RSA fluctuation in major depressive disorder

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Abstract

Cardiac vagal control, as measured by indices of respiratory sinus arrhythmia (RSA), has been investigated as a marker of impaired self-regulation in mental disorders, including depression. Past work in depressed samples has focused on deficits in resting RSA levels, with mixed results. This study tested the hypothesis that depression involves abnormal RSA fluctuation. RSA was measured in depressed and healthy control participants during rest and during two reactivity tasks, each followed by a recovery period. Relative to controls, depressed persons exhibited lower resting RSA levels as well as less RSA fluctuation, primarily evidenced by a lack of task-related vagal suppression. Group differences in RSA fluctuation were not accounted for by differences in physical health or respiration, whereas group differences in resting RSA level did not survive covariate analyses. Depression may involve multiple deficits in cardiac vagal control.

Descriptors: Cardiac vagal control, Depression, Reactivity, Stress

Major Depressive Disorder (MDD) is a mood disorder associated with significant distress and impairment that afflicts nearly one-fifth of the American population (Kessler, 2002). MDD is the leading cause of psychiatric hospitalizations and accounts for over 20% of economic costs for all mental illness (Greenberg, Stiglin, Finkelstein, & Berndt, 1993). The high personal and societal costs associated with MDD have motivated extensive research designed to uncover biobehavioral vulnerability factors associated with this disorder.

Cardiac vagal control, as measured by indices of respiratory sinus arrhythmia (RSA), has been linked to a variety of self-regulatory processes (e.g., Porges, 1995). RSA indices of impaired cardiac vagal control have been investigated as a risk factor for several forms of psychopathology, including depression (Rottenberg, 2007). Research on cardiac vagal control in psychopathology has primarily focused on two aspects of RSA: (1) RSA level, often measured in a resting state, and (2) RSA fluctuation (i.e., changes in RSA level), usually measured in response to changing environmental demands. Although accumulating evidence suggests that RSA level and RSA fluctuation represent distinct constructs that independently predict physical and mental health outcomes (Salomon, 2005), mood disorders research to date has focused almost exclusively on low RSA level and has yet to produce strong evidence that low RSA level is in fact a MDD liability marker. The present study is one of the first to examine abnormalities in RSA fluctuation in MDD: More specifically, we tested the hypothesis that MDD would be associated with abnormal RSA fluctuations during, and after, experimental stressors. In the following sections, we develop the general rationale for exploring RSA level and RSA fluctuation as risk factors for MDD, and the specific rationale for this study.

Nature and Significance of RSA Level and RSA Fluctuation

At the broadest level, RSA level and RSA fluctuation index the functioning in the parasympathetic nervous system, a branch of the autonomic nervous system concerned with homeostasis and growth. Emerging knowledge suggests that RSA level and RSA fluctuation are generated by cortical and subcortical areas that integrate cardiac autonomic activity with cognitive and emotional behavioral processes (e.g., Lane, Reiman, Ahern, & Thayer, 2001). By virtue of its anatomy, the 10th cranial, or vagus, nerve has particular potential to exert bio-behavioral effects on self-regulation. The efferent vagal nerve projection that generates RSA level and RSA fluctuation is well positioned to coordinate motor pathways involved in vocalizations, facial expressions, and the communication of internal states to others (Porges, 1995, 1997; Thayer & Lane, 2000). This efferent nerve projection emerges from the nucleus ambiguus in the brain stem and terminates on the sinoatrial node of the heart (the heart’s pacemaker), as well as several visceral organs notable for their role in emotion and communication (soft palate, pharynx, larynx, esophagus, bronchi, and facial muscles). The vagal pathway is also highly sensitive to changing environmental conditions, enabling it to exert rapid bio-behavioral effects. When a mammal is at rest, the vagal pathway works to “brake” energy expenditure. 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, Friedman, & Borkovec, 1996), and extreme threats to life or limb (George et al., 1989). The rapid application and withdrawal of the vagal brake, which we refer to as RSA fluctuation, is thus thought to be an important substrate for flexible behavioral routines.

RSA level and RSA fluctuation measures quantify the influence of vagal nerve activity on oscillations in heart rate. Vagal influence on heart rate is typically assessed indirectly, through an analysis of beat-to-beat variability in heart rate, which can be readily quantified from an electrocardiogram (ECG). Estimates of cardiac vagal control can be extracted from the ECG signal using several related techniques (for more detailed discussions, see Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). For example, spectral analysis is a mathematical procedure to decompose autonomic mediators of heart rate variability at specific frequency components (for reviews, see Berntson et al., 1997; Task Force of the European Society of Cardiology and the North American Society of Pacing and Electrophysiology, 1996). Slowest fluctuations (<0.04 Hz) are thought to be influenced by temperature, vasomotor, hormonal, and metabolic regulation (Cohen, Matar, Kaplan, & Kotler, 1999); a mid-frequency component (0.04–0.10 Hz) primarily reflects baroreceptor-mediated BP regulation (Pellizzer, Kamen, Jackman, Brazzale, & Krum, 1996). The present focus is on the high frequency component of heart rate variability (0.15–0.50 Hz), which represents vagally mediated oscillations related to the respiratory cycle (Berntson et al., 1997).

