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Preliminary communication

Respiratory sinus arrhythmia as a predictor of outcome in major depressive disorder

Jonathan Rottenberg[a], Frank H. Wilhelm[b], James J. Gross[c], Ian H. Gotlib[a,*]

[a]*Mood and Anxiety Disorders Laboratory, Department of Psychology, Stanford University, Jordan Hall, Bldg. 420, Stanford, CA 94305-2130, USA*

[b]*Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, and VA Palo Alto Health Care System, Palo Alto, CA 94305-2130, USA*

[c]*Stanford Psychophysiology Laboratory, Department of Psychology, Stanford University, Stanford, CA 94305-2130, USA*

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Abstract

Background: Respiratory sinus arrhythmia (RSA) is a noninvasive measure of parasympathetic tone that has been related to emotion regulatory capacity. While some previous work indicates that clinically depressed persons exhibit lower levels of RSA than do normal controls, there is nevertheless considerable between-subject variation in RSA among depressed persons. The current study evaluated the significance of variation in RSA among depressed persons by examining whether levels of RSA predicted concurrent symptomatology and the course of depressive illness. *Methods:* The RSA levels of 55 diagnosed depressed individuals were assessed during a paced breathing procedure at Time 1. Six months later (Time 2), participants were interviewed again to determine whether or not each had fully recovered from depression. Multinomial regression analyses were conducted to examine whether RSA predicted Time 2 clinical status. *Results:* Although RSA levels were not related to overall depression severity, they were associated with specific symptoms of depression: RSA was positively associated with the report of sadness and negatively associated with the report of suicidality. More strikingly, however, higher levels of RSA at Time 1 predicted non-recovery from depression at Time 2, even when statistically controlling for initial depression severity, age and medication use. *Limitations:* Treatment and medication use were not controlled during the follow-up period and a group of nonpsychiatric controls was not included in this study. *Conclusions:* A relatively high level of RSA among depressed individuals predicts a more pernicious course of illness than do lower RSA levels.

Keywords: Major depression; Respiratory sinus arrhythmia; Self-regulation; Outcome

1. Introduction

Increasingly, Major Depressive Disorder (MDD) is being conceptualized as a disorder of emotion

*Corresponding author. Tel.: +1-650-725-9216; fax: +1-650-725-5699.

E-mail address: gotlib@psych.stanford.edu (I.H. Gotlib).

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regulation (Barlow, 1988; Gross and Muñoz, 1995). One physiological parameter that has been linked to emotion regulation is respiratory sinus arrhythmia (RSA; e.g. Porges, 1995). RSA, the rhythmic oscillation in heart period accompanying breathing, is a non-invasive measure of cardiac vagal control (Berntson et al., 1997). RSA is a result of the phasic changes in vagal nerve activity at the cardiac sino–atrial node that are linked to breathing frequency. Vagal control of the heart reflects the basal (tonic) firing rate of the cardiac vagal motor neuron projections from the nucleus ambiguous, which are influenced by several central projections, for example from the amygdala and hypothalamus. This tonic vagal firing is modulated by a respiratory-related phasic signal from the brainstem respiratory generator. Whereas the heart period decrease is associated with phases of inspiration when respiratory mechanisms in the brainstem attenuate the vagal efferent action on the heart, the heart period increase is associated with phases of expiration when the vagal efferent influence to the heart is reinstated. The amplitude of this heart period oscillation reflects the level of cardiac vagal control and thus allows its non-invasive assessment (Taylor et al., 1999). Measures of RSA extract only the relatively fast components of heart-period variability that are associated with the respiratory frequency and not the slower variability components that are assumed to be mediated vagally and sympathetically (Saul et al., 1991).

