Specifically, participants were directed to attend to sensory and response events (sights, smells, sounds, physiological, and behavioral reactions) that occurred during the emotional experience. For the preparation portion of the task, participants were asked to think about the situation, focusing on visualizing its different aspects (e.g., location, persons involved), and concentrating on associated thoughts and feelings as they prepared for the speech they are about to give. For the speech task, participants were asked to recreate the incident from beginning to end, relaying what was said and done and describing associated thoughts and feelings. If participants stopped before 3 minutes elapse, they were prompted to provide more information about the event. A brief recovery period followed. EEG and cardiovascular recordings were obtained continuously during the task.

Qualitative information about the event discussed were obtained at the end of the task period. Participants were provided with a full oral debriefing following study completion.

Measures

Beck Depression Inventory-II (BDI-II; Beck et al., 1996). Depressive symptoms were assessed using the 21-item BDI-II (Beck et al 1996) self-report measure. Participants were asked to choose one statement that best describe themselves during the past two weeks. Nineteen of the items were on a 4-point scale ranging from 0 (absence of symptom) to 3 (highest level of severity for a given symptom), and the remaining 2 items allowed participants to indicate increases or decreases in these behaviors. Higher scores indicated greater depression. One sample item is “I do not feel sad (scored 1)”; “I feel sad much of the time (scored 2)”; “I am sad all of the time (scored 3)”; “I am so sad or unhappy that I can’t stand it (scored 4).” Item 9 was omitted from the questionnaire because of ethical concerns related to the report of suicide ideation/plan/intent.

Recall questionnaire. A Recall Questionnaire was used to qualitatively assess the nature of the event participants choose to discuss. They were asked to choose which category (i.e., romantic, occupation/job, family, academic, friendship, roommate-related, other) best describes the event. They were also asked to describe the event they discussed in 2-3 sentences, including different aspects of the situation (e.g., location, persons involved) and associated thoughts and feelings.

Demographic Measures. The questionnaire packet also included items on demographics, such as age, gender, and ethnic or racial background.

EEG Recording and Analyses. EEGs were recorded with a Lycra electrode cap (Electro-Cap International, Eaton, OH) from 19 scalp locations: AFz, Fz, F3/4, F7/8, FCz, Cz, C3/4, T3/4, Pz, P3/4, T7/8, O7/8 (International 10/20 system). The ground electrode was mounted in the cap on the midline between the frontal pole and the frontal site. The reference electrode was placed on the left ear, and data was also be acquired from an electrode placed on the right ear. Electrode impedances were all under 5000 Ω , and the

impedances for homologous sites were within 1000 Ω of each other. Electrooculogram (EOG) was recorded from the external canthus and supra-orbit of one eye to facilitate blink artifact reduction. EEG and EOGs were amplified with Neuroscan Synamps (Herndon, VA) that was band-pass filtered at 0.1-100 Hz, with a 60-Hz notch filter, and digitized at 500 Hz.

All placements were referenced to averaged mastoids (M1M2), manually scored for movement artifact, and submitted to a regression-based blink-correction procedure available in Neuroscan (Herndon, VA). Artifact-free epochs that were 1.024 s in duration were extracted through a Hamming window. Contiguous epochs overlapped by 75%. A fast Fourier transform was used to calculate the power spectra. Because alpha power is inversely related to cortical activity (Cook, O'Hara, Uijtdehaage, Mandelkern, & Leuchter, 1998), total power within the alpha (8-13 Hz) frequency range was obtained. The power values were log-transformed for all sites to normalize the distributions.

Frontal asymmetry indices were computed as the natural log of alpha power on the right minus the natural log of alpha power on the left, using midfrontal and lateral frontal sites F3/4, F 7/8. Because alpha power is inversely related to cortical activity, lower scores on the indices indicated greater relative right-hemisphere activity. For purposes of this paper, data were recoded such that higher values indicated more right dominant activity.

Cardiovascular Measures. HR, SBP, and DBP were measured using a DINAMAP Pro 100 (GE Healthcare) automated BP and HR monitor and by placing an occluding cuff around the participant's nondominant arm. SBP and DBP were measured in millimeters of mercury (mmHg), and HR was measured in beats per minute (bpm). HR was measured based on the detection of pulses in the brachial artery during cuff inflation. HR, SBP, and DBP readings were obtained at each minute of the baseline, the speech preparation task, and the speech task itself. To account for habituation, baseline

cardiovascular measures (SBP, DBP, HR) were computed as the mean of the Minutes 7 and 8 readings. Cardiovascular reactivity for each task was calculated by subtracting baseline measures from the mean of the Minutes 1, 2, and 3 readings for the speech task.