The Potential Relevance of RSA Level and RSA Fluctuation to MDD

A network of empirical findings implicates RSA level and RSA fluctuation in psychobiological adaptation. High RSA level, for example, is associated with social competence (Eisenberg et al., 1995) and resiliency in the face of stressors (e.g., Fabe & Eisenberg, 1997). Moreover, a high degree of appropriate RSA fluctuation (i.e., large decreases from rest) has been shown to have a buffering effect against the development of psychopathology (e.g., El-Sheikh, 2001) and child behavior problems (Calkins & Keene, 2004). In turn, low RSA level and a low capacity for appropriate RSA fluctuation have been shown to predict poor outcomes, including anxiety (e.g., Cohen et al., 2000; Thayer et al., 1996), hostility (Sloan et al., 1994), alexithymia (Neumann, Sollers, Thayer, & Waldstein, 2004), and disorders of impulse control (Beauchaine, 2001). The potential role of RSA level and RSA fluctuation in psychopathology is also underscored by the good general risk marker characteristics of these constructs, such as relations with temperament (Izard et al., 1991) and stability across tasks (Berntson, Cacioppo & Fieldstone, 1996; Berntson et al., 1994; Salomon, Matthews, & Allen, 2000; Sloan et al., 1995) and time (Sloan et al., 1995; Suess & Bornstein, 2000). Finally, MDD appears to involve the kinds of behavioral and social deficits that are consistent with RSA compromise. For example, depressed persons often exhibit unresponsive social behavior during naturalistic social interactions (Rottenberg & Gotlib, 2004), with fewer displays of facial expressions and reduced gaze behavior (Ellgring, 1989), as well as constricted and stereotyped emotional responses to a variety of laboratory situations (for reviews, see Rottenberg, 2005; Rottenberg, Gross, & Gotlib, 2005). Thus there is a strong theoretical rationale for undertaking empirical studies of aberrations in RSA level and RSA fluctuation to better understand psychopathology generally, and MDD risk specifically.

Empirical Studies of RSA Level and RSA Fluctuation in MDD

The empirical literature on cardiac vagal control in MDD has focused overwhelmingly on RSA level. Summarizing the RSA level literature, it is commonly stated that findings are mixed (e.g., Bär et al., 2004). That is, some investigations report that depressed patients have lower RSA levels than do nondepressed controls (e.g., Dalack & Roose, 1990; Lehofer et al., 1999; Rechlin, Weis, Spitzer, & Kaschka, 1994), whereas others report no differences in RSA levels between depressed subjects and nondepressed controls (e.g., Lehofer et al., 1997; Moser et al., 1998; Veraguth et al., 1991). Consistent with this mixed literature, the only quantitative review of this research area found a reliable but modest overall effect size for depression on RSA levels ($d = .3$; Rottenberg, 2007).

The weighting of the MDD literature toward RSA level at the expense of RSA fluctuation is unfortunate because RSA level and RSA fluctuation have coequal status in most theoretical approaches (e.g., Porges, 1995, 1997). An emphasis on RSA level over RSA fluctuation is also unfortunate because the two constructs appear to be empirically distinct. Consistent with the discriminability of these constructs, published data indicate RSA level–RSA fluctuation intercorrelations in the .4 to .6 range (e.g., Donzella, Gunnar, Krueger, & Alwin, 2000; Movius & Allen, 2005). Investigators have only recently begun to address the incremental validity of RSA level and RSA fluctuation in predicting physical and psychological health outcomes (Gianaros et al., 2005; Movius & Allen, 2005; Salomon, 2005). The incremental validity of RSA level and RSA fluctuation with respect to depressive phenomena is largely unknown.

Despite the promise of the RSA fluctuation construct, few methodologically strong studies of RSA fluctuation in MDD have been performed. Hughes and Stoney (2000) found RSA fluctuation abnormalities among dysphoric individuals reporting elevated levels of depression symptoms, but it not clear whether findings in dysphoric persons are generalizable to diagnosed MDD. Rottenberg, Wilhelm, Gross, and Gotlib (2003) found low RSA fluctuation in a subgroup of depressed patients (patients who cried) but the task used to elicit RSA fluctuation (a sad film) did not elicit robust RSA fluctuation. Finally, null results have been reported in studies using medicated MDD patients (Straneva-Meuse, Light, Allen, Golding, & Girdler, 2004) and patients who were elevated on cardiovascular risk factors (Taylor et al., 2006), but these sample characteristics may obscure measurement of RSA fluctuation in MDD (Rottenberg, 2007).

