

# Vagal withdrawal to a sad film predicts subsequent recovery from depression

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## Abstract

Cardiac vagal tone, as indexed by abnormalities in the level and/or reactivity of respiratory sinus arrhythmia (RSA), has been related to psychiatric impairment, including risk for depression. Longitudinal studies of depression have focused on RSA levels and have found mixed support for the hypothesis that low RSA levels predict a more pernicious course of depression. The current investigation focuses on the relation between RSA reactivity and the course of depression. We measured depressed persons' RSA reactivity to sadness-, fear-, and amusement-inducing emotion films and reassessed participants' diagnostic status 6 months later. Depressed persons who exhibited a higher degree of vagal withdrawal to the sad film were more likely to recover from depression. Implications for the study of RSA in depression are discussed.

**Descriptors:** Depression, Vagal tone, Etiological significance, Emotion

Major Depressive Disorder (MDD) is a mental disorder associated with significant distress and impairment that afflicts nearly one-fifth of the American population (Kessler, 2002). It is the leading cause of psychiatric hospitalizations and accounts for over 20% of economic costs for all mental illness (Greenberg, Stiglin, Finkelstein, & Berndt, 1993). Due to its high prevalence and its impact, a large body of research has focused on elucidating the mechanisms underlying MDD.

One biological construct that has attracted considerable attention is cardiac vagal tone, which has been shown to be related to several forms of psychiatric impairment, including risk for depression. Psychiatric research typically employs indirect measures of cardiac vagal tone derived from an electrocardiogram (EKG). Variability in the time between heart beats (i.e., heart period) is controlled by a number of factors, one of which is respiration. Respiration acts as a gate through which efferent parasympathetic control via the vagus is admitted (during exhalation) or obstructed (during inhalation). The variability in heart period that corresponds with respiration is known as respiratory sinus arrhythmia (RSA). RSA as an estimate of the degree of vagally mediated cardiac control is often measured by quantifying heart-period variability occurring in the range of respiration ( $\sim 0.15$ – $0.40$  Hz; Berntson et al., 1997). Two of the most commonly assessed aspects of RSA are RSA level and RSA reactivity. Indeed, accumulating evidence suggests that RSA level

and RSA reactivity each contribute unique information in predicting adverse physical health and mental health outcomes (Salomon, 2005).

The majority of research on RSA and psychiatric disorders has focused on low resting levels of RSA, which are posited to index poor coping and impaired self-regulation (e.g., Porges, 1995, 1997). In cross-sectional investigations, low RSA levels have been associated with a broad range of problems, including anxiety (e.g., Thayer, Friedman, & Borkovec, 1996), hostility (Sloan et al., 1994), and disorders of impulse control (Beauchaine, 2001). With respect to depression, evidence of low RSA levels is more equivocal (e.g., Lehofer et al., 1997; Rechlin, Weis, Spitzer, & Kaschka, 1994): In a recent meta-analysis, a diagnosis of depression was found to be associated with a modest effect on RSA levels ( $d = .3$ ; Rottenberg, in press).

Cross-sectional studies of links between RSA levels and depression do not afford strong inferences about the etiological role of RSA. For this reason, researchers have begun to conduct longitudinal investigations, examining whether RSA levels predict subsequent depression. Specifically, a number of researchers have evaluated the hypothesis that low RSA levels among depressed individuals will predict a more pernicious course of disorder, as indexed by a failure either to recover or to demonstrate symptomatic improvement. Support for this hypothesis has been mixed. Several investigators have found low RSA levels to predict a more pernicious course of depression (Agelink et al., 2004; Balogh, Fitzpatrick, Hendricks, & Paige, 1993; Carney et al., 2000; Chambers & Allen, 2002; de Geuvara et al., 2004). Other researchers, however, have found either no association between RSA levels and the course of depression (Agelink et al., 2001; Karpyak, Rasmussen, Hammill, & Mrazek 2004; Khaykin et al., 1998; McFarlane et al., 2001; Nahshoni et al., 2004) or para-

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doxical relations between RSA levels and the course of depression, in which *lower* levels of RSA actually predict a more benign course of MDD (Rottenberg, Wilhelm, Gross, & Gotlib, 2002; Schultz, Anderson, & van de Borne, 1997). Thus, research on the etiological significance of RSA level in depression has so far failed to produce a clear pattern of findings.