Data analyses

Raw data were inspected to determine whether or not assumptions for the general linear model are met. Specifically, normality, skew, kurtosis, and homoscedasticity were evaluated and influential outliers were excluded.

Multiple regression analyses were performed to examine relations between the predictor (i.e., depressive symptoms), EEG frontal asymmetry, and each of the baseline cardiovascular measures (i.e., HR, SBP, DBP) [Hypotheses 1, 2, and 4]. Subsequently, a hierarchical, mixed-model multiple regression analysis was used to examine the effects of the main study variables on HR, SBP, and DBP reactivity to the speech task [Hypotheses 3 and 5]. To determine whether the data supported EEG asymmetry as a moderator, a depression x cortical asymmetry product term (Step 2) was added to the main effects model for each cardiovascular measure [Hypothesis 6].

RESULTS

Descriptive Statistics

Each of the independent and dependent variables, except for BDI scores, were normally distributed as determined from visual inspection of histograms and assessment of skewness and kurtosis. Means and standard deviations are provided in **Table 1** (p.39). BDI scores were negatively skewed and therefore were log-transformed. Subsequent analyses were conducted with and without transformation. One participant who had a biologically implausible resting HR (126 bpm) was excluded from analyses.

Depression and Cortical Asymmetry

Regression analyses were conducted with BDI scores as the predictor and each cortical asymmetry value (F4/3, F8/7) as the dependent variable. There were no significant main effects of depression on cortical asymmetry, $F_s < 0.63$, $p_s > .43$.

Depression and Resting Cardiovascular Activity

Regression analyses were conducted with BDI scores as the predictor and each baseline cardiovascular measure (SBP, DBP, HR) as the dependent variable. There were no significant main effects of depression on resting cardiovascular activity, $F_s < 1.00$, $p_s > .60$.

Depression and Cardiovascular Reactivity to Speech Task

Regression analyses were conducted with BDI scores as the predictor and each cardiovascular reactivity change score as the dependent variable, with the associated baseline cardiovascular value included in the model as a covariate. Baseline HR was a significant independent predictor of HR reactivity ($B = -0.17$, $SE = .08$, $p < .04$). Baseline SBP and DBP did not significantly predict SBP or DBP reactivity, respectively, $p_s > .40$). There were no significant main effects of depression on cardiovascular reactivity to the speech task, $F_s < 0.96$, $p_s > .20$.

Cortical Asymmetry and Resting Cardiovascular Activity

Regression analyses were conducted with each cortical asymmetry value (F3/4, F7/8) as the predictor and each baseline cardiovascular measure (SBP, DBP, HR) as the dependent variable. There were no significant effects of cortical asymmetry on cardiovascular activity, $F_s < 1.00$, $p_s > .60$.

Cortical Asymmetry and Cardiovascular Reactivity to Speech Task

Regression analyses were conducted with each cortical asymmetry value (F3/4, F7/8) as the predictor and each cardiovascular reactivity change score as the dependent variable, with the associated baseline cardiovascular value as a covariate. Covariates did not significantly predict reactivity values, $ps > .09$. There were no significant main effects of cortical asymmetry on cardiovascular reactivity to the speech task, $F_s < 1.73$, $ps > .20$.

Interaction between Depression and Cortical Asymmetry

BDI scores, each cortical asymmetry value (F3/4, F7/8), and each baseline cardiovascular measure (SBP, DBP, HR) were centered around their means. Product terms, to represent interaction effects, were computed such that BDI scores were multiplied by cortical asymmetry values. Hierarchical regression analyses were conducted for each dependent variable (change scores for SBP, DBP, HR), with main effects for the associated baseline cardiovascular values, BDI scores and cortical asymmetry values entered in Step 1, and BDI x Cortical Asymmetry product terms entered in Step 2. There were no significant interaction effects on cardiovascular reactivity, $F_s < 1.27$, $ps > .30$.

Median Split Variables.

