Cardiac vagal control in depression: A critical analysis

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Abstract

Rapidly developing research has found abnormal cardiac vagal control (CVC) in several physical and mental health conditions. CVC findings in depression are mixed, and the degree to which CVC is compromised in depression is unclear. A meta-analysis of 13 rigorous cross-sectional studies reveals that a diagnosis of depression exerts a small-to-medium effect size on CVC, and explains only about 2% of the overall variance in CVC. More robust data may emerge from alternative approaches to the depression–CVC relationship, such as the use of CVC to predict the course of the disorder. Despite the vigor of recent work on CVC and depression, overall findings are suggestive rather than conclusive. Methodological desiderata and priorities for future research are discussed, including the need to clarify the etiological significance of CVC.

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1. Introduction

There has been a recent surge of research on biological predictors of health. One active area of work has been on cardiac vagal control (CVC), as indexed by the beat-to-beat variability in the timing of heart beats. A substantial scientific literature on CVC has accumulated. In fact, if one types CVC-relevant keywords such as “heart rate variability” and “respiratory sinus arrhythmia” into the PsycINFO database, these phrases return 538 and 201 hits, respectively. Indeed, the study of CVC has become sufficiently large and differentiated as to constitute a vigorous subfield, as seen in the convening of this special issue of Biological Psychology.

CVC is associated with an impressive array of physical and mental health outcomes. Included among the psychological correlates of high CVC are social competence (Eisenberg et al., 1995) and resiliency in the face of stressors (e.g. Fabes and Eisenberg, 1997). In turn, low CVC has been associated with negative mental health outcomes including anxiety (e.g. Thayer et al., 1996), disorders of impulse control (Beauchaine, 2001), and childhood behavior problems (e.g. Pine et al., 1998). Moreover, CVC exhibits relations with physical health. Low CVC is associated with a number of health problems; for instance, it is a prognostic indicator of risk for cardiac disease even after adjustment for known cardiovascular risk factors, and low CVC has been shown to confer increased relative risk of cardiovascular disease mortality (Dekker et al., 1997, 2000), and increased risk of coronary insufficiency, myocardial infarction, and death from both coronary heart disease and congestive heart failure (Tsuji et al., 1996).

The explosion of CVC correlates, while highlighting the relevance of CVC for psychobiological functioning, also suggests the need to take stock of existing findings (Beauchaine, 2001). For example, how should low resting levels of CVC be interpreted, when it is observed in illnesses as diverse as dyspepsia (Haug et al., 1994) and posttraumatic stress disorder (Cohen et al., 1997)? With the mushrooming number of findings, comparative analyses and close analyses of CVC in the context of individual disorders are sorely needed. This paper joins this effort by conducting a systematic analysis of the relation between CVC and one crippling psychiatric condition, major depressive disorder (MDD).

1.1. The aims of this paper

There are compelling reasons to investigate CVC in major depressive disorder. MDD not only involves the kinds of self-regulatory deficits that are often coincident with abnormal CVC, it also imposes a heavy burden of morbidity and mortality on society. In fact, MDD afflicts nearly one-fifth of the population over the lifetime (Kessler, 2002), and it is a leading cause of psychiatric hospitalizations, accounting for over 20% of economic costs for all mental illness (Greenberg et al., 1993).
The high prevalence and pervasive impact of depression underscore the need to elucidate factors, such as CVC, that may underlie depressed persons deficits in self-regulation and be implicated in the generation or maintenance of depressive episodes.

The literature on depression and CVC – though rapidly growing – has yet to receive a comprehensive review. Accordingly, this article will consider the depression–CVC relationship in several sections. The first briefly defines CVC and its theorized significance for general psychobiological adaptation and for major depression. The second considers the cross-sectional literature on levels of CVC in depression, including (a) the mixed reports of effects for CVC and depression, (b) the role of confounding factors that may contribute to this mixed pattern, and (c) methodological strategies to minimize these confounds. To estimate effect sizes of depression more accurately, the third section presents two meta-analyses of cross-sectional studies of depression and levels of CVC. Relatively modest effect sizes for depression are obtained; three possible explanations of these data are discussed. Alternative approaches to CVC and depression are presented in the fourth section, with indications that these approaches – such as the use of CVC to predict the course of depression – may yield a more robust and meaningful harvest. The paper concludes by highlighting several priorities for future research, including the need to clarify causal relations between cardiac vagal control and depression.

1.2. What is CVC?

Mammalian heart rate exhibits considerable beat-to-beat variation. Much of this variation reflects the parasympathetic control of heart rate by brain stem regions that project to the heart via the vagus nerve. Vagal nerve activity thus leads to regular oscillations in heart rate. Cardiac vagal control, essentially, reflects the degree to which there is tonic vagal influence on the heart, and more specifically reflects the extent of variability in heart rate that is gated by the respiratory cycle. That is, during inspiration, there is decreased vagal activity and heart rate speeds up, whereas, during expiration, vagal activity is reinstated and heart rate slows down. This coupling of heart rate by the vagus nerve that show first differentiation in mammals. The theory has focused on the evolutionarily newer branch of the vagus, in particular, an effenter pathway that emerges from a brain stem area called the nucleus ambiguous. This branch of the vagus terminates on a number of visceral organs (heart, soft palate, pharynx, larynx, esophagus, bronchi, facial muscles) that are notable for their role in emotion and communication. In other words, this vagal effenter projection, in addition to generating CVC, is theorized to play a critical role in motor pathways involved in vocalizations, facial expressions, and the communication of internal states to others, in other words, a large proportion of the unique social and survival behaviors observed in mammals.