In addition to the mixed empirical record, it is important to note that investigators have focused almost exclusively on RSA level. This exclusivity is puzzling because, in many ways, *RSA level* and *RSA reactivity* have been conceptualized as co-equal parameters that shape human self-regulation (Porges, 1995, 1997). In particular, Porges's Polyvagal Theory has been clear in elaborating the significance of vagal reactivity and its function in regulating biobehavioral responses to changing environmental demands (e.g., Porges, 1995; Porges, Doussard-Roosevelt, Portales, & Greenspan, 1996). This theory proposes that the vagal pathway works to "brake" energy expenditure when a mammal is at rest. This vagal brake, however, can be actively and rapidly withdrawn when environmental conditions become more taxing to meet several metabolic demands, including increased attention and information processing (Suess, Porges, & Plude, 1994), exercise, coping with negative emotion (Beauchaine, 2001; Friedman & Thayer, 1998; Thayer et al., 1996), and extreme threats to life or limb (George et al., 1989). The withdrawal of the vagal brake is thus thought to be adaptive and an important substrate for flexible behavioral routines (Porges, 1995, 1997).

Consistent with this formulation that a high degree of RSA reactivity is adaptive, investigators have found that greater RSA reactivity (i.e., large decreases from rest) has a buffering effect against the development of psychopathology (e.g., El-Sheikh, 2001). Individuals with various forms of psychopathology, such as anxiety disorders (Cohen et al., 2000; Thayer et al., 1996), are characterized by a low degree of RSA reactivity. Importantly, low RSA reactivity has, in some contexts, been shown to predict future behavioral problems (Porges et al., 1996). Underscoring the potential relevance of RSA reactivity to depression, cross-sectional research has shown RSA reactivity abnormalities both in clinically depressed persons (Rottenberg, Wilhelm, Gross, & Gotlib, 2003; Tulen et al., 1996) and in individuals reporting high levels of depressive symptoms (Hughes & Stoney, 2000; Sheffield et al., 1998; but see also Straneva-Meuse, Light, Allen, Golding, & Girdler, 2004).

From this perspective, it seems reasonable to postulate that impaired RSA reactivity should predict a more pernicious course of disorder for those with MDD. Despite the obvious promise and importance of this hypothesis, however, no study to date has examined the ability of RSA reactivity to predict the course of depression.

The current longitudinal study investigated RSA reactivity as a predictor of the course of depression. Diagnosed depressed individuals were shown sadness-, fear-, and amusement-inducing emotion films and RSA reactivity to each film was assessed. Emotion films were chosen because of their known capacity to elicit vagal withdrawal (e.g., Frazier, Strauss, & Steinhauer, 2004), as well as their strong experimental control and relatively low demand characteristics (Rottenberg, Ray, & Gross, in press). To examine the predictive utility of RSA reactivity, the diagnostic status of depressed persons was reassessed 6 months following the RSA assessment, and a determination of recovery was made for each participant. Assuming that relatively robust RSA reactivity in the face of negative emotion should be associated with better outcome, we predicted that those depressed persons who

exhibited the highest degree of vagal withdrawal to the sad and fear-eliciting films would be the most likely to fully recover from depression 6 months later.

## Method

### *Clinical Diagnostic Assessments*

*Time 1.* Fifty-five depressed participants took part in two waves of the study. The recruiting procedures, interviewing protocol, and clinical characteristics of this sample have been described in more detail elsewhere (Rottenberg et al., 2002). Briefly, all depressed participants reliably met DSM-IV criteria for Major Depressive Disorder using the Structured Clinical Interview for DSM-IV Axis I ( $\kappa = 1.00$ ; SCID-I; First, Gibbons, Spitzer, & Williams, 1995). All participants were fluent English speakers between the ages of 18 and 60. All participants provided written informed consent and were paid \$25 per hour.

