Differential Autonomic Nervous System Reactivity in Depression and Anxiety During Stress Depending on Type of Stressor

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ABSTRACT

Objectives: It remains unclear whether depressive and anxiety disorders are associated with hyporeactivity or hyperreactivity of the autonomic nervous system (ANS) and whether deviant reactivity occurs in all types of stressors. This study compared ANS reactivity in people with current or remitted depression/anxiety with reactivity in healthy controls during two stress conditions.

Methods: From the Netherlands Study of Depression and Anxiety, data of 804 individuals with current depression/anxiety, 913 individuals with remitted depression/anxiety, and 466 healthy controls (mean age = 44.1 years; 66.4% female) were available. Two conditions were used to evoke stress: a) an n-back task, a cognitively challenging stressor, and 2) a psychiatric interview, evoking personal-emotional stress related to the occurrence of symptoms of depression/anxiety. Indicators of ANS activity were heart rate (HR), root mean square of differences between successive interbeat intervals (RMSSD), respiratory sinus arrhythmia (RSA), and preejection period.

Results: As compared with controls, participants with psychopathology had significant hyporeactivity of HR (controls = 4.1 ± 4.2 beats/min; remitted = 3.5 ± 3.5 beats/min; current psychopathology = 3.1 ± 3.4 beats/min), RMSSD (controls = −6.2 ± 14.5 milliseconds; remitted = −5.4 ± 17.8 milliseconds; current psychopathology = −3.5 ± 15.4 milliseconds), and RSA (controls = −9.3 ± 17.0 milliseconds; remitted = −7.4 ± 16.5 milliseconds; current psychopathology = −6.9 ± 15.0 milliseconds) during the n-back task. In contrast, during the psychiatric interview, they showed significant hyperreactivity of HR (controls = 2.7 ± 3.4 beats/min; remitted = 3.5 ± 3.4 beats/min; current psychopathology = 4.0 ± 3.3 beats/min), RMSSD (controls = −3.4 ± 12.2 milliseconds; remitted = −4.1 ± 12.1 milliseconds; current psychopathology = −5.6 ± 11.8 milliseconds), and RSA (controls = −3.8 ± 8.1 milliseconds; remitted = −4.3 ± 7.9 milliseconds; current psychopathology = −5.0 ± 7.9 milliseconds). The lack of group differences in preejection period reactivity suggests that the found effects were driven by altered cardiac vagal reactivity in depression/anxiety.

Conclusions: The direction of altered ANS reactivity in depressed/anxious patients is dependent on the type of stressor, and only the more ecologically valid stressors may evoke hyperreactivity in these patients.

Key words: autonomic nervous system, heart rate, depression, anxiety, stress, n-back.

INTRODUCTION

Depressive and anxiety disorders, both important causes of disability-adjusted life years according to the World Health Organization, have been associated with an increased risk of cardiovascular disease, the leading cause of disability-adjusted life years (1–5). It is intuitively appealing that depressive and anxiety disorders—characterized by distress and fear (6)—may be associated with negative alterations of the autonomic nervous system (ANS) involved in the

ANS = autonomic nervous system, **ATC** = anatomical therapeutic chemical, **BMI** = body mass index, **ECG** = electrocardiogram, **HR** = heart rate, **IBI** = interbeat interval, **ICG** = impedance cardiography, **MDD** = major depressive disorder, **NE** = norepinephrine, **NESDA** = Netherlands Study of Depression and Anxiety, **PEP** = preejection period, **PNS** = parasympathetic nervous system, **RMSSD** = root mean square of differences between successive interbeat intervals, **RSA** = respiratory sinus arrhythmia, **SNRI** = selective serotonin and noradrenalin reuptake inhibitors, **SNS** = sympathetic nervous system, **VU-AMS** = Vrije Universiteit Ambulatory Monitoring System