The Present Study

To ascertain whether persons with MDD exhibit RSA fluctuation deficits, the present study was designed to address three methodological limitations of prior studies that have clouded investigation of this question.

1. Presumably, tasks that elicit robust RSA fluctuation in healthy subjects are best suited to test hypotheses about group differences in RSA fluctuation. Unfortunately, mood disorders research has often used tasks that in healthy persons elicit RSA fluctuation only modestly (emotion films; Rottenberg et al., 2003) or not at all (orthostatic challenge; Tulen et al., 1996). To better probe group differences in RSA
fluctuation, we selected tasks (mirror tracing and speech) that were expected to elicit normatively robust RSA fluctuation.

2. Because few studies of RSA fluctuation in depression have been conducted in cardiovascularly healthy samples, this investigation took care to exclude participants who suffered from medical conditions likely to distort measures of RSA fluctuation. Moreover, prior studies of MDD have not typically considered or controlled for physical health factors, such as physical inactivity, obesity, and sleep problems. This omission is important because these physical health factors may be related to both depression and cardiac vagal control, and ignoring these factors may inflate estimates of the effect of depression on cardiac vagal control (see Rottenberg, 2007). For example, physical inactivity is associated with low RSA levels (Moglaard, Hermansen, & Bjerregaard, 1994), and depressed persons tend to be physically inactive (Hollenberg & Haight, 2004), raising the concern that low RSA levels in depression more accurately reflect sedentary behavior. To address the role of these physical health factors, measures of physical activity, obesity, and sleep quality were integrated into analyses of group differences in cardiac vagal control.

3. Finally, past studies have concentrated heavily on task-related vagal withdrawal (i.e., decreased cardiac vagal control during stressors), with less attention to the recovery of the vagal system after stressors. In fact, the vagal system is capable of rapid recovery, a process that may track important homeostatic functions. For example, Mezzacapa and colleagues postulated that increases in cardiac vagal control are crucial for restoring cardiovascular homeostasis (decreasing stressor-related HR elevations) and subsequently found that diminished vagal rebound during recovery from stress was associated with higher scores on standard risk factors for cardiovascular disease (Mezzacappa, Kelsey, Katkin, & Sloan, 2001). Rottenberg et al. (2003) observed rapid increases in cardiac vagal control among healthy individuals during a 90-s period after crying. Interestingly, recovery of cardiac vagal control after crying was absent among depressed individuals, possibly indicative of compromised self-regulation in MDD. To study recovery of vagal function, data were collected during a 2-min posttask period immediately following each task.

Table 1. Demographic and Clinical Characteristics of the Sample

<table>
<thead>
<tr>
<th>Variable</th>
<th>Depressed (n = 25)</th>
<th>Healthy control (n = 25)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, M (SD)</td>
<td>30.36 (9.37)</td>
<td>32.95 (11.93)</td>
</tr>
<tr>
<td>% Caucasian</td>
<td>68%</td>
<td>68%</td>
</tr>
<tr>
<td>% Female</td>
<td>80%</td>
<td>80%</td>
</tr>
<tr>
<td>Education</td>
<td>4.76* (1.56)</td>
<td>5.76 (1.90)</td>
</tr>
<tr>
<td>Income</td>
<td>2.09* (1.12)</td>
<td>2.70 (1.52)</td>
</tr>
<tr>
<td>BDI, M (SD)</td>
<td>29.54 (5.60)</td>
<td>1.48 (1.69)*</td>
</tr>
<tr>
<td>BAI, M (SD)</td>
<td>19.24 (11.17)</td>
<td>2.64 (2.55)*</td>
</tr>
<tr>
<td>BMI, M (SD)</td>
<td>27.29 (5.39)</td>
<td>23.59 (3.66)</td>
</tr>
<tr>
<td>Total kcal, M (SD)</td>
<td>442.54 (483.34)</td>
<td>1855.39 (1561.36)*</td>
</tr>
<tr>
<td>PSQI, M (SD)</td>
<td>11.92 (3.08)</td>
<td>3.88 (1.70)*</td>
</tr>
</tbody>
</table>

Note. BDI: Beck Depression Inventory, 2nd Edition, BAI: Beck Anxiety Inventory, BMI: Body Mass Index, Total kcal: average total kilocalories expended per week, PSQI: Pittsburgh Sleep Quality Index.

*a*Education was assessed on an 8-point scale with higher numbers representing more education—a score of 4.76 reflects some college.

**Income was assessed on a 6-point scale with higher numbers representing higher income—a score of 2.09 represents an income of $10,000 to $25,000.

*p*Significant difference between depressed and healthy control groups, p <.001.