To measure the severity of depression, depressed participants also completed the Beck Depression Inventory (BDI; Beck, Rush, Shaw, & Emery, 1979). The 21 items on the BDI assess cognitive, affective, behavioral, and physiological symptoms of depression, with the total score representing a combination of the number of symptom categories endorsed and the severity of the particular symptoms.

*Time 2.* Six months following entry to the study, a modified version of the SCID-I was administered. We used guidelines recommended by the National Institute of Mental Health (NIMH) Collaborative Program on the Psychobiology of Depression (e.g., Keller et al., 1992) to define recovery from depression. Depressed participants were considered to be recovered if they reported that essentially no signs of depressive illness were present in each of the past 8 weeks (e.g., no more than two symptoms experienced to more than a mild degree). We adopted this stringent definition of recovery because of the significant functional impairment associated with residual depressive symptoms (Judd, Paulus, Wells, & Rapaport, 1996).

### *Assessment of RSA Reactivity*

*Emotion film stimuli.* Selection of the three films was based on criteria recommended by Rottenberg, Ray, and Gross (in press). The fear film was 140 s in length and depicted heavy turbulence in the cabin of a commercial airliner. The sad film was 170 s and depicted a boy who was distraught at the death of his father. The amusing film lasted 120 s and depicted antic, slapstick-type comedy. Each of the emotion films was immediately preceded by a 60-s neutral film that depicted coastal landscape scenery. To maximize sensitivity to changes in RSA that were due to viewing each emotion film, each preceding 60-s neutral film was used as a baseline. Films and instructions were presented on a 20-in. television monitor at a viewing distance of 1.75 m.

*Procedure.* Participants were greeted and then positioned in a comfortable chair facing a video monitor in a quiet, well-furnished laboratory room. Following an orientation period and the attachment of physiological sensors, the two negative films were shown in counterbalanced order, separated by a 120-s arithmetic task to minimize carryover. The amusing film was shown last. All emotion films were immediately preceded by a neutral baseline film and were immediately followed by a 90-s period of quiet

**Table 1.** Initial Sample Characteristics by Time 2 Depression Status

Group	N	Age (years)	% Female	Education	BDI <sup>a</sup>	% Treated
Nonrecovered	44	34.0 (10.9)	66.3	6.5 (1.5)	23.9 (7.2)	60.9
Recovered	11	33.7 (11.2)	72.7	6.3 (1.5)	22.9 (6.4)	54.5

Note: Numbers in parentheses are standard deviations. All group comparisons  $p > .05$ .

<sup>a</sup>BDI: Beck Depression Inventory score.

sitting. After each period of quiet sitting, participants completed a short questionnaire that is outside the scope of the current investigation. Finally, participants were disconnected from monitoring devices, paid, and reminded that they would be contacted for follow-up interviews in 6 months time.

**Measurement of RSA.** EKG was recorded using Beckman miniature electrodes, placed in a bipolar configuration on opposite sides of the participant's chest and was conditioned via an SA Instruments 12-channel bioamplifier. Signals were sampled at 400 Hz using a Data Translation 3001 PCI 12-bit 16-channel analog-to-digital converter. Heart period (HP) was calculated as the interval (in milliseconds) between successive R waves. Because changes in respiratory rate and depth can confound the measurement of RSA (Grossman, Karemaker, & Wieling, 1991), two channels of respiration were measured with inductive plethysmography bands (Ambulatory Monitoring, Ardsley, NY) placed around the chest and abdomen. Calibration against fixed volume bags was accomplished by the least-squares method. Respiratory rate and tidal volume were calculated breath by breath using customized programs.