Decreased levels of RSA have been linked to self-regulatory difficulties in samples of both children (e.g. Pine et al., 1998) and adults (e.g. Thayer et al., 1996). Interestingly, despite the clear emotion regulatory difficulties that characterize individuals who are diagnosed with depression, cross-sectional studies examining levels of RSA in depressed individuals have yielded equivocal results. For example, whereas several investigators have found depressed patients to have lower RSA than do nondepressed controls (e.g. Carney et al., 1995; Dalack and Roose, 1990; Rechlin et al., 1994), other researchers have found depressed and nondepressed participants to be indistinguishable with respect to their baseline levels of RSA (e.g. Carney et al., 1988; Jacobsen et al., 1984; Lehofer et al., 1997; Moser et al., 1998)

There have been fewer longitudinal studies examining the association between RSA and depression, but they, too, have yielded inconsistent findings. For example, Balogh et al. (1993) recorded heart rate before and after a therapeutic trial of antidepressant medications in 17 adult patients diagnosed with MDD. Balogh et al. examined whether pretreatment heart-rate variability (HRV), measured by successive mean squared differences in R–R interval, was associated with treatment outcome and whether HRV changed over time in concert with changes in severity of depression. Their results indicated that although pretreatment HRV levels did not predict treatment response, improvement in depressive symptoms was associated with increases in HRV. In contrast, Schultz et al. (1997) found exactly the opposite pattern of results: improvement in depressive symptoms in response to a course of electroconvulsive therapy was associated with decreases in high-frequency heart rate variability. Finally, Khaykin et al. (1998) found no relation between treatment response and changes in high-frequency HRV.

One reason for the inconsistent findings of these studies involves the likely heterogeneity of individuals diagnosed with depression (see Gotlib and Hammen, 1992; in press). Indeed, some investigators have suggested that depressed persons are heterogeneous specifically with respect to RSA (Moser et al., 1998), an inference that has been applied to other measures of physiological functioning in depression (e.g. Noble and Lader, 1972). Another reason for the discrepant findings involves limitations of these investigations. For example, most of these studies had relatively small sample sizes. Moreover, the longitudinal investigations studied outcome over a short follow-up period and had either no criteria or very liberal criteria for defining recovery. Finally, quantification of RSA in these studies was based solely on heart-period measurement. Importantly, several lines of evidence now indicate that respiratory rate and depth are significant confounds in the assessment of cardiac vagal control. Independent of changes in cardiac vagal control, rapid low tidal volume breathing will reduce RSA levels, while slow high tidal volume breathing will increase RSA levels (e.g. Grossman and Kollai, 1993; Saul et al., 1989).

The present study was designed to address these limitations in examining whether levels of RSA

assessed in diagnosed clinically depressed individuals are related to (a) concurrent clinical characteristics such as depression severity; and (b) clinical course of depression, as assessed 6 months later by a structured clinical interview. We enrolled a large sample of depressed individuals into the study at Time 1 and used an assessment procedure and mathematical quantification of RSA that was not confounded by respiratory rate or depth. We followed this sample for 6 months (Time 2) and then used strict interview-based diagnostic criteria to divide the sample into recovered and non-recovered depressives. Based on the literature in which RSA is associated with self-regulatory capacity and psychological health, we hypothesized that higher levels of RSA at Time 1 would be associated concurrently with less severe depression and would predict recovery from depression at Time 2.

2. Methods

2.1. Participants

Participants were 55 unipolar depressed persons (73% female) who were fluent in English and were between 18 and 60 years of age. Approximately half of the depressed participants were recruited from two outpatient psychiatry clinics in a university teaching hospital and half were self-referred from the community. Clinical participants had no reported lifetime history of brain injury or primary psychotic ideation and showed no behavioral indications of possible impaired mental status or mental retardation. Potential participants were also excluded from the sample if they were alcohol or substance dependent or if they showed signs of substance or alcohol abuse within the past 6 months. Twenty-five of the depressed participants were receiving pharmacotherapy (ten individuals were taking SSRIs, two were taking tricyclics, fourteen were taking other antidepressants, such as venlafaxine and thirteen individuals were taking other types of psychotropic medications, such as benzodiazepines, hypnotics, or anticonvulsants). All participants were paid $25 per hour and provided written informed consent prior to the experimental session.

2.2. Clinical assessments

All depressed subjects met DSM-IV (American Psychiatric Association, 1994) criteria for MDD using the Structured Clinical Interview for DSM (SCID-I; First et al., 1995). SCID-I interviewers had previous experience with administering structured clinical interviews and were trained specifically to administer the SCID-I interview prior to beginning work on this study. An independent trained rater who was blind to group membership evaluated 15 randomly selected audiotapes of SCID interviews with depressed and nondepressed participants and with non-participants who met diagnostic criteria for disorders other than depression (e.g. panic disorder) and for each determined whether the participant met DSM-IV diagnostic criteria for MDD. In all 15 cases, ratings matched the diagnosis made by the original interviewer, $\kappa = 1.00$.