Based on original hypotheses, all variables were analyzed continuously, as described above. However, a majority of the studies on depression and cortical asymmetry (Bell et al., 1998; Bruder et al., 1997; Debener et al., 2000; Pauli et al., 1999; Reid et al., 1998) or cardiovascular reactivity (Light et al., 1998; Sheffield et al., 1998; Thornton & Hallas, 1999; Guinjoan et al., 1995) examine depression as a categorical variable. In these studies, clinically depressed patients were compared to healthy

controls, or a median or quartile split was conducted such that more depressed patients were compared to less depressed patients. Thus, analyses of variance (ANOVAs) were run wherein BDI scores (high vs. low) and cortical asymmetry values (right dominant vs. left dominant) were split at their respective medians to create dummy variables.

ANOVA using BDI scores (high vs. low) and cortical asymmetry values (right dominant vs. left dominant) with baseline cardiovascular DBP activity revealed a significant main effect of right dominant midfrontal cortical activity on DBP reactivity, such that individuals with right dominant midfrontal cortical activity tended to have more pronounced DBP responses $F(1, 63) = 4.10, p < .05$ (see **Figure 1**, p.40). Using the same model, there were no main effects of cortical asymmetry on SBP or HR ($ps > .10$). Additional analyses with midfrontal cortical asymmetry treated as a categorical variable (right dominant vs. left dominant), depression as a continuous variable, and baseline DBP activity as a covariate revealed a significant main effect of cortical asymmetry on DBP reactivity, such that individuals with right dominant midfrontal cortical activity tended to have more pronounced DBP responses, $B = .255, df = 62, p < .04$. There was no significant interaction between depression and cortical asymmetry on any cardiovascular measure.

DISCUSSION

The purpose of this study was to examine cortical asymmetry as a potential mechanism by which depressive symptoms are associated with cardiovascular reactivity. Findings indicated that greater self-reported depression was neither associated with right-dominant prefrontal EEG asymmetry nor cardiovascular resting activity or reactivity to a stressor. Exploratory analyses revealed that EEG asymmetry did not moderate the effect of depression on cardiovascular reactivity. However, in line

with hypotheses, right dominant midfrontal cortical activity was a significant predictor of increased DBP reactivity to the speech stressor when electrocortical activity was treated as a categorical variable. Given that cortical asymmetry did not predict SBP or HR reactivity, however, the aforementioned association between asymmetry and cardiovascular reactivity must be interpreted with caution.

Depression and Cortical Asymmetry

Our findings converge with data from several EEG studies (see Hagemann, Naumann, Becker, Maier, & Bartussek, 1998 for review), that did not reveal a significant association between anterior asymmetry and depression. There are many inconsistencies in prior literature on depression and prefrontal cortical asymmetry. Some lesion data (House, Dennis, Warlow, Hawton, & Molyneux, 1990) failed to replicate previous observations (Robinson & Price, 1982; Robinson, Kubos, Starr, Rao, & Price, 1984; see review by Robinson & Downhill, 1995) of an increase in depression following left prefrontal lesions. Whereas some work has shown asymmetrical decreases in frontal activation in depressed patients (see Davidson & Henriques, 2000 for review), several studies using both positron emission tomography (PET) and EEG methods have reported bilateral decreases in frontal activation in depressed patients compared with controls (described in Reid et al., 1998). Hagemann and colleagues (1998) also discuss several EEG studies that fail to find an association between depression and resting anterior asymmetry or emotion-induced changes in asymmetric anterior activation.

Our findings do not replicate those of Davidson and colleagues (1998), who have repeatedly found an association between anterior asymmetry and depression. While Davidson's original models emphasized valence, an updated version of this model emphasizes motivation and valence, proposing that two major forms of motivation and

emotion are represented in separate neural circuits in the prefrontal cortex and subcortical structures (Davidson, 1998; Davidson & Tomarken, 1989). Davidson and colleagues propose that “individual differences in prefrontal asymmetry are diatheses that bias a person’s affective style, and then in turn modulate an individual’s vulnerability to develop depression” (Davidson, 1998, p. 608). The emphasis is *not* on psychopathology. Instead, the model suggests that the proximal result of these individual differences in this circuitry is variation in components of affective style. The motivational direction hypothesis, however, would posit that emotions are either approach- or withdrawal-related and that cortical asymmetry is an indicator of one’s motivational tendency. For example, individuals with left dominant prefrontal activity would exhibit anger that is more hopeful or outwardly expressed, whereas individuals with right dominant prefrontal activity would exhibit anger that is more hopeless or inwardly expressed. However, analyses did not support an association between cortical asymmetry and behavioral inhibition/approach systems.