**Data reduction.** A customized computer program written in MATLAB (Wilhelm, Grossman, & Roth, 1999) was used for computation of RSA. The HP values were edited for outliers due to artifacts or ectopic myocardial activity, linearly interpolated, and converted into instantaneous time series with a resolution of 4 Hz. HP time series were linearly detrended and the power spectral densities were derived for each period using the Welch algorithm, which ensemble averages successive periodograms (overlapping 256-point segments were Hanning windowed and subjected to fast Fourier transform, and estimates of power were adjusted to account for attenuation produced by the Hanning window). For each epoch, RSA was computed by summing power spectral density values over the frequency band associated with respiration (0.15–0.50 Hz), and resulting values were normalized using the natural logarithm. RSA reactivity scores for each emotion film were computed by subtracting baseline RSA levels from emotion film RSA levels. RSA reactivity effects with  $p$  values less than .05 were regarded as statistically significant.

## Results

### Vagal Reactivity and Participant Characteristics

First, we examined whether vagal reactivity to emotional films was related to the demographic or clinical characteristics of the sample at Time 1. Few associations were observed. More specifically,  $t$  tests indicated that RSA reactivity to sad, fear, and amusing films was unrelated to gender, treatment status (treated vs. untreated), and medication use at Time 1 (medicated vs. unmedicated), all  $ps > .05$ . RSA reactivity to any film was also not

related to depression severity at Time 1 ( $r$  range,  $-.03 - .15$ ), all  $ps > .05$ .

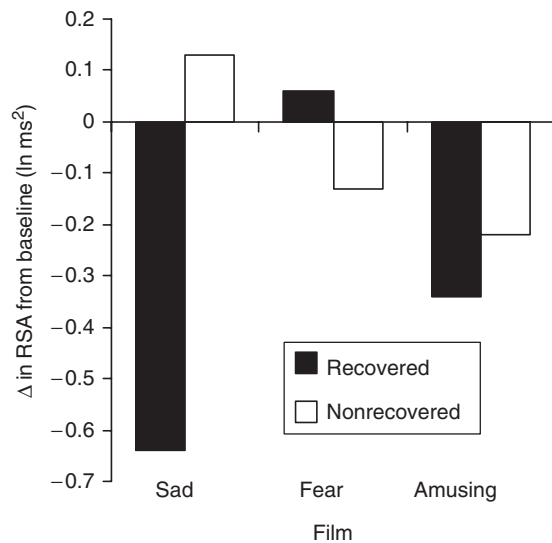
### Prediction of Time 2 Depression Status

Based on the SCID interviews at Time 2, 11 of the 55 depressed participants (20%) were completely recovered from depression and 44 (80%) were not recovered. The demographic and clinical characteristics of these two groups are summarized in Table 1. Because RSA reactivity scores can be susceptible to floor and ceiling effects, we first examined whether baseline RSA was related to Time 2 recovery status using Time 1 RSA baseline scores to predict Time 2 depression status (recovered, not recovered). None of the RSA baseline scores were significantly related to diagnostic outcome (fear baseline:  $\beta = -.35$ ,  $p > .05$ ; sad baseline:  $\beta = -.02$ ,  $p > .05$ ; amusing baseline:  $\beta = -.27$ ,  $p > .05$ ).

For our primary analysis, we conducted binary logistical regression analyses using Time 1 RSA reactivity to each emotion film to predict Time 2 depression status. Neither RSA reactivity to the fear film nor RSA reactivity to the amusing film predicted Time 2 depression status (fear:  $\beta = .41$ ,  $p > .05$ ; amusing:  $\beta = -.26$ ,  $p > .05$ ). In contrast, RSA reactivity to the sad film predicted recovery from depression at Time 2,  $\beta = -1.42$ ,  $p < .05$ . Follow-up  $t$  tests indicated that depressed persons who later recovered exhibited significant vagal withdrawal to the sad film at Time 1,  $M = -0.641$ ,  $t(10) = -2.40$ ,  $p < .05$ ; depressed persons who did not recover at Time 2 exhibited nonsignificant increases in RSA to the sad film at Time 1,  $M = 0.127$ ,  $t(44) = 1.28$ ,  $p > .05$ . In sum, vagal withdrawal to the sad film at Time 1 uniquely predicted recovery from depression 6 months later. This emotion-specific pattern of RSA reactivity data is displayed in Figure 1.