SDC Supplemental Content

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human stress response (7), and that dysregulation of this system, in turn, may lead to diseases of the heart. The existence and nature of these autonomic dysregulations remain debated (3). For instance, when Licht et al. (8–10) investigated sympathetic nervous system (SNS) and parasympathetic nervous system (PNS) activity in more than 1000 patients with depression and anxiety disorders (9–11), they found no associations between these disorders and autonomic dysregulation independent of a robust association with use of antidepressants. However, these studies focused on overall levels of ANS activity and did not include a contrast between the resting level and a condition evoking a stress response, which may explain the lack of evidence for an altered ANS in depressed and anxious patients. Several studies have implied altered ANS reactivity to stressors among depressed patients rather than ANS dysregulation during baseline conditions (12,13). For example, Hughes and Stoney (12) found that depressed mood was related to increased heart rate (HR) responses and stronger withdrawal of parasympathetic cardiac control during stressors, but not to HR and vagal control at baseline. Interestingly, both hyperreactivity (14–16) and hyporeactivity (17–24) have been implied in depression and anxiety. Hyporeactivity was seen in a study of 1608 participants by Phillips et al. (17), who found higher depression scores to be associated with lower HR reactivity to psychological stress. Illustrating the lack of unanimity among research in this area, a number of studies have reported no relationship at all between ANS stress reactivity and psychiatric disorders (25,26).

A possible explanation for the discrepant findings is that many of the above studies were limited by small sample sizes and did not adjust for numerous potential confounding factors, such as life-style, medication use, and chronic diseases. In addition, a large proportion of the studies had limited breadth of ANS measurements or focused on resting levels of ANS activity and did not include one or more specific stress conditions. Besides, the studies that did induce stress used different stressors and it is possible that participants with psychopathology do not have increased sensitivity to all types of stress.

The aim of the current study was to investigate stressor-induced sympathetic and parasympathetic reactivity in the 2-year follow-up assessment of a large depression and anxiety cohort (the Netherlands Study of Depression and Anxiety, or NESDA). Four indicators of ANS activity were used: a) HR, controlled by both parasympathetic and sympathetic cardiac innervation (27); b) root mean square of differences between successive interbeat intervals (RMSSD), an index of cardiac vagal control (28); c) respiratory sinus arrhythmia (RSA), a second index of cardiac vagal control that combines interbeat intervals (IBI) with the respiration signal (27–29); and d) preejection period (PEP), an index of cardiac sympathetic control (27,30). Hyperreactivity of the ANS is characterized by a greater increase in HR and greater decrease in RMSSD, RSA, and PEP in people with psychopathology compared with controls, whereas hyporeactivity is indicated by a smaller increase in HR and smaller decrease in RMSSD, RSA, and PEP.

To evoke ANS reactivity, two types of stressors were used: a) an n-back task and b) a psychiatric interview. The n-back task represents the "classical" cognitively challenging tasks that are often used to evoke stress in controlled laboratory settings. The rationale for using the psychiatric interview is that questions about psychiatric symptoms, recent life events, and the reliving of anxious and depressing memories are likely to be particularly stress evoking for patients with psychopathology. Ultimately, affective dysregulations are what distinguishes people with depression and anxiety from mentally healthy individuals. Accordingly, we hypothesized that there is ecological validity behind investigating the stress reactivity of people with psychopathology when confronted with recalling negative life events and anxious and depressing moments.

NESDA's large sample size allowed us to consider important covariates and, in response to the research results of Licht et al. (8–11), to specifically examine the confounding effects of antidepressants.

METHODS

Participants

Participants belonged to the NESDA, an ongoing longitudinal cohort study to examine the long-term course of depression and anxiety. The NESDA sample includes 2981 participants aged 18 to 65 years with a current diagnosis of depression and/or anxiety disorder, a history of these disorders, and healthy controls. Participants were recruited from community, primary care, and mental health care in the Netherlands. A 4-hour baseline measurement was conducted by specially trained clinical research staff between September 2004 and February 2007, and follow-up assessments took place after 1, 2, 4, and 6 years. Demographic, psychiatric, and biological assessments were included, as well as collection of blood and saliva samples. People were excluded when they had a primary clinical diagnosis of other severe psychiatric disorders, such as psychotic disorder, obsessive compulsive disorder, bipolar disorder, or severe addiction disorder, and when they lacked fluency in Dutch. A detailed description of the rationale, objectives, and methods of the NESDA study can be found elsewhere (31). The study protocol was approved by the ethical review board of each participating center, and written informed consent was provided by all participants.