Participants also completed the Beck Depression Inventory (BDI; Beck et al., 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.

Six months following entry to the study (i.e. Time 2), a modified version of the SCID-I was administered to the participants. We used guidelines recommended by the 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 et al., 1996). Therefore, participants who exhibited subsyndromal or syndromal depression were considered to be non-recovered.

2.3. Physiological assessment

An SA Instruments 12-channel bioamplifier was used to record physiological responses. Signals were

sampled at 400 Hz. Data were acquired using a Pentium PC that used a data translation 3001 PCI 12-bit 16-channel analog to digital converter. Data were reduced off-line using custom laboratory software. During the psychophysiology assessment, instructions were presented on a 20 in. television monitor at a viewing distance of 1.75 m.

Participants were greeted and were seated in a comfortable chair in a quiet, well-furnished laboratory room. Following an orientation period and the attachment of physiological sensors, participants were instructed to listen to a soft tone and to breathe in when they heard the tone rising, to breathe out when they heard the tone falling and to pause between breaths when there was no tone. The paced breathing trial was initiated when participants indicated that they understood these instructions. The tonal pattern was modulated to induce a respiratory frequency of 9 cycles/min with a normal fractional inspiratory ratio of 40% and was presented for 2 min. The paced breathing procedure was recommended to keep respiratory rate constant both within and between individuals during RSA assessment (Wilhelm et al., 1998) because changes in respiratory rate can potentially confound the relationship between cardiac vagal control and RSA. Finally, after participating in several tasks not reported here, participants were disconnected from monitoring devices, were paid and were reminded that they would be contacted for a follow-up interview in 6 months time.

An electrocardiogram was recorded using Beckman miniature electrodes, placed in a bipolar configuration on opposite sides of the participant's chest. In addition, two channels of respiration were measured with inductive plethysmography bands (Ambulatory Monitoring, Ardsley, NY, USA) that were placed around the chest and abdomen. Respiration was calibrated against fixed volume bags by the least-squares method.

2.4. Computation of RSA

A customized computer program written in MATLAB (Wilhelm et al., 1999) was used to compute RSA. Raw signals of the two respiratory bands were converted to lung volume change using regression weights derived from calibrations and resampled to 4 Hz. The heart period (HP) was calculated from the ECG as the interval (in ms) between successive R waves (R–R interval). The R–R intervals 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.

To adjust for the confounding effects of variations in tidal volume in the assessment of cardiac vagal control from heart period oscillations, transfer function analysis was employed for the paced breathing data of each study participant. The level of transfer function respiratory sinus arrythmia (RSA_{TF}) was estimated as the magnitude of the transfer function relating heart period oscillations to lung volume oscillations at the peak respiratory frequency. This frequency was identified as the greatest local maximum in the 0.15–0.50 Hz lung volume power spectral density function. RSA_{TF} was thus adjusted for the confounding effect of within- and between-subject variation in respiratory depth.

RSA_{TF} was derived from the data using spectral analysis according to the following procedure: HP and lung volume (LV) time series were first linearly detrended and the power spectral densities (P_{HP} and P_{LV}) are derived for each period using the Welch algorithm (Welch, 1967), which ensemble averages successive periodograms. Averages were derived from spectra estimated for 60-s data segments, overlapping by half. For each 60-s segment, 256 points were analyzed, which includes 240 sampled points with zero padding. The segments were Hanning windowed and subjected to Fast Fourier transform. Estimates of power were adjusted to account for attenuation produced by the Hanning window. The products of the segments of P_{LV} and P_{HP} were averaged to form $P_{LV,HP}$, the cross spectral density of P_{LV} and P_{HP}. The transfer function $T_{LV,\,HP}$ was computed as the quotient of $P_{LV,HP}$ and P_{LV}. RSA_{TF} was the value of $T_{LV,\,HP}$ at the respiratory frequency. The respiratory frequency was identified as the greatest local maximum in the 0.13–0.50 Hz lung volume power spectral density function (and was 0.15 ± 0.01 Hz for all participants during paced breathing). Spectral coherence at this frequency was required to be above 0.5 (which was met for all participants) to ensure that measured HP oscillations were truly due to respiratory sources and not due to non-RSA variation. The resulting value of RSA_{TF}

reflects the average magnitude of heart period oscillations per lung volume change in ms/ml during the paced breathing.