An important aspect of this vagal pathway is its responsiveness to environmental demand. When a mammal is at rest, the vagal pathway works to “brake” energy expenditure (e.g. inhibiting the sympathetic influences to the heart, dampening the HPA axis). Accordingly, mammalian CVC is highest during unchallenged situations (e.g. non-REM sleep). In the context of the heart, the role of the vagal pathway in energy conservation is clear: the vagal input to the sino-atrial node of the heart slows heart rate well below its autonomous rhythm. Importantly, as environmental conditions become more taxing, this vagal brake can be actively and rapidly withdrawn to meet several metabolic demands, including increased attention and information processing, exercise, or coping with threats to life or limb (Suess et al., 1994; George et al., 1989). In sum, the application and withdrawal of the vagal “brake” is thought to play an important role in enabling the greater flexibility of mammalian behavioral routines (relative to other animals like reptiles).

In tying the vagal pathway to the evolution of attention, motor behavior, emotion, and communication in mammals, Polyvagal Theory has obvious implications for human adaptation. More specifically, high resting levels of CVC and a high capacity to appropriately withdraw CVC in the face of environmental demand are thought to facilitate physical and psychological functioning. In turn, low levels of resting CVC and a low capacity to appropriately withdraw CVC are expected to predict poor outcomes, reflecting weak regulatory control.

1.3. CVC’s theorized significance

CVC is of interest in part for the non-invasive window it affords onto activity in the parasympathetic nervous system, which is believed to perform broad homeostatic, growth, and restorative functions. Porges’s Polyvagal Theory (1995, 1997, this issue) has offered an influential account of the functional and adaptive significance of CVC. Briefly, Polyvagal Theory links developments in the evolution of the mammalian autonomic nervous system to affective experience, emotional expression, facial gestures, vocal communication, and contingent social behavior. The poly in polyvagal refers to evidence of two vagal systems, functionally indicated by two branches of the vagus nerve that show first differentiation in mammals. The theory has focused on the evolutionarily newer branch of the vagus, in particular, an effenter pathway that emerges from a brain stem area called the nucleus ambiguous. This branch of the vagus terminates on a number of visceral organs (heart, soft palate, pharynx, larynx, esophagus, bronchi, facial muscles) that are notable for their role in emotion and communication. In other words, this vagal effenter projection, in addition to generating CVC, is theorized to play a critical role in motor pathways involved in vocalizations, facial expressions, and the communication of internal states to others, in other words, a large proportion of the unique social and survival behaviors observed in mammals.
over attentional and emotional systems as well as behavioral inflexibility. In sum, Polyvagal Theory outlines the ontogenetic and phylogenetic significance of the vagal pathway and its role in self-regulation and self-regulatory problems. Because this theory operates at a relatively high level of abstraction, additional work is required to apply the theory to depression, or to other categories in psychopathology research (i.e. DSM-IV disorders).

1.4. Should depression be associated with CVC compromise?

Polyvagal Theory posits that CVC subserves social engagement and flexible adjustment to environmental demands. If so, one would expect CVC to be compromised in depression. First, depression is clearly associated with reduced social engagement (Rottenberg and Gotlib, 2004). Depressed persons not only withdraw from social activities, they also report experiencing social impairments that range from rejection, marital difficulties, and social isolation, to poor relationship quality with parents, spouses, and friends (reviewed in Segrin and Abramson, 1994). Second, depression is also clearly associated with inflexible responding to environmental demands (Rottenberg, 2005). For example, during naturalistic social interactions depressed persons often appear unresponsive, displaying fewer facial expressions and evidencing reduced gaze behavior (Ellgring, 1989). Moreover, experimental findings converge on the idea that depressed persons respond inflexibly to changing environments. For example, in paradigms that expose participants to both positive and negative emotional stimuli, depressed persons exhibit a constricted range of response in their self-report of emotion (e.g. Rottenberg et al., 2002a, 2005), facial expressions (e.g. Greden et al., 1986) and startle magnitude (e.g. Allen et al., 1999). Interestingly, the phenomenology of depression itself often involves perceptions that the environment is unchanging: patients often describe their world as being flat, dull, and empty, and remark that “everything is the same” (Healy, 1993). In sum, the kinds of inflexibility that are theoretically identified with compromised CVC appear evident in depressed persons.

Theorizing being clear, we are left with the empirical question: Do depressed persons actually exhibit compromised CVC? I now take up this empirical literature, first focusing on a body of work that compares levels of CVC between depressed and non-depressed persons.

2. Studies of CVC in depression

2.1. A mixed literature

It is common for empirical articles on CVC levels in depression to state that findings are mixed (e.g. Bär et al., 2004; Agelink et al., 2002a). That is, whereas several investigations report that depressed patients have lower levels of CVC than do non-depressed controls (e.g. Dalack and Roose, 1990; Lehofer et al., 1999; Rechlin et al., 1994c; Roose et al., 1989), others report no differences in CVC between depressed subjects and non-depressed controls (e.g. Lehofer et al., 1997; Jacobsen et al., 1984; Yeragani et al., 1991; O’Connor et al., 2002), even in the presence of higher heart rates among depressed than non-depressed participants (e.g. Moser et al., 1998).