Data for the present study were drawn from the 2-year follow-up assessment (because the N-back task was not introduced until then) and consisted of 2596 respondents (32). Participants were divided into three groups according to the DSM-IV–based Composite International Diagnostic Interview, version 2.1: a) a control group with no lifetime history of psychiatric disorders; b) a remitted psychopathology group with major depressive disorder (MDD) or anxiety disorder (panic disorder, social phobia and/or generalized anxiety disorder) earlier in life but not in the past 6 months; and c) a current psychopathology group with either MDD, anxiety disorder, or both in the past 6 months. Of the participants, five individuals were excluded from the sample because they did not meet our group criteria (e.g., people with solely dysthymia), and 408 individuals were excluded because of missing physiological data due to equipment failure during assessment or poor electrocardiogram (ECG) quality, or because they

did not complete either stress conditions. Consequently, we conducted our analyses with 2183 participants, including 466 controls, 913 people with remitted psychopathology, and 804 people with current psychopathology.

Stress Conditions

Stress reactivity was evoked by two types of stressors. First, the n-back task is a well-validated task for working memory (33,34) but also used as a laboratory stressor (35). The second stressor consisted of a psychiatric interview, evoking personal-emotional stress related to the occurrence of symptoms of anxiety and depression in daily life.

N-Back Task Stressor

A spatial variant of the n-back task for which the participant had to remember the location of a stimulus presented a certain number "*n*" of stimuli back was administered. A 1-back, a 2-back, and two 3-back conditions were presented to the participants, each consisting of 20 trials. The n-back task is stress evoking due to task difficulty and performance pressure. Furthermore, false feedback and negative comparisons to other participants were provided to evoke a stronger stress response. Before the n-back task, participants were presented with the n-back rest, during which a series of neutral pictures were shown for approximately 2 minutes. This rest condition was used as a baseline measurement to compare against the n-back task stressor.

Psychiatric Interview Stressor

The psychiatric interview lasted approximately 45 minutes and included various indicators of presence, symptoms, and history of anxiety and depressive disorders, as well as suicide ideation, mood disorder symptoms, and experience of adverse life events. A general interview of approximately 30 minutes was used as a baseline measurement to compare against the psychiatric interview stressor. Integrated into this general interview were topics such as smoking behavior, use of medication, somatic health, daily functioning, and health care use. Both the general and psychiatric interviews have been previously described elsewhere (31).

Physiological Measurement

Physiological data were measured by the "Vrije Universiteit Ambulatory Monitoring System" (VU-AMS), a lightweight portable device that records ECGs and changes in thorax impedance (impedance cardiography [ICG]) from a six-electrode configuration (27). Recording is unobtrusive and participants retain full freedom of movement. Participants wore the VU-AMS device during most of the assessment at baseline and follow-up. An event marker was used to divide the recording into distinct assessment conditions. Movement registration through vertical accelerometry was used to remove periods where the participants were not sitting (e.g., breaks and moving between locations).

From the VU-AMS recordings, the following outcome variables were computed: HR, RMSSD, RSA, and PEP. HR and RMSSD were directly derived from the IBI time series (28). RSA was obtained by peak-valley estimation that combined the ECG with the respiration signal obtained from the thorax impedance (27–29). PEP was extracted from the interval between the Q-onset in the ECG, indicating onset of left ventricular electrical activity, and the upstroke (B-point) of the ICG signal, indicating the beginning of left ventricular ejection (27,30).

During automated and visual data cleaning, suspicious IBIs and breathing cycles were corrected or discarded when displaying irregularities. An automated scoring algorithm was also used to detect crucial landmarks in the ICG, which were then visually inspected and manually corrected.