Current depression criteria. The Structured Clinical Interview for DSM-IV Axis I (SCID-I; First, Gibbon, Spitzer, & Williams, 1995). All subjects met the following inclusion and exclusion criteria as determined by an initial telephone screening and a subsequent in-person SCID-I interview: fluent in English, between 18 and 60 years of age, no reported history of brain injury, no lifetime history of primary psychotic ideation, no lifetime diagnoses of bipolar disorder, no behavioral indications of possible impaired mental status, and no reported substance abuse within the past 6 months. To minimize the confounding effects of health conditions upon cardiovascular recordings, participants were also excluded if they had a history of medication-dependent diabetes, heart disease, hypertension, mood episodes secondary to general medical conditions or general medical conditions of the central nervous system or current use of any medications known to have significant effects on cardiac vagal control. These excluded medications included tricyclic antidepressants, antipsychotic agents, antihistamines, and beta-blockers.

Current depression criteria. The Structured Clinical Interview for DSM-IV Axis I (First et al., 1995) was used to confirm that the depressed group met current diagnostic criteria for current Major Depressive Disorder. Interviews were conducted by clinical psychology doctoral students. In prior work we have achieved good interrater reliability for a diagnosis of Major Depressive Disorder (Rottenberg, Wilhelm, Gross, & Gotlib, 2002).

Healthy control criteria. Healthy control participants satisfied the same general medical exclusion criteria as the patient groups and did not have any lifetime diagnoses of an Axis-I disorder when assessed with the SCID-I.

Severity of depression and anxiety. To measure overall depression severity, participants completed the Beck Depression Inventory-II (BDI-II), a 21-item self-administered scale of depression symptom severity with demonstrated validity and reliability (Beck, Steer, & Brown, 1996). To index the severity of anxiety symptoms, participants completed the Beck Anxiety Inventory (BAI), a widely used 21-item self-administered
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The mirror tracing device (Stoelting Co., Chicago, IL) provided feedback to participants in the form of a loud noise when the metal stylus was not in contact with the star. This task has previously been shown to elicit vagal withdrawal (Salomon, 2005). (2) A speech task required participants to prepare a speech on a specific topic (i.e., defending themselves against an unfair traffic ticket in court) and to deliver the speech. The preparation and delivery phases of the speech task were each 2 min. Speech tasks have been shown to be particularly effective in eliciting vagal withdrawal (d = .97, Keltikangas-Järvinen & Heponiemi, 2004). Participants were monitored by the experimenter via an unobtrusive, ceiling-mounted camera during both laboratory tasks to ensure compliance with task instructions. The experimenter pointed out the presence of the camera before baseline recordings. To further increase evaluation apprehension during the speech task, an experimental observer was present in the room and silently took notes on the participant’s behavior.

Recovery periods. Although past work offers only limited guidance on the conditions that foster the rapid recovery of cardiac vagal control, rapid vagal recovery appears most likely to occur and be most robust during an unchallenged period immediately subsequent to stressors (e.g., 60–90 s poststressor; Rotenberg et al., 2003; Mezzacappa et al., 2001). Thus, ECG data were recorded during a 2-min recovery period immediately following each RSA fluctuation task. Participants were instructed to sit quietly for the recovery period.

Procedure

Participants were first assessed for height and weight and underwent a laboratory orientation period, which included the attachment of physiological sensors. Participants were seated comfortably in front of a television monitor and were asked to view a neutral film, which was used as a baseline assessment. Speech and mirror tracing tasks followed the baseline assessment and were performed in counterbalanced order. A 10-min buffer period separated the reactivity tasks to reduce any potential carryover effects. During the first half of the buffer period, participants completed the Sleep Quality Index and the Paffenbarger Physical Activity Questionnaire. After the second reactivity task, participants completed the BDI-II and the BAI, sensors were removed, and participants were paid and debriefed.

Data Recording and Analysis

Equipment. A Biopac MP150 system with an ECG100 electrocardiogram amplifier amplified the ECG. The ECG was recorded using Cleartrace LT disposable Ag/AgCl electrodes (Conmed Andover Medical, Haverhill, MA), placed in a modified Lead II configuration on the participant’s chest. Respiration was obtained using the thoracic impedance method described by Ernst, Litvack, Lozano, Cacioppo, and Berntson (1999). A Biopac EBI100 impedance cardiograph measured transthoracic impedance (Z0) using four mylar-band electrodes fully encircling the neck and torso according to published guidelines (Sherwood et al., 1990). Acquisition of ECG and Z0 used AcqKnowledge 3.7.2 software. Signals were sampled at 1000 Hz.