The present study did not reveal an association between self-reported depression and left or right prefrontal cortical asymmetry and thus did not support the application of models of affective style to cortical asymmetry and emotion. Therefore, assuming our findings can be replicated, individual differences in prefrontal cortical asymmetry did *not* act as diatheses that modulated an individual’s vulnerability for self-reported depression under the conditions of this study. These results neither supported a valence model, a motivational direction model, nor a valenced-motivational model. Rather, they suggest that self-reported depressive symptoms as assessed by the Beck Depression Inventory-II (BDI-II) may not be associated with a specific pattern of prefrontal activity. It is noteworthy that Davidson’s diathesis-stress model of asymmetry and depression acknowledges that individuals with right-dominant activity will not necessarily become depressed. However, his model posits that individual differences in

asymmetry will alter vulnerability to depression by affecting components of affective style, which has been defined by Davidson (2000) as a specific pattern of emotional responding. If the BDI-II provides an index of a depressive affective style, then this assertion was not supported by the present study.

Negative findings may also be attributed to several methodological limitations. First, for practical reasons, test-retest stability of cortical asymmetry was not examined. Several studies (e.g. Davidson & Hugdahl, 1996; Tomarken, Davidson, Wheeler, & Kinney, 1992) have tested individuals on two occasions to examine stability, to obtain a “true” score on the asymmetry metric, and to identify extreme individuals for comparison purposes. Although the present study involved only one session, analyses showed good internal consistency reliability between eyes-open and eyes-closed segments of the baseline period as well as within-hemispheric measurements (i.e., F4 and F8—right; F3 and F7—left) of alpha activity. The absolute level of alpha activity was also in concordance with previously published findings.

Second, individuals in the present study were not clinically depressed. Although it is possible that the neurobiology of subclinically depressed participants might not indicate cortical asymmetry, Davidson’s model (1998) explicitly states that the proximal result of cortical asymmetry is variation in components of affective style, *not* psychopathology. We found no such pattern, even when we compared more depressed to less depressed participants. Nonetheless, it would have been beneficial to have studied a larger cohort of moderately to severely depressed participants.

Depression and Cardiovascular Reactivity

Data from the present study revealed no association between depression and cardiovascular reactivity to an emotional recall task in medically well individuals with subclinical levels of depressive symptoms. Many studies have found autonomic nervous

system dysregulation in medically well and cardiac patients with major depressive disorder (e.g. Barnes et al., 1983; Veith, Lewis, Linares, Barnes, Raskind, Villacres et al., 1994). Fewer studies have examined ANS dysregulation in individuals comparable to those in the present study. Kibler and Ma (2004) examined 11 studies in their meta-analysis of literature on depressive symptoms and cardiovascular reactivity to laboratory behavioral stress. Although the samples, depression indices, stressor tasks, and CVR measures varied considerably across the 11 studies, several studies were similar to the present one in terms of methodology. Studies that assessed CVR using speech or recall tasks sampled African and White women and men (Haeri, Mills, Nelesen, Berry, Ziegler, Dillon, et al., 1996), chronic low back pain women and men (Burns, Wiegner, Derleth, Kiselica, & Pawl, 1997), women (Light et al., 1998), and women and men with CVD (Sheffield et al., 1998). Several studies used the BDI as the depression index (Burns et al., 1997; Light et al., 1998) and SBP, DBP, and HR as the CVR indices (e.g., Guinjoan et al., 1995; Haeri et al., 1996; Burns et al., 1997). The meta-analysis concluded that HR reactivity is moderately related to depressive symptoms and is more strongly related to depressive symptoms than SBP and DBP reactivity, suggesting that cardiac autonomic activation is more likely to relate to depression than vascular activation.

Our findings do not replicate the study that is most comparable to the present one in terms of methodology (Light et al., 1998). Light and colleagues (1998) tested the hypothesis that cardiovascular and sympathetic nervous system responses before and during behavioral stressors are exaggerated among women with depressed mood who do not have a clinical depressive disorder. Women underwent stress testing including baseline, postural challenge, a speech task describing responses to a recent anger-arousing experience and recovery. They found elevated SBP and DBP levels in individuals who had the highest BDI scores (N=15) compared to those who had the lowest BDI scores (N=15). The former group also evidenced increased autonomic

activity on several additional indices, including pre-ejection period, plasma norepinephrine, and cardiac output responses to the speech task. It is noteworthy that the sample sizes within each subgroup are small. The generalizeability of their findings might therefore be questioned. Our studies would not diverge if their findings were idiosyncratic due to sample nonrepresentativeness, in which case it may be that women with depressed mood who do not have a clinical depressive disorder do not exhibit cardiovascular reactivity. Additional studies are needed to determine whether there is an association between depression and cardiovascular reactivity in the absence of significant psychopathology and cardiovascular disease.