Although it is accurate to state that CVC findings in depression are mixed, it is also important to pursue the reasons why findings are mixed. In particular, it is critical to address the role of confounding factors that may suppress or magnify the true effects of depression. One way to estimate the effects of depression on CVC more accurately is to perform a meta-analysis of methodologically strong studies. Such a meta-analysis is presented below.

2.2. Medication confounds

Medication is a well-recognized confound in the study of depression and CVC. The literature on antidepressant effects on CVC is particularly well developed. For example, there is overwhelming evidence that tricyclic antidepressants suppress CVC in both depressed individuals (e.g. Rechlin, 1994; Rechlin et al., 1994a,b) and in other patient groups (e.g. McLeod et al., 1992), although it should be cautioned that this effect on CVC may well reflect anticholinergic effects at the sino-atrial node, rather than altered central control mechanisms. Between-group designs nicely illustrate this medication effect: When depressed patients taking tricyclics were compared to depressed patients who were unmedicated and to healthy control subjects, only the tricyclic depressed group had lower CVC relative to healthy controls (Lehofer et al., 1997). Longitudinal within-subject designs further explicate this effect: depressed patients who do not differ on CVC from non-depressed controls before tricyclic therapy exhibit lower CVC than controls after tricyclic therapy is initiated (e.g. Rechlin et al., 1994a).

Tricyclic antidepressant effects on CVC have also been documented in within-group analyses of depressed individuals undergoing medication treatment. For example, Tulen et al. (1996a) measured high frequency heart rate variability before and 4 weeks after treatment with imipramine and found that patients exhibited a 44% post-treatment decline in high frequency heart rate variability. Moreover, in a sample of 104 depressed patients, the negative correlations between plasma concentration of amitriptyline and suppression of CVC was \( r = -0.5 \), a substantial effect (Rechlin et al., 1995a), reinforcing earlier findings of a strong relation between CVC suppression and tricyclic dosage (\( r = -0.78 \); Jacobsen et al., 1984). In sum, the suppressive effects of tricyclic antidepressants effects on CVC are robust, and appear to vitiate the probative value of studies that include patients on these medications.

There is active debate concerning the extent to which other types of antidepressant medication influence CVC. Briefly, some work finds that selective serotonin reuptake inhibitors (SSRIs) are relatively benign and do not share tricyclic antidepressants’ suppressive effect on CVC (Rechlin, 1994; Rechlin et al., 1994b; Roose et al., 1998). However, other studies conflict, indicating that SSRIs either elevate (Tucker
et al., 1997) or suppress CVC (Rissanen et al., 1998; Volkers et al., 2004; Bär et al., 2004). Non-selective serotonin reuptake inhibitors (NaSSRIs) have also been found to have depressive effects on CVC (Tulen et al., 1996a; Agelink et al., 2001; Bär et al., 2004) that equal or even exceed those of SSRIs (paroxetine; Straneva-Meuse et al., 2004). In a dramatic demonstration of antidepressant effects on CVC, Bär et al. (2004) reported no initial differences in CVC between unmedicated depressed patients and non-depressed controls, but after only two days of treatment with NaSSRI and SSRI antidepressants, patients exhibited lower CVC than non-depressed controls; this lower CVC continued to characterize the antidepressant treated group even as it showed clinical recovery 6–9 months later.

Beyond antidepressants, there are a host of other medications with definite or probable effects on CVC. These medications include beta-blockers, anti-histamines, and anti-psychotics (e.g. Silke et al., 2002; Lampert et al., 2003). Although these medications have not been specifically assessed as confounds for CVC in depression, it is clearly desirable for studies of CVC to exclude these medications. Fortunately, a number of studies of depression and CVC have followed this practice, and are hence included in the primary meta-analysis below.

2.3. Physical health confounds

Physical health confounds have been less well recognized in the study of depression and CVC. For example, physical activity level is positively associated with CVC (Mølgaard et al., 1994). Importantly, depression is associated with reduced physical activity and impaired exercise performance (Hollenberg et al., 2003), raising the concern that low CVC in depression more accurately reflects sedentary behavior. Unfortunately, studies of depression have not typically measured or statistically controlled for physical activity levels (e.g. regular exercise). The lack of such control may inflate estimates of the effect of depression on CVC.

Likewise, a number of physical illnesses are known to compromise CVC (e.g. diabetes). Perhaps most notably, CVC tends to be reduced among individuals who have cardiovascular problems, such as a myocardial infarction (Dekker et al., 2000). In fact, low CVC may constitute a component of the well-known risk for depressed persons to develop cardiovascular disease (Musselman et al., 1998). Noting the potential for physical health confounds, many studies of CVC in depression have followed the practice of excluding data when individuals have health conditions likely to affect CVC. Accordingly, the primary meta-analysis below considers studies of CVC in medically healthy samples.