Computation of RSA. RSA was calculated using MindWare HRV 2.16 Software module (MindWare Technologies, Ltd., Gahanna, OH). R-wave markers in the ECG signal were evaluated for artifacts by visual inspection and by the MAD/MED artifact detection algorithm (Berntson, Quigley, Jang, & Boysen, 1990) implemented in the MindWare software. Suspected

| Table 2. Interbeat Interval and Respiratory Rate (SD) by Epoch and Group |
|---------------------------------|----------------|----------------|
|                                | Depressed | Healthy control |
| Interbeat interval              |            |                |
| Baseline                        | 736.17 (130.1) | 899.97 (136.6) |
| Speech prep                     | 698.45 (112.5) | 782.37 (111.2) |
| Speech delivery                 | 670.41 (118.2) | 700.03 (119.2) |
| Speech recovery                 | 732.52 (108.1) | 870.11 (114.6) |
| Mirror tracing                  | 709.27 (114.0) | 816.94 (127.5) |
| Mirror recovery                 | 734.34 (68.8) | 881.31 (123.0) |
| Respiratory rate                |            |                |
| Baseline                        | 18.53 (3.22)  | 16.15 (4.16)   |
| Speech prep                     | 17.79 (3.87)  | 16.65 (3.18)   |
| Speech delivery                 | 15.98 (3.56)  | 14.25 (2.78)   |
| Speech recovery                 | 16.06 (3.58)  | 14.27 (3.36)   |
| Mirror tracing                  | 16.05 (4.12)  | 16.69 (3.85)   |
| Mirror recovery                 | 17.20 (4.15)  | 14.35 (3.08)   |

Note. Interbeat Interval [ms]; Respiratory Rate [breaths/minute].

Physical health variables. In addition to matching the groups on several factors that may influence cardiac vagal control, such as age and gender composition, we collected data that allowed us to address the role of several physical health variables (through analyses of covariance). The Paffenbarger Physical Activity Questionnaire (PPAQ; Paffenbarger, Wing, & Hyde, 1978) was included as a measure of physical activity. The PPAQ has been a commonly used instrument in epidemiological studies and studies of exercise, and PPAQ data have been validated against measures of cardiorespiratory fitness, body fatness, motion detection, and physical activity records (Ainsworth, Leon, Richardson, Jacobs, & Paffenbarger, 1993). Scores are computed as the sum of energy expended in stair climbing, walking, and sports and recreational physical activity as recalled from the past week (see Ainsworth, Haskell, et al., 1993 for scoring).

The Pittsburgh Sleep Quality Index (PSQI; Buysse, Reynolds, Monk, Berman, & Kupfer, 1989) was administered to measure sleep quality. The PSQI has been frequently used with clinical populations and has been validated against polysomnographic results (Buysse et al., 1989). To afford quantification of obesity, height was measured with a fixed steel tape in a standing position and weight was measured on a beam scale. The ratio of weight to height squared (kg/m²) was calculated to compute Body Mass Index (BMI) for each participant.

Psychophysiological Assessment

Resting baseline RSA level. Baseline RSA level was recorded during the last 5 min of a 10-min rest period in which participants viewed a neutral travelogue film (Salomon, 2005). We selected this film baseline on the strength of prior research indicating that minimally demanding tasks (i.e., vanilla baselines) afford more stable estimates of physiological functioning than rest or no-task baselines (Jennings, Kamarck, Stewart, Eddy, & Johnson, 1992).

RSA fluctuation tasks. Two tasks were used to elicit changes in RSA. (1) A 2-min mirror tracing task required participants to trace around the image of a star as quickly and accurately as possible while only seeing a mirror image of their hand and the star. The mirror tracing device (Stoelting Co., Chicago, IL) provided feedback to participants in the form of a loud noise when the metal stylus was not in contact with the star. This task has previously been shown to elicit vagal withdrawal (Salomon, 2005). (2) A speech task required participants to prepare a speech on a specific topic (i.e., defending themselves against an unfair traffic ticket in court) and to deliver the speech. The preparation and delivery phases of the speech task were each 2 min. Speech tasks have been shown to be particularly effective in eliciting vagal withdrawal (d = .97, Keltikangas-Järvinen & Heponiemi, 2004). Participants were monitored by the experimenter via an unobtrusive, ceiling-mounted camera during both laboratory tasks to ensure compliance with task instructions. The experimenter pointed out the presence of the camera before baseline recordings. To further increase evaluation apprehension during the speech task, an experimental observer was present in the room and silently took notes on the participant’s behavior.