Unlike Light and colleagues (1998), we did not find any significant differences between more depressed and less depressed women on SBP or DBP reactivity to a speech stressor. Several methodological discrepancies between these studies exist. Light and colleagues (1998) had a 21-minute baseline period, after which participants completed a postural challenge (i.e. rising from sitting to standing for 3 minutes), a 2 minute preparation period for a speech task, and ultimately the speech task, where they were asked to talk for 3 minutes about a recent personal incident that had made her angry. In the present study, the baseline period was only 8 minutes, participants did not complete a postural challenge, and they spoke about a personally relevant depressing event. The equipment used and the size of the subgroup samples in the study by Light and colleagues (1998) also differed from the present study. Although many studies have recorded 8 to 10 minutes of baseline to obtain resting CV measurements, it is conceivable that our baseline was not long enough to enable full habituation to the experimental situation. If our resting baseline cardiovascular values were relatively elevated, there would be less intense increases in cardiovascular reactivity, which might have made it more difficult to detect an association with depression scores.

Additionally, Light and colleagues (1998) used a different speech task than that in the present study. We chose to ask participants about a depressing event because we were interested in examining EEG data on mood-induced cortical asymmetry. Hamer and colleagues (2007) used this task to examine the effects of depressive symptoms on cardiovascular and catecholamine responses to the induction of different mood states among fifty-five healthy men and women. They also used an angry recall task. Blood pressure, HR, and total peripheral resistance (TPR) were significantly increased in response to both tasks. Averaged over conditions, higher DBP and higher norepinephrine metabolite levels were observed in high depressive symptoms participants. Moreover, they used a 10-minute baseline period. These results provide evidence that the use of a depression-related speech task is sufficient for producing significantly elevated CVR. We also used Lang's (1979) theory of emotional imagery in the present study, which appears to be a useful strategy for inducing physiological correlates of mood. It is nevertheless possible that participants in our study were not fully attending to the task at hand or were not sufficiently involved to exhibit heart reactivity. Again, this might have resulted in relatively smaller change scores from baseline to speech task, which would make it more difficult to detect an association with depression.

Depression, Cortical Asymmetry, and Cardiovascular Reactivity

Contrary to the relevant theoretical models, we noted few significant relationships between frontal EEG activity and cardiovascular responses. One of the few exceptions indicated that a group of individuals with more right dominant activity exhibited significantly greater DBP reactivity compared to a group of individuals with more left dominant activity. These findings must be interpreted with caution because it is difficult to explain why individuals would show DBP reactivity, but not concomitant SBP or HR

reactivity. However, the pattern of data we obtained would be consistent with a link between cortical asymmetry and underlying increases in peripheral vascular resistance, rather than in myocardial activity. Examination of more direct indices of parasympathetic function (e.g., HR variability) and hemodynamic adjustments (e.g., cardiac output, peripheral vascular resistance) could help to clarify these findings. Moreover, given that self-reported depression did not predict DBP reactivity, further confirmation of these preliminary findings would suggest that cortical asymmetry may be a more sensitive indicator of emotion-related neurobiological activity than self-reported depression. Therefore, it remains a promising focus of research concerned with psychological determinants of cardiovascular reactivity and CVD risk.

Overall, this relative absence of findings may suggest a significant degree of dissociation between EEG and cardiovascular indices. Nonetheless, results of asymmetry analyses revealed partial support for the predictions formulated on the basis of Lane and Schwartz's (1987) theory that lateralized central autonomic activity could increase cardiovascular reactivity. That is, as predicted, participants who showed asymmetric right frontal EEG activity showed greater DBP responses to a stressor. The few available studies to date on this topic do not address resting electrocortical activity, but instead examine mood-induced central nervous system (CNS) activation as it relates to cardiovascular reactivity. This novel area of inquiry aims to clarify actual brain–heart interconnections. Such studies are critical first steps in the identification of brain–heart linkages that may be relevant to the development of cardiovascular disease or the elicitation of acute coronary events. While some work links CNS activation to emotional arousal and other work links emotional arousal to cardiovascular reactivity, these parameters are rarely examined in conjunction in one study. One of the only studies of this kind was conducted by Waldstein and colleagues (2000), who investigated electrocortical and cardiovascular reactivity among 30 healthy young adults during