Depression is well known to impair medical health, and depression among individuals with cardiovascular compromise appears particularly strong in its association with premature death (e.g. de Guevara et al., 2004). In one estimate, moderately or severely depressed patients with coronary artery disease were 84% more likely to die than non-depressed coronary artery disease patients over a 5–10 year period (Barefoot et al., 1996). Low CVC may be one of the key factors that mediates the increased risk for cardiac mortality and morbidity observed in depressed individuals (e.g. Carney et al., 1988, 1995; reviewed in Musselman et al., 1998). Therefore, the CVC–depression relation in cardiovascular disease has major public health implications. For these reasons, a secondary meta-analysis of the effects of depression on CVC in cardiovascular disease is also presented below (see Table 1).

<table>
<thead>
<tr>
<th>Study</th>
<th>Measures</th>
<th>Sample</th>
<th>Task(s)</th>
<th>Follow-up period</th>
<th>Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Agelink et al. (2001)</td>
<td>HF power, RMSSD</td>
<td>MDD (25)</td>
<td>Rest, deep breathing</td>
<td>(1) Pre- and (2) post-antidepressant treatment (21 days)</td>
<td>No relation between change in depression and change in CVC</td>
</tr>
<tr>
<td>Agelink et al. (2004)</td>
<td>Normalized HF power</td>
<td>MDD (23), Baseline</td>
<td>(1) Pre- and (2) post-antidepressant treatment (21 days)</td>
<td>Increases in CVC predict improved HAM-D scores</td>
<td></td>
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<tr>
<td>Balogh et al. (1993)</td>
<td>MSSD</td>
<td>MDD (17)</td>
<td>Rest</td>
<td>(1) Pre- and (2) post-antidepressant treatment (4–8 weeks)</td>
<td>Increases in CVC predict improved HAM-D scores</td>
</tr>
<tr>
<td>Carney et al. (2000)</td>
<td>RMSSD</td>
<td>MDD (30)</td>
<td>24 h recording</td>
<td>(1) Pre- and (2) post-cognitive behavioral therapy (4 months)</td>
<td>CBT associated with increased daytime CVC in severe patients; no effect in mild patients</td>
</tr>
<tr>
<td>Chambers and Allen (2002)</td>
<td>log HF power</td>
<td>MDD (16)</td>
<td>Quiet sitting</td>
<td>(1) Pre- and (2) post-acupuncture treatment (8 weeks)</td>
<td>Increases in CVC predict decreases in depression severity</td>
</tr>
<tr>
<td>Khaykin et al. (1998)</td>
<td>RMSSD</td>
<td>MDD (14)</td>
<td>24 h recording</td>
<td>(1) Pre- and (2) post-antidepressant therapy (6 weeks)</td>
<td>CVC unrelated to course</td>
</tr>
<tr>
<td>Nahshoni et al. (2004)</td>
<td>HF power</td>
<td>MDD (10)</td>
<td>Rest</td>
<td>(1) Pre- and (2) post-last ECT</td>
<td>CVC unrelated to course</td>
</tr>
<tr>
<td>Rottenberg et al. (2002b)</td>
<td>TF-RSA</td>
<td>MDD (55)</td>
<td>Deep breathing</td>
<td>(1) Baseline and (2) 6 months later</td>
<td>Lower baseline CVC predicts later remission</td>
</tr>
<tr>
<td>Schultz et al. (1997)</td>
<td>HF power</td>
<td>MDD (9)</td>
<td>Spontaneous breathing</td>
<td>(1) Pre- and (2) post-ECT</td>
<td>CVC lower after ECT; improved depression associated with reduced CVC</td>
</tr>
<tr>
<td>Volkers et al. (2004)</td>
<td>HF power</td>
<td>MDD (41)</td>
<td>Rest orthostatic challenge</td>
<td>(1) Pre- and (2) post-pharmacotherapy (4 weeks)</td>
<td>CVC unrelated to clinical state</td>
</tr>
</tbody>
</table>

Key: MSSD, mean squared successive difference of R–R intervals; RMSSD, square root of the mean squared differences of successive normal R–R intervals; HF power, high frequency power of heart period; TF-RSA, transfer function, respiratory sinus arrhythmia.
2.4. Psychiatric confounds

Low CVC has been observed in a variety of psychiatric conditions and CVC has been shown to be strongly influenced by the presence of co-occurring disorders, or comorbidity (e.g., Beauchaine et al., 2000). Depression is associated with considerable psychiatric comorbidity with other disorders (Kessler, 2002), and particularly with comorbid anxiety (Clark et al., 1994), which is a factor strongly associated with low CVC (Watkins et al., 1998; Friedman and Thayer, 1998a; Friedman, this issue). Depressed samples will almost inevitably contain many individuals with substantial anxiety symptomatology, if not outright anxiety disorders. It is possible that low CVC in depression may be a consequence of this comorbid anxiety. Justifying this concern about anxiety confounds, a stronger link between anxiety and cardiac vagal control than depression has been found in correlational data (Watkins et al., 1999). A rare group-level comparison of anxiety and depression indicated that CVC was lower in panic disorder patients than in depressed patients (Yeragani et al., 1991; but see also Yeragani et al., 1995). Finally, and also highlighting this concern about anxiety confounds, Tulen et al. (1996b) compared anxious and non-anxious depression and found that only the anxious depressed patients had lower CVC relative to non-depressed controls.