Recovery periods. Although past work offers only limited guidance on the conditions that foster the rapid recovery of cardiac vagal control, rapid vagal recovery appears most likely to occur and be most robust during an unchallenged period immediately subsequent to stressors (e.g., 60–90 s poststressor; Rotenberg et al., 2003; Mezzacappa et al., 2001). Thus, ECG data were recorded during a 2-min recovery period immediately following each RSA fluctuation task. Participants were instructed to sit quietly for the recovery period.
artifacts were corrected manually (<1% of all R-waves in past work needed correction). Our approach accords with current guidelines for frequency domain methods to determine heart rate variability (Bernston et al., 1997; Task Force, 1996) and is well suited for short-term (~ 5 min) recordings. To arrive at minute-by-minute estimates of heart rate and RSA during baselines and tasks, a 60-s time series of interbeat intervals (IBIs: the time in milliseconds between sequential ECG R spikes) was created from an interpolation algorithm that has a 250-ms sample time. This 60-s IBI time series was (a) linearly-detrended, (b) mean-centered, and (c) tapered using a Hanning window. Spectral-power values were determined (in ms²/Hz) with fast Fourier transformations, and the power values in the 0.15–0.50 Hz spectral bandwidth were integrated (ms²). These spectral-power values were natural-log transformed prior to statistical analyses because of distributional violations. The natural-logged spectral-power value in the 0.15–0.50 Hz bandwidth was the indicator of RSA for each experimental epoch.

Respiration rate and amplitude. The MindWare software package calculated respiration rate and inspiratory depth from spectral analysis of the Z₀ signal according to methods described by Ernst et al. (1999). These variables were used as potential control variables to analyze the contribution of respiratory parameters to group differences in RSA fluctuation.

Hypothesis Testing
To provide continuity with earlier research on RSA level, baseline RSA level during the rest period was first analyzed for potential group differences in an ANOVA using group (depressed, control) as a between-subjects factor. Our major hypothesis was that depressed persons would exhibit abnormal RSA fluctuation during and after stressors. This hypothesis was tested in several steps. First, for each task we conducted an omnibus repeated measures ANOVA on RSA using group (depressed, control) as a between-subjects factor and epoch (baseline, task, recovery) as a within-subjects factor. We expected a significant effect of epoch, indicating that the task elicited RSA fluctuation, and a Group × Epoch interaction, indicating group differences in RSA fluctuation. We expected that follow-up tests within the healthy group would reveal vagal withdrawal during task periods and rapid recovery of vagal functioning during the recovery periods. We anticipated that depressed persons would fail to exhibit this normative pattern of RSA fluctuation. For repeated measures analyses with more than two levels, Greenhouse–Geiser corrected p values are reported.

Secondary analyses were conducted to address whether group differences in RSA level or RSA fluctuation were accounted for by physical health variables (body mass index, total calories, and sleep quality) and respiratory parameters (respiratory rate and respiratory amplitude). To achieve this goal, the primary analyses were rerun with these possible confounding variables entered as covariates. If the effects remained significant with these covariates included, we would infer that group differences in RSA level or RSA fluctuation were not accounted for by these other factors.

Results
Clinical and Demographic Characteristics
Clinical and demographic characteristics are reported in Table 1. As expected, MDD participants reported higher depression severity, anxiety severity, sleep disturbance, and physical inactivity than healthy controls (all ps < .001), but did not differ significantly on BMI. The MDD and control groups did not differ on demographic variables including percentage Caucasian, percentage female, education level, and reported income (see Table 1). Given prior evidence of gender effects on RSA, we conducted exploratory analyses on RSA using gender as a factor. These analyses indicated no main effects or interactions concerning gender; thus, gender was not considered further. Approximately one-third of the MDD participants (9 of 25) were taking psychotropic medications. Initial exploratory analyses using medication status indicated no main effects or interactions on this factor. As an added precaution, significant analyses in repeated measures ANOVA were repeated without the medicated participants included. In all cases, significant results replicated in the unmedicated subsample.

Missing Data
Of the 50 participants, RSA data from 4 were unusable because of suspected heart arrhythmias (3) or equipment failure during baseline (1). Two participants were missing RSA data from an individual task (1 speech, 1 mirror) but were used in other analyses. Respiration data were excluded for 2 subjects because of suspected artifacts in the signal leading to anomalous RR values (i.e., > 40 cycles/min).

Resting RSA Level
An ANOVA on RSA level during the baseline period found a significant effect of group, F(1,48) = 10.15, p < .01, partial η² = .175, with depressed persons exhibiting lower RSA than that of healthy controls. Secondary analyses of this effect found that when the physical health and respiratory variables were included (ANCOVA), the effect of group did not survive covariation with these factors, F(1,41) = 3.83, p > .05, partial η² = .086, supporting the inference that variation in these factors may account for group differences in RSA level.

RSA Fluctuation to Speech Task
A repeated measures ANOVA on RSA with group (control, depressed) as a between-subjects factor and epoch (baseline, preparation, speech, recovery) as a within-subjects factor found a significant effect of epoch, F(3,43) = 7.03, p < .01, partial η² = .090, indicating that the speech task induced RSA fluctuation, and a main effect of group on RSA, F(1,45) = 5.08, p < .05, partial η² = .101, indicating that depressed persons’ RSA level was generally lower than that of healthy controls. However, these effects were modified by the predicted Group × Epoch interaction, F(3, 43) = 4.23, p < .05, partial η² = .125 (see Figure 1).