### Control Analyses

To control for three potential confounds, we assessed whether the predictive power of RSA reactivity might be secondary to respiratory changes during the sad film, to medication use, or to initial depression severity. We first repeated the binary logistic regression with change in respiratory rate and tidal volume entered as covariates. Neither respiratory rate nor tidal volume predicted Time 2 diagnostic status, whereas RSA reactivity remained a significant predictor of outcome,  $\beta = -1.26$ ,  $p = .05$ . Second, we repeated the regression analysis using only the subsample of 31 unmedicated participants. As was the case in our previous analysis, RSA reactivity to the sad film continued to predict recovery from depression,  $\beta = -1.73$ ,  $p < .05$ . Finally, we repeated the regression with Time 1 depression severity included as a covariate in both the full sample and in the unmedicated subsample. In both cases, RSA reactivity to the sad film predicted recovery from depression (full:  $\beta = -1.45$ ,  $p < .01$  subsample:  $\beta = -2.10$ ,  $p < .05$ ).



**Figure 1.** Respiratory sinus arrhythmia reactivity ( $\Delta$  from baseline  $\log \text{ms}^2$ ) to sad, fearful, and amusing films at Time 1 by recovery status at Time 2.

## Discussion

Empirical and theoretical perspectives have converged on the construct of cardiac vagal tone as a potentially important substrate for biobehavioral regulation in the face of changing environmental demands. The current study was the first to investigate the significance of vagal tone reactivity with respect to understanding the course of clinically significant depression. Demonstrating the promise of this approach, our principal finding was that a higher degree of vagal withdrawal to a sad film (but not to a fearful or an amusing film) predicted full recovery from depression 6 months later. Importantly, vagal withdrawal continued to predict 6-month outcome even after controlling for respiratory changes exhibited during the sad film, medication use, and severity of Time 1 depressive symptoms.

Importantly, analyses of baseline RSA cast doubt on the possibility that a floor effect explained the predictive power of RSA reactivity. More specifically, there was no evidence that the lack of vagal withdrawal seen among depressed persons who

failed to recover reflected unusually low baseline RSA levels in this group: In fact baseline RSA levels in nonrecovered persons were actually nonsignificantly *higher* than among depressed persons who recovered. Finally, and also inconsistent with a floor effect, RSA reactivity predicted outcome in an emotion-specific fashion. Indeed, the specificity of the findings to the sad context merits comment.

Given the salience of negative emotion to vagal withdrawal, we originally predicted that vagal withdrawal to both negative films would predict recovery. Instead we found unique predictive power in the sad context. In fact, no trace whatsoever of a fear effect is evident in Figure 1, which suggests that this null finding was not simply a result of insufficient statistical power. At the same time, the novelty of this vagal reactivity paradigm and the relatively small number of patients who achieved full recovery from depression suggest that caution is warranted and replication is needed before concluding that there is etiological specificity for sadness in this context. Interestingly, in a very different paradigm, we found some evidence of etiological specificity for sadness: In an independent sample, those depressed persons who related the saddest autobiographical memories (but not the happiest autobiographical memories) were the most likely to exhibit symptomatic improvement (Rottenberg, Joormann, Brozovich, & Gotlib, in press).

In closing, we should point out two limitations of the current study that suggest important future directions for extending these encouraging findings and delineating more finely the nature and significance of RSA reactivity in depression. First, although the current study employed emotion films that are well-controlled stimuli and are known to elicit vagal withdrawal, the degree of vagal withdrawal elicited during emotion films is relatively modest. Thus, it would be useful to extend these findings using experimental tasks that reliably elicit more pronounced vagal withdrawal (e.g., speech preparation task). Second, this was a naturalistic study of the course of depression. RSA reactivity predicted 6-month outcomes even though depressed participants were heterogeneous with respect to the medications and treatments they received during the follow-up period. Although our analysis suggests that the predictive power of RSA reactivity was unrelated to treatment or medication, more controlled designs (i.e., a random assignment to treatment) are needed to completely eliminate these variables as possible explanations for our findings.

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