An issue related to anxiety confounds is that low CVC in depression could be a consequence of anxiety-related laboratory behaviors: More specifically, depressed persons may exhibit shallow (low tidal volumes) and rapid (fast respiratory rate) breathing, an anxiety-related respiratory pattern associated with low CVC (Tulen et al., 1996b, see also Wilhelm et al., 2004). To help address respiratory confounds, some studies have used procedures to control for respiratory rate and depth in CVC assessment (paced breathing procedure, Rottenberg et al., 2002b; see also, Grossman et al., 1991; Wilhelm et al., 2004).

In the main, however, the literature on depression and CVC has largely dodged the issue of anxiety and other psychiatric comorbidity. To the extent that other disorders are associated with suppressed CVC, unaddressed comorbidity may serve to inflate the effect sizes for depression reported in the literature. Clearly a priority for future work in this area will be to address comorbidity confounds—either through statistical procedures and/or through the use of non-comorbid depressive samples.

3. Meta-analyses of the effect of depression on CVC level

3.1. Procedure

A meta-analytic procedure was used to estimate depression’s effects on CVC. To achieve the most accurate estimate of effect sizes, methodologically strong studies that minimized the above confounds were sought. I performed a keyword-driven search using Medline and PsychINFO to identify potential studies for inclusion. In addition, I searched the reference sections of the located articles and reviews for additional sources. A research assistant in parallel independently performed a similar search, and the resulting sources were pooled. Only peer-review empirical journal articles that reported either a time or frequency-domain measure of the fast vagal respiratory-coupled influences on heart rate variability were considered further. To be included in the primary meta-analysis, the study had to include both depressed patients (diagnosed by clinical interviews) and a non-depressed comparison group, both of adult age (+18). For the primary meta-analysis, studies were also required to exclude participants who had health conditions that compromise CVC (cardiovascular problems), or who took medications with known or likely effects on CVC (including antidepressants). The secondary meta-analysis of cardiovascularly compromised samples of necessity relaxed these health and medication criteria. For several studies, where reported data were not complete (missing standard deviations), study authors were contacted for missing information, which was supplied in all cases but one.

For the primary meta-analysis, full data meeting all of these criteria were available for a total of 13 studies, which included 312 depressed persons and 374 non-depressed persons. For the secondary meta-analysis of individuals with cardiovascular conditions, data were available from six studies, which included 262 depressed persons and 334 non-depressed persons. Analyses included the following analyses of CVC level between depressed and non-depressed participants: (a) the percentage of all possible group comparisons that reached conventional levels of statistical significance; (b) the mean effect size for each study; (c) the overall average effect size (all studies pooled, weighted by sample size). Effect sizes are reported as the standardized mean difference, denoted by d (Cohen, 1988).

3.2. Effects in healthy participants

Results of the primary meta-analysis are reported in Fig. 1. Only 6 of 39 of all possible group comparisons (15%) between depressed participants and non-depressed participants reached conventional levels of statistical significance. The average effect for depression was significant in 3 of the 13 individual studies (23%). The overall effect size for depression across the 13 studies was $d = 0.332$ (95% CI, $d = 0.179–0.485$), with individual study $d$s ranging from 0.834 to $-0.078$. As expected, the overall effect of depression on CVC was significant, $t = 4.26$, $p < 0.001$. According to Cohen (1988) conventions for effect sizes, the overall effect of depression on CVC was small to medium-sized ($d$ small = 0.2, $d$ medium = 0.5).

3.3. Effects in cardiovascularly compromised participants

A secondary meta-analysis examined effects of depression on CVC in cardiovascularly compromised samples. In general, one would expect CVC to be low in cardiovascularly compromised samples because of impaired cardiac functioning, advancing age, and/or use of medications that suppress CVC. If CVC in cardiovascularly compromised individuals is indeed close to a...
floor value, there would be limited variability in these samples, presumably obscuring the effects of depression. The meta-analytic data displayed in Fig. 2 appear to belie these concerns about reduced effects, however, five of the 16 group comparisons (31%) between depressed and non-depressed participants reached statistical significance. Average effects of depression were significant in two of six individual studies (33%). The overall effect size for depression across the six studies was $d = 0.280$ (95% CI, $d = 0.126–0.434$), with individual study $d$s ranging from 0.701 to 0.112. As expected, this overall effect of depression was significant, $t = 3.57$, $p < 0.001$. In sum, in both healthy and cardiovascularly compromised samples, the effect of depression on CVC was of a similar magnitude, small to medium by Cohen’s conventions.

3.4. Summary and discussion of findings

Consistent with the predictions of Polyvagal Theory, depression is associated with an overall reduction in CVC level. At the same time, this effect is of small-to-medium size and explains only about 2% of the overall variance in CVC. From this standpoint, the effect of depression on CVC is smaller than expected. To put this difference in some perspective, a large meta-analysis of studies of cognitive psychophysiology in schizophrenia found the average group difference in performance between patients and controls was a full standard deviation ($d = 1$; Heinrichs, 2005). Another, more local point of comparison is with anxiety disorders and CVC where the literature suggests anxiety may involve a robust suppression of CVC. While there are as yet no comparable meta-analytic reviews of CVC and anxiety, one widely cited study (Friedman and Thayer, 1998b), reported a $t$ value of 5.67 in comparing panic disorder subjects to controls on HF power, panic subjects having less. This $t$ translated into a $d$ of 0.77, a large effect by Cohen’s conventions (B.H. Friedman, personal communication, August 27, 2004). Importantly, it appears that large effects of anxiety on CVC recur in the literature (e.g. $d = 0.69$; Thayer et al., 1996). To address the intriguing hypothesis that anxiety has more substantial effects on CVC than depression, a systematic comparative meta-analysis is needed.