To decompose the Group × Epoch interaction, separate ANOVAs within each group were performed. The control group exhibited a significant effect of epoch, F(3,20) = 4.98, p < .01, partial η² = .163. Post hoc paired t tests revealed that this epoch effect was due to RSA decreasing below baseline levels during the speech task t(24) = 2.44, p < .05, and rebounding above baseline...
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levels in the recovery period, \( t(23) = 2.32, p < .05 \). Thus, among healthy persons, and consistent with the intended manipulation, the speech task elicited vagal withdrawal, which was completely reversed in the recovery period. A separate ANOVA conducted within the depressed group revealed an effect of epoch, \( F(3,21) = 5.14, p < .01 \), partial \( \eta^2 = .222 \). Post hoc paired \( t \) tests revealed that depressed persons’ RSA actually increased during the speech task over baseline levels, \( t(24) = 2.56, p < .05 \). Depressed persons did not exhibit posttask increases in RSA in the recovery period (unlike healthy controls), but their increased RSA levels carried over from the speech task to the recovery period, leaving recovery period values elevated over baseline levels, \( t(24) = 3.55, p < .01 \).

Given that the predicted Group \( \times \) Epoch interaction (RSA fluctuation) was significant, secondary analyses addressed the possible contribution of physical health and respiratory variables by including these factors as covariates (i.e., repeated measure ANCOVA, respiratory parameters were entered as changing covariates). Importantly, the Group \( \times \) Epoch interaction for the speech task remained significant, \( F(3,39) = 9.40, p < .01 \). Thus, unlike what was observed for RSA level, secondary analyses of group differences in RSA fluctuation indicated that physical health and respiratory parameters do not account for group effects.

**RSA Fluctuation to Mirror Task**

The repeated measures ANOVA on RSA found a significant effect of epoch, \( F(2,44) = 22.78, p = .001 \), partial \( \eta^2 = .181 \), indicating that the mirror task induced RSA fluctuation, and a main effect of group, \( F(1,45) = 7.57, p < .01 \), partial \( \eta^2 = .144 \), indicating that depressed persons’ RSA level was generally lower than that of healthy controls. Our hypothesized Group \( \times \) Epoch interaction did not reach significance, \( F(2,44) = 1.68, p = .13 \), partial \( \eta^2 = .047 \) (see Figure 1). Given our strong a priori hypotheses, we conducted exploratory follow-up one-way group ANOVAs for descriptive purposes and to compare the results with the speech task. In these analyses, the healthy control group exhibited a significant effect of epoch, \( F(2,23) = 20.91, p < .001 \), partial \( \eta^2 = .255 \). Paired \( t \) tests revealed that, as expected, the epoch effect was due to a marginal decrease in RSA below baseline levels during the mirror tracing task, \( t(24) = 1.90, p < .07 \), and a significant rebound in RSA above baseline levels in the recovery period, \( t(23) = 2.40, p < .05 \). In sum, consistent with the intended manipulation, in healthy controls the mirror task modestly elicited vagal withdrawal, which was completely reversed in the recovery period. A separate ANOVA within the depressed group also revealed an effect of epoch, \( F(3,21) = 6.21, p < .05 \), partial \( \eta^2 = .251 \). Unlike healthy controls, post hoc paired \( t \) tests revealed that depressed persons failed to exhibit vagal withdrawal from the baseline to the mirror task, \( t < 1 \). Despite the lack of task-related vagal withdrawal, depressed persons’ RSA levels nevertheless increased in the recovery period over baseline values, \( t(21) = 2.30, p < .05 \). In summary, although the pattern of group differences in RSA fluctuation during the mirror task did not reach significance, the overall pattern of data was similar to the speech task.

**Discussion**

RSA level and RSA fluctuation have been interpreted as important indices of biobehavioral flexibility and self-regulatory capacity and have been widely investigated in psychopathology. To date, the depression literature has obtained mixed findings for RSA level and has neglected RSA fluctuation. To our knowledge this was the first study to examine RSA level and RSA fluctuation (both reactivity and recovery) using tasks that elicit normatively robust RSA fluctuation in MDD patient and control groups free of diagnosed cardiovascular pathology. Five principal findings were obtained.

First, it appears that this paradigm was well suited to examining group differences in RSA fluctuation. As anticipated, in both the speech task and the mirror task, healthy controls exhibited task-related vagal withdrawal, which was completely reversed in the posttask recovery periods. Because standardized VF protocols have been lacking in clinical psychophysiology, we hope the replicability and generalizability of this protocol will be examined in future work.