For comparison, the conventional RSA measure, high frequency power of heart period (HF-RSA), was computed by summing P_{HP} values over the frequency band associated with respiration (0.13–0.50 Hz) and resulting values were transformed using the natural logarithm.

3. Results

Based on the SCID interviews at Time 2, 11 of the 55 depressed individuals in this study (20%) were completely recovered from depression and 44 (80%) were not recovered. Table 1 shows that the non-recovered subjects were similar to the fully recovered participants with respect to self-reported depression severity at Time 1, $t(53) < 1$, current treatment status, $\chi^2 < 1$, gender composition, $\chi^2 < 1$, age, $t(53) < 1$ and level of education, $t(53) < 1$, all P values > 0.15. In addition, recovered and non-recovered participants did not differ in their overall use of psychotropic medications at Time 1 or in their use of any individual subcategory of psychotropic medication (e.g. tricyclics, SSRIs.), all $\chi^2 < 1$, all P values > 0.15.

Variability in RSA_{TF} was not significantly related to overall depression severity as measured by the BDI, ($r = -0.16$, $P > 0.15$). RSA_{TF} was, however, significantly correlated with two individual depression symptom severity scores (as measured by the BDI): positively with sadness, $r = 0.30$, $P < 0.05$ and negatively with suicidal impulses, $r = -0.27$, $P < 0.05$ (see Table 2). An identical pattern of significant correlations was obtained when the analyses were repeated with the conventional measure of RSA, high frequency power of heart period (HF-RSA). Not surprisingly, the two measures of RSA (HF-RSA and $RSA_{TF)}$ were significantly correlated with each other, $r = 0.76$, $P < 0.001$.

Table 2
Correlations of RSA_{TF} and symptoms of depression

Sadness	0.30*
Loss of interest	−0.11
Guilt	0.09
Worthlessness	−0.19
Indecisiveness	0.06
Insomnia	−0.03
Fatigue	−0.05
Weak appetite	−0.07
Weight loss	0.04
Suicide	−0.27*

*, $P < 0.05$.

A multinomial logistic regression analysis was conducted using initial RSA_{TF} levels to predict Time 2 depression status. The results of this analysis indicated that RSA_{TF} levels at Time 1 significantly predicted diagnostic status at Time 2, $\chi^2 = 4.90$, df = 1, $P < 0.05$. In contrast, the results of a similar analysis using Time 1 HF-RSA indicated that this variable did not predict subsequent diagnostic status, $\chi^2 = 2.87$, df = 1, $P > 0.05$. As can be seen in Table 1, depressed individuals who did not recover by Time 2 had higher RSA_{TF} values at Time 1 ($M = 0.153$, S.D. = 0.098) than did depressed persons who went on to recover fully ($M = 0.087$, S.D. = 0.065). Because initial levels of RSA_{TF} were associated with medication use (depressed participants taking psychotropics had marginally lower levels of RSA_{TF} than did depressed participants who were not taking medication, $t(53) = 1.83$, $P < 0.07$) and with age ($r = -0.53$, $P < 0.01$), the logistic regression analysis was repeated using psychotropic medication use, age and Time 1 depression severity (as assessed by

Table 1
Initial sample characteristics by subsequent diagnostic status

Group	n	Age (years)	Female (%)	Education	BDI	Treated (%)	RSA^{*}_{TF}
Nonrecovered	44	33.4 (10.5)	66.3	6.5 (1.5)	23.6 (7.2)	60.9	0.153 (0.098)
Recovered	11	32.3 (11.7)	72.7	6.6 (1.4)	22.9 (6.4)	54.5	0.087 (0.065)

BDI, Beck Depression Inventory score; RSA_{TF}, transfer function respiratory sinus arrhythmia, ms/ml. Note: Numbers in parentheses are standard deviations.
*, $P < 0.05$.