Moreover, the overall $d$ of 0.332 reported here should be interpreted cautiously, as a liberal, upper-bound estimate of the effect size of depression on CVC. This meta-analysis was, for one, derived from published sources, which are likely to be biased toward larger effect sizes. Limited journal space (and other professionalizing pressures) prioritize the publication of positive findings over non-significant results. Additionally, the studies in the meta-analysis did not correct for several confounds that are likely to inflate reported effects for depression: (1) sedentary behavior; (2) comorbidity with other psychiatric disorders that suppress CVC; (3) depression-related respiratory influences on CVC. It is thus quite possible that once unpublished studies and confounding factors are taken into account depression’s effect on CVC is very modest indeed (e.g. $d = 0.2$).

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Fig. 1. Effect sizes (dots) and 95% confidence intervals (lines) for healthy samples. CIs that cross the zero line are non-significant (Volker et al., 2003; Yeragani et al., 2002).

Fig. 2. Effect sizes (dots) and 95% confidence intervals (lines) for cardiovascularly compromised samples. CIs that cross the zero line are non-significant (Stein et al., 2000).
3.5. Why are effects so modest?

It is not entirely clear why observed effects for depression are relatively small and inconsistent. The first, and perhaps the simplest, explanation of mixed findings is that depression is an incredibly heterogeneous disorder (Gollib and Hammen, 1992). For instance, patients often differ with respect to patterns of diurnal mood variation, a factor which has been associated with different patterns of CVC functioning (Rechlin et al., 1995b). Moreover, depressed patients also can differ appreciably in their severity, another factor that has been shown to be negatively related to CVC in some work (e.g. Agelink et al., 2001, 2002a; Guinjoan et al., 2004; but see also Moser et al., 1998; Watkins et al., 1999). Finally, evidence of gender differences in CVC has also been obtained among individuals with depressive symptoms (Thayer et al., 1998). Therefore, variation in sample severity, differences in clinical presentation, or even demographic characteristics may all contribute to the variation in obtained effect sizes observed across different samples of depressed persons.

A second, related explanation of mixed findings departs from the symptomatic complexity of the depressive syndrome (e.g. Sullivan et al., 2002). Taking a symptom-by-symptom approach to CVC, it may be that some depressive symptoms are associated with increased CVC, whereas others are associated with decreased CVC, a pattern which would tend to mute the overall effect of depression on CVC. Consistent with this possibility, Rottenberg et al. (2002b) reported no overall association between depression severity and CVC, but found that the sadness symptom was associated with increased CVC, whereas the suicide symptom was associated with decreased CVC. It is intriguing that an association between sad mood states and increased heart rate variability has been found elsewhere (Miller and Wood, 1997). The negative association between suicidality and CVC is likewise intriguing in light of elsewhere (Miller and Wood, 1997). The negative association between suicidality and CVC is likewise intriguing in light of elsewhere (Miller and Wood, 1997).

A third possible explanation for muted effects of depression on CVC level draws upon the theorized role of the vagal pathway in energy conservation. It is well-known that CVC tends to be higher during periods of energy conservation (e.g. sleep). Recent evolutionary approaches to the depressive syndrome view energy conservation and the suspension of motivated activity as evolved responses to harsh environmental conditions (Nesse, 2000). Indeed, parallels have been drawn between depression features such as behavioral inactivity and fatigue and other mammalian behaviors such as hibernation (Whybrow and Bahr, 1989). This admittedly speculative explanation of higher than expected CVC in depression awaits further testing, but it is interesting to note that high CVC has been found during winter among individuals with sub-syndromal seasonal affective disorder (Austen and Wilson, 2001).

4. Alternative approaches to CVC in depression

Cross-sectional studies of CVC level in depression are characterized by modest effects. This work is, of course, also essentially correlational. Thus, it is clear that alternative approaches will be needed to elaborate the functional relationships between depression and CVC. In particular, longitudinal designs are essential for elucidating the etiological significance of CVC. Moreover, it will be important to evaluate CVC reactivity in depression with the same care that has characterized studies of CVC level. Indeed, it has been shown that CVC level and CVC reactivity are distinct constructs that each contribute unique information to the prediction of risk (Salomon, 2005). In taking a broader perspective on the CVC–depression relationship, the following sections describe both recent work, and challenges that lie ahead.

4.1. Vagal reactivity in depression

Polyvagal theory describes the low capacity to appropriately withdraw CVC in the face of environmental demands as a major form of vagal compromise. Indeed, the capacity to temporarily suppress vagal influence – i.e. phasic regulation – appears to mediate attentional and emotional processes that permit an organism to optimally engage or cope with current challenges (e.g. Porgeres et al., 1996). Anxious individuals have been found to exhibit diminished vagal reactivity relative to non-anxious counterparts during and after emotion challenges (e.g. Cohen et al., 2000). Is this the case for depressed persons?