Second, given the strength of the paradigm, it is notable that depressed persons failed to exhibit vagal suppression to either task. In fact, far from exhibiting vagal withdrawal, depressed persons actually exhibited increased RSA during speech in the speech task. Although increases in RSA during speech may appear to be paradoxical, evidence that these types of tasks consistently produce vagal withdrawal in all subjects is sparse. Further, although some evidence suggests that, on average, these types of tasks produce decreases in RSA (Allen & Crowell, 1989; Allen & Matthews, 1997; Burleson et al., 2003; Houtven, Rietveld, & de Geus, 2002, 2003), others have reported mean increases for certain tasks (Bernston et al., 1996) or specific groups of individuals (Sahar, Shalev, & Porges, 2001; Quigley & Stifter, 2002).

Line of work that may have considerable potential for reducing cardiovascular vagal control in young children. Developmental Psychobiology, 42, 64–78.


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In addition to several strengths, this study also had four main limitations. First, although medications with known effects on cardiac vagal control were excluded, nine MDD participants were taking medications. Allaying this concern, our principal findings replicated in the unmedicated subsample, despite the reduced power of this analysis. Second, although experimenters monitored participants for task compliance and all participants complied with task instructions, no finer-grained measurements of behavior were obtained. Given the possibility of multiple deficits in cardiac vagal control in MDD, one critical direction for future work will be to elucidate the behavioral correlates of these deficits. Third, effects of task for the mirror task were less robust than task effects for the speech task; these effects should be interpreted with caution pending replication, especially because post hoc analysis did not correct for alpha inflation. Fourth and finally, this study was cross-sectional and, therefore, cannot speak to causal links between deficits in cardiac vagal control and MDD.

Although this was a cross-sectional study, findings suggest the merit of exploring potential prospective linkages between low RSA fluctuation and depression proneness. This direction is an especially high priority in light of recent findings showing that low RSA fluctuation within a depressed group predicted nonrecovery of depression (Alkon et al., 2002; Berntson et al., 1994, 1996; Quigley & Stifter, 2006; Salomon, 2005; Salomon et al., 2000). For example, Quigley and Stifter found that the majority of their participants exhibited autonomic patterns involving no change or an increase in RSA during tasks.

Third, equivocal evidence of abnormal recovery processes in MDD was obtained: From one perspective, depressed persons did fail to exhibit posttask vagal recovery after the speech task, as they did not exhibit posttask increases in RSA. From another perspective, it may be problematic to interpret these data in terms of recovery because persons with MDD did not exhibit prior vagal withdrawal during the reactivity task. However it is considered, these data suggest that, at least for some tasks, depression may involve reduced posttask vagal fluctuation (see also Rottenberg et al., 2003).

Fourth, group differences in RSA fluctuation survived covariate analyses involving physical health variables and respiratory differences. Fifth, and in contrast, a corresponding covariate analysis of baseline RSA level indicated that group differences in RSA levels did not survive when variables measuring physical health status and respiratory patterns were taken into account. These results point toward the potential discriminability of RSA level and RSA fluctuation deficits and suggest that RSA fluctuation deficits may be independent of the transient symptom features of MDD. In fact, a skeptic might interpret these covariate analyses for RSA level as suggesting that low RSA level in MDD is an artifact of transient bio-behavioral changes that accompany the depressive syndrome such as physical inactivity or more rapid breathing rather than an enduring group difference. At the least, these findings suggest that routine measurement of these subject characteristics is needed to understand the proximal sources of MDD-related differences in cardiac vagal control. On a related note, these findings have implications for understanding the mixed literature on RSA level in MDD. That is, based on these results, we would anticipate that the magnitude of group differences in RSA level will be greatest in MDD samples exhibiting relatively high levels of physical inactivity, sleep disturbance, or BMI, and will be smallest when the patient group does not exhibit these characteristics markedly. The well-known symptomatic and clinical heterogeneity of MDD renders this prediction plausible and in need of further testing.

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Finally, because the vagal pathway exhibits plasticity under some circumstances, it is possible that RSA level and RSA fluctuation deficits in MDD are significant not only as markers of dysfunction but as targets for intervention. For example, direct electrical stimulation of brain regions that control the vagus nerve has been investigated as a potential treatment for severe, intractable depression (Rush et al., 2005). Even more germane, a host of behavioral changes, such as exercise, smoking cessation, relaxation, and brief biofeedback or breathing training sessions, have been shown to alter RSA level (Hatch, Borcherding, & German, 1992; Reyes del Paso, Godoy, & Vila, 1992). Nolan et al. (2005) recently combined biofeedback and breathing techniques to successfully modify RSA fluctuation in a sample of cardiac disease patients. In closing, we believe the present findings highlight the need to investigate potential antidepressant effects of modifying RSA fluctuation in depressed populations, a line of work that may have considerable potential for reducing the burden of depressive illness.