BDI) as covariates. In this analysis, Time 1 RSA_{TF} levels continued to predict Time 2 depression outcome, even with these other variables included in the model, $\chi^2 = 8.69$, df = 1, $P < 0.005$.

4. Discussion

The broad aim of this study was to examine the clinical significance of heterogeneity in RSA within a sample of depressed individuals. To this end, we examined the association between levels of RSA and concurrent depressive symptomatology and the clinical course of depression over a 6-month follow-up period. We found levels of RSA to be related to individual symptoms of depression, but not to overall concurrent depression severity. Perhaps more strikingly, despite our expectation that higher levels of RSA would be associated with better outcome, our data indicated the opposite association: higher levels of RSA at Time 1 predicted worse clinical outcome at Time 2, 6 months later. This unexpected finding warrants comment.

Our hypothesis that high RSA would be associated with recovery from depression was derived primarily from the general RSA literature in which high RSA has been found to be related to psychological health in unselected samples. For example, Fabes and Eisenberg (1997) found RSA to be associated with the ability to cope with life stressors in a sample of adults. From a different perspective, other investigators have found that psychological stress (e.g. Allen and Crowell, 1989) and rumination (Thayer et al., 1996) led to lower levels of RSA and that psychological relaxation increases RSA levels (Skakibara et al., 1994). Because this work was conducted with samples of nondepressed individuals, one obvious issue in the present context involves the generalizability of these findings to clinically depressed individuals.

Interestingly, in previous studies the relation of RSA to psychological health among depressed individuals has been both weak and ambiguous. We described earlier the inconsistent findings concerning lowered RSA in depressed individuals relative to controls. It is also the case that several investigations (including the present study) have failed to find the expected inverse relation between depression severity and RSA level in samples of currently depressed persons (e.g. Moser et al., 1998; Watkins et al., 1999). Finally, in none of the short-term longitudinal studies of depressed individuals was RSA found to play a protective role with respect to predicting improvements in depression symptoms or in other measures of psychological health. Importantly, the lack of previous findings indicating a protective role for RSA for the psychological health of depressed individuals stands in sharp contrast to the domain of physical health, in which robust evidence exists that decreased RSA may mediate the increased risk for cardiac mortality and morbidity that is observed in individuals with MDD (Musselman et al., 1998).

The data reported here represent the first evidence that RSA may be of great clinical importance in depression. In the present study, which examined the largest sample of depressed participants to date and which used spectral analytic measures to assess cardiac vagal control, lower levels of RSA were found to predict recovery from depression at 6 months, even when initial depression severity and a number of other potentially confounding variables were controlled statistically. Moreover, our measures of RSA were psychometrically sound, exhibiting the expected relations with age (Hellman and Stacey, 1976) and medication use (Jacobsen et al., 1984).

It is not yet clear by what mechanisms RSA might affect the course of depression. Indeed, the correlations we obtained between RSA and different symptoms of depression suggest that the nature of the relation between RSA and the larger construct of depression is likely to be complex. The significant positive association between RSA and reports of acute sadness is intriguing because persistent sad mood is, in many ways, the defining emotional feature of MDD. The present finding of greater sadness among depressed individuals with higher levels of RSA is consistent with within-subjects research demonstrating a relation between increases in HRV and increases in sad mood state (Miller and Wood, 1997). At the same time, however, RSA was inversely related to the symptom of suicidality. While these correlational findings should be regarded as exploratory, these data raise the possibility that inconsistency in the results of prior RSA studies relates to the clustering of different depression symptom profiles in different patient samples.

In closing, we should point out that this was a naturalistic study of the course of depression. RSA 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 RSA-associated differences appear to be unrelated to the use of treatment or medication, only random assignment to treatment could rule this out as an explanation for our findings. Finally, in future work assessing RSA variation among depressed persons it would be useful to have RSA data from nonpsychiatric controls as a reference point. Nevertheless, we believe that our conclusion that higher RSA leads to a more pernicious course of illness in depression is intriguing and warrants replication.

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