Unfortunately, here the database of studies on this question is somewhat limited. Two analog studies of individuals who were high in depressive symptoms found abnormalities in vagal reactivity during speech and cold pressor tasks (Hughes and Stoney, 2000; Sheffield et al., 1998). On the other hand, work with patients with a diagnosis of depression is mixed, with some work indicating greater vagal reactivity to orthostatic challenge in depression (Tulen et al., 1996a) but other studies...
finding no group differences (Straneva-Meuse et al., 2004). In clarifying whether depressed individuals in fact exhibit deficits in vagal reactivity, it will be important to report data in terms of change scores and to select tasks that reliably elicit vagal reactivity in healthy persons.

CVC has also been considered in terms of organismic resiliency in the face of stress (Porges, 1995; Fabes and Eisenberg, 1997). Thus, depression-related abnormalities in vagal reactivity may emerge after stress rather than during acute stress. In one test of this idea, my colleagues and I measured CVC fluctuations that occurred over the course of tearful crying episodes. We predicted that, whereas non-depressed persons who cried would exhibit increases in CVC as their crying episodes resolved, depressed individuals would not show increased CVC. As predicted, coincident with the resolution of their crying, healthy control participants who cried exhibited very large increases in CVC that, in fact, rebounded over baseline levels. By contrast, depressed participants who cried did not exhibit vagal rebound over this period (Rottenberg et al., 2003), a finding consistent with the idea of impaired homeostatic capacity in depression. Efforts to replicate these vagal rebound effects are clearly warranted.

### 4.2. CVC and the course of depression

CVC is a plausible factor to implicate in the precipitation and maintenance of depressive episodes. As mentioned above, CVC is theoretically related to self-regulatory capacity and it has shown to be predictive of other mental health outcomes in children and adults (Porges et al., 1996). Furthermore, CVC has been shown to exhibit some independence from clinical state, exhibiting correlates with temperament (Porges et al., 1996) and demonstrating moderate stability over time (Salomon, 2005; Rottenberg et al., 2001).

Fortunately, as can be seen from the array of studies listed in Table 1, investigation of a possible etiological role for CVC in depression is well underway. This work has focused on the use of CVC to predict the course of disorder among persons who are already depressed (see also Agelink et al., 2004 for reviews). At the outset, we do not expect that CVC will bear a one-to-one relation to the course of depression. For example, tricyclic antidepressants exert a strong suppressive relation on CVC, despite being quite effective in alleviating depressive symptoms (Rechlin et al., 1994b). The question then becomes: under what circumstance does higher CVC predict a more benign outcome in depression?

A number of positive findings have been obtained in this area. For example, in an early study, Balogh et al. (1993) recorded 5 min of heart-rate rhythm strip before and after a therapeutic trial of antidepressant medications in 17 adult patients diagnosed with major depressive disorder (MDD). Balogh et al. examined both whether pretreatment CVC was associated with treatment outcome, and whether CVC changed over time in concert with changes in severity of depression. The results of this study indicated that although pretreatment CVC did not predict treatment response, as measured by changes in Hamilton Rating Scale for Depression (HAM-D) scores, improvement in depressive symptoms was associated with increases in CVC. Agelink and colleagues, in an re-analysis of earlier CVC data, reported robust inverse correlations between changes in HAM-D scores and a measure of normalized HF power in two separate samples taking either nefazodone ($N = 23$, $r = -0.43$) or reboxetine ($N = 21$, $r = -0.40$) for 3 weeks (described in Agelink et al., 2004; see also Agelink et al., 2001, 2002b). Finally, in a sample of acute coronary event survivors in which significant depression symptoms were often present, de Guevara et al. (2004) reported a robust inverse correlation, $r = -0.49$, between decreases in HAM-D scores over 6 months and increases in CVC (as measured by HF power). Tempering these positive findings, however, a number of studies have found null effects when examining the relationship between CVC and course in the context of pharmacotherapy (Khaykin et al., 1998; McFarlane et al., 2001; Agelink et al., 2001; Volkers et al., 2004).

One concern about designs that measure CVC pre- and post-pharmacotherapy is medication confound. That is, without an untreated comparison group, drug effects on CVC are hard to disentangle from the effects of symptomatic improvement on CVC. Fortunately, a number of studies have assessed the relationship between CVC and the course of depression outside of pharmacotherapy. Perhaps most convincingly, Chambers and Allen (2002) examined depressed patients undergoing an 8-week trial of acupuncture therapy and found an association between increases in CVC and decreases in depression severity after 8 weeks. Similarly, a course of cognitive-behavioral therapy has been found to be associated with increased CVC, albeit among severely depressed patients (Carney et al., 2000).

Several studies adopting different approaches to the issue of treatment response in depression provide additional confidence that CVC has meaningful relations with clinical outcome. For example, in one study of phototherapy, a group of depressed patients who responded to four bright light treatment sessions with mood improvement exhibited acute increases in CVC (HF power) at the fifth bright light session, whereas depressed phototherapy non-responders did not show increased CVC after the fifth bright light session (Rechlin et al., 1995c). In a very different paradigm, O’Connor et al. (2005) found that CVC predicted outcome among bereaved individuals, who, of course, typically report significant depressive symptoms. More specifically, among those bereaved individuals who engaged in written disclosure of emotion, baseline CVC predicted the degree of improvement in depressive symptoms; CVC was unrelated to outcome in a bereaved control group who did not engage in written disclosure.