positive and negative emotion, and examined the relation of asymmetric frontal lobe activation to cardiovascular responses. They found that both greater left frontal EEG response and greater right frontal EEG response were correlated significantly with increased HR reactivity during an anger-inducing recall of a personal event. In addition, a right lateralized frontal EEG response during anger-inducing tasks was associated with greater concomitant SBP. Given the growing emphasis on studies of emotional arousal, CNS activation, and cardiovascular reactivity, it is of interest in future studies to investigate a potential link between frontal EEG activation during a sadness-inducing recall task and cardiovascular reactivity. Based on models of Davidson (1998) and Lane and Schwartz (1987), it is theoretically conceivable that induced sadness would be associated with right dominant frontal EEG activation which, in turn, might contribute to lateralized sympathetic output and ultimately cardiovascular reactivity to a stressor. In one study, activation of thalamus and medial prefrontal cortex was noted during the viewing of films or recall of personal experiences evoking sadness (Lane, Reiman, Ahern, Schwartz, & Davidson, 1997). In line with Lane and Schwartz's brain-heart laterality model, it might be hypothesized that subcortical and cortical activation of these regions may contribute to cardiovascular reactivity.

Contrary to our predictions, there was no evidence of an interaction between cortical asymmetry and depression on cardiovascular reactivity. Interestingly, however, additional analyses indicated that individuals with BDI scores that were above the clinical threshold for depression showed a significant association between right dominant frontal EEG activity and cardiovascular reactivity. At a general level, these findings suggest that cortical asymmetry might moderate the effect of depression on cardiovascular reactivity among clinically depressed individuals. That is, in concordance with our predictions, it is possible that the combination of clinical depression and right dominant frontal EEG activity is most detrimental to one's cardiovascular system. However, this

investigation had limited statistical power due to a minimal sample of individuals who were above the clinical threshold for moderate depression (N=7). It is of interest to enroll more individuals to interpret these findings with more confidence.

CONCLUSION

The present findings suggest that frontal EEG activity may play a role in the magnitude or patterning of cardiovascular reactivity, especially among individuals with clinically relevant depression. Future research should test the validity of the valenced motivational model and determine whether it is beneficial to supplement self-report assessments with EEG measurements of affective style. Future research should also determine whether brain-heart linkages could play a role in eliciting myocardial instability or cardiac arrhythmias in vulnerable populations. Future studies should also aim to refine and standardize EEG methodology, assess additional cardiovascular measures of parasympathetic activity, and sample a larger cohort of clinically depressed individuals. Continued investigation of cortical asymmetry as a potential link between depressive symptoms and cardiovascular reactivity may be useful in identifying high-risk groups for CVD, assessing cognitive-behavioral treatment efficacy, and developing biofeedback treatments for enhanced cardiovascular reactivity.

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Table 1. Descriptive Statistics^a

	<i>N</i>	<i>Min.</i>	<i>Max.</i>	<i>Mean</i>	<i>Std. Deviation</i>	<i>Variance</i>
Depression						
BDI scores	6	0	28	7.89	6.38	40.77
Cortical Asymmetry^b						
LN(F8)	5	-1.2	1.7	0.1	0.7	0.5
LN(F7)	5	-1.2	1.9	0.1	0.7	0.5
LN(F4)	5	-1.0	2.2	0.6	0.7	0.5
LN(F3)	5	-0.8	2.3	0.6	0.7	0.5
Right dominance (F8/7)	5	-0.7	0.4	-0.8	0.2	0
Right dominance (F4/3)	5	-0.3	0.1	0	0.1	0
Baseline Cardiovascular Activity						
SBP	6	93.5	137.0	111.7	8.8	77.0
DBP	6	58.0	87.0	68.7	5.2	27.0
HR	6	47.0	96.0	72.5	10.4	109.0
Cardiovascular Reactivity (change scores)^c						
DBP	6	-14.2	26.2	7.7	6.5	44.2
HR	6	-6.8	49.2	12.6	9.1	82.8

^a One outlier was excluded prior to these analyses due to biologically implausible resting heart rate (126 bpm)

^b Data are missing from 11 participants due to insufficient experimental personnel (N=8) participant discomfort (N=2), or significant data artifact (N=1).

^c Data are missing from 1 participant due to equipment malfunction.

Figure 1. Individuals with right dominant frontal EEG activity exhibit significantly increased DBP reactivity compared to those with left dominant frontal EEG activity.