Despite the obvious promise of this area of study, it would be remiss to ignore a number of other negative and unexpected findings. For example, in our own laboratory we paradoxically

It should be pointed out that, in a number of studies, coarser measures of overall heart rate variability (Karpayak et al., 2004; Khaykin et al., 1998) and measures of low frequency power were predictive of depression outcomes (Khaykin et al., 1998). Thus future work may find that non-vagal influences on the heart have equal or greater etiological significance for depression.
found that lower levels of CVC in a large sample of depressed persons predicted 6-month recovery from depression (Rottenberg et al., 2002b). Several negative or paradoxical findings have also arisen in the context of electroconvulsive therapy (ECT), a well-established treatment for severe, intractable depression. Schultz et al. (1997) using spectral analysis to quantify CVC found that CVC was lower after ECT, and that the degree of improvement in depressive symptoms after ECT was associated with decreased CVC. In two other small patient study samples, measures of CVC assessed before and after ECT were both unrelated to course (N = 10; Nahshoni et al., 2004; N = 11; Karpyak et al., 2004).

One factor that complicates the synthesis of these discrepant findings (and the course literature on the whole) is the striking variation in how the primary data are reported and analyzed. Some investigators use initial levels of CVC to predict later symptoms of depression. Other use initial levels of CVC to predict change in depressive symptoms. Still others analyze the concurrent relation between change in CVC levels and change in depressive symptomatology as the primary analysis. While these analytic strategies are all doubtlessly related, and perhaps all are defensible, the choice of one strategy over another appears arbitrary. Thus, it would be useful to develop an a priori, theoretically grounded rationale for data analysis and reporting in prospective studies of CVC. This would improve the standardization the literature, replicability of results, as well as reducing the problem of Type I error.

In sum, these alternative ways of studying the CVC–depression relation show promise for elucidating the functional relationships between depression and CVC. At the same time, there is a continuing need for methodological refinement and additional empirical work. I close this article with recommendations to move this work forward.

5. Conclusions and unanswered questions

5.1. Conclusions

Rapid growth in the field of CVC has generated an impressive array of empirical findings, a situation which breeds both opportunities and hazards. In the area of depression and CVC, the flood of new work has oftentimes come at the expense of thoughtful assimilation of findings and careful methodology. This review indicates that when data from stronger cross-sectional studies are arrayed, CVC levels are a relatively a weak indicator of depression. Moreover, despite the development of different approaches to study CVC and depression, the causal chain between these two constructs remains largely unknown. In sum, the depression literature has generated many interesting leads but few strong conclusions concerning the CVC–depression relationship. In a young and vigorous subfield like this one, however, there is also much cause for optimism. If the literature can be made as systematic as it is energetic, the depression–CVC relation can be clarified in the near term. I close with three suggestions to guide the collection of more conclusive data.

5.2. Is there a vagal subtype of depression?

A major theme of this review has been the heterogeneity of depression, which is seen both clinically and with respect to CVC findings. A natural path for future work is to “clean-up” this heterogeneity by investigating possible subtypes or symptomatic presentations of depression that may be more clearly related to vagal compromise. Although initial investigations of depressive symptom patterns have not yet found strong evidence for a vagal subtype (Chambers et al., 2003), this is clearly an important future arena. Further clarification of a vagal subtype of depression will depend upon (a) additional theoretical work to generate more precise predictions concerning the putative depressive subtypes, and (b) the development of measurement strategies to identify predicted depressive subtypes (e.g. performance tasks, other physiological measures, novel vagal reactivity tasks, etc.).

5.3. How does CVC relate to other biomarkers of depression?

The empirical task of documenting CVC abnormalities in depression will continue. At the same time, the task of documenting the meaning of abnormal CVC becomes ever more pressing. Surprisingly little has been published that relates CVC to the larger neurobiology of depression. It is desirable in future work to assess CVC concurrently with other proposed biomarkers of depression, such as hypofrontality of the left frontal lobes or hypercortisolemia. Integrating CVC with other biological systems presents will present daunting theoretical and methodological challenges (Thayer and Lane, 2000; Agelink et al., 2004). Notwithstanding these challenges, CVC research will be greatly enhanced if CVC abnormalities can be mapped to other central and autonomic nervous system dysfunctions in depression.

5.4. Does CVC have a causal relation to depression?

Finally, a critical area of uncertainty concerns the causal relationship between CVC and depression. Work on CVC and depression course provides tantalizing clues that CVC may be involved in depression maintenance. Additional prospective designs are needed to develop stronger claims about CVC as a risk factor for depression. Among the most important kinds of designs will be studies that use CVC to predict (a) new episodes of depression in never-depressed individuals and/or (b) recurrence of depression in recovered persons.

Investigating a possible etiological role for CVC in depression is not only a matter for basic science. The vagal pathway is known to be plastic and is modifiable though direct electrical stimulation of brain regions that control the vagus nerve (George et al., 2000a,b) or non-invasive techniques such as biofeedback or breathing training (Hatch et al., 1992; Reyes del Paso et al., 1992). Indeed, vagal modification has potentially important future applications to the treatment of depression, and it is likely that there will be continuing investigation of this area in the coming years. Therefore, even as the final outcome
of this work is uncertain, the payoffs in clarifying the causal status of CVC in depression are likely to be large.

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References