Covariates

Because it has been linked to HR variability (36,37), respiration rate was included as a covariate. Adjustments were also made for sociodemographic characteristics, including age, sex, and education in years, as well as for health indicators associated with psychopathology and ANS activity, including body mass index (BMI), physical activity measured by the International Physical Activity Questionnaire (38), current smoking status (yes/no), alcohol use (units per week), self-reported presence of heart disease (coronary disease, cardiac arrhythmia, angina, heart failure, and myocardial infarction), and number count of other chronic conditions (epilepsy, diabetes, osteoarthritis, stroke, cancer, chronic lung disease, thyroid disease, liver disease, intestinal disorders, and ulcer). In addition, we adjusted analyses of the n-back task stressor for n-back task performance. Participants were required to bring their medication containers to the assessments so that medication use could be determined. We adjusted for regular medication use, including heart medication (anatomical therapeutic chemical (ATC) codes C01, C02, C03, C04, C05, C07, and C08), but specifically the following antidepressants: tricyclic antidepressants (ATC code N06AA), selective serotonin reuptake inhibitors (ATC code N06AB), and selective serotonin and noradrenalin reuptake inhibitors (ATC code N06AX).

Statistical Analyses

Data were analyzed using IBM SPSS Statistics for Windows, version 20.0 (IBM Corp).

Because preliminary analyses showed that ANS reactivity association results for MDD and anxiety were very similar, we chose to merge these psychiatric disorders into groups based on the presence of either of the disorders (full details per psychopathology group are available in Tables S1–S4, Supplemental Digital Content 1, http://links.lww.com/PSYMED/A274). RMSSD and RSA values were highly skewed and these values were therefore ln-transformed for all analyses.

Analysis of variance and χ^2 statistics were used to compare sample characteristics across the controls, participants with remitted psychopathology, and participants with current psychopathology. For descriptive purposes, analysis of variance was also used to outline the differences between ANS baseline and stress values, and absolute stress reactivity values across the groups. Absolute stress reactivity values for n-back were calculated by subtraction of averaged ANS values during the n-back rest from averaged ANS values during the n-back task. Similarly, absolute stress reactivity values for interview were calculated by subtraction of averaged ANS values during the general interview from averaged ANS values during the psychiatric interview.

To formally examine the differences in HR, RMSSD, RSA, and PEP between the three psychopathology groups, we conducted linear mixed-model analyses. Two models were used: one to estimate the main effects of group (remitted psychopathology and current psychopathology versus control) and condition (stress versus baseline), and the other model to additionally estimate the interaction effect of group by condition (stress reactivity differences across the psychopathology groups). These models were separately run for the n-back conditions and the interview conditions. The mixed models were then repeated with adjustments for covariates (respiration rate, age, sex, education, BMI, smoking, alcohol use, physical activity, heart disease, chronic disease, heart medication, and, for analyses of the n-back conditions, n-back performance). In addition, adjustments for antidepressants were added to the analyses. To entirely rule out effects of antidepressants, we conducted sensitivity analyses in which antidepressant users were excluded. The criterion for statistical significance was $p < .05$.

RESULTS

Our sample (n = 2183) had a mean (standard deviation) age of 44.1 (13.2) years, and 66.4% of the participants was female.

Table 1 shows that compared with participants without psychopathology, individuals with psychopathology were more likely to be female, had fewer years of education, were more likely to smoke and less likely to drink, and had higher BMIs. In addition, the psychopathology group had lower systolic blood pressure but higher diastolic blood pressure, had more chronic diseases, were more likely to

TABLE 1. Sample Characteristics for Controls, Remitted Psychopathology Participants, and Current Psychopathology Participants

Characteristics	Participants			p^a
	Control (n = 466)	Remitted Psychopathology (n = 913)	Current Psychopathology (n = 804)	
Age, y	43.5 (14.7)	44.1 (13.0)	44.5 (12.3)	.45
Female sex (%)	60.3	66.8	69.4	.004
Education, y	13.3 (3.3)	12.7 (3.2)	12.1 (3.3)	<.001
Smoking (%)	20.6	29.9	38.1	<.001
Alcohol use				
Nondrinker (%)	23.6	32.0	36.3	<.001
Mild/Moderate drinker (%)	61.6	53.3	48.9	
Heavy drinker (%)	14.8	14.7	14.8	
Physical activity, METhours/wk, median (IQR)	62.8 (32.4–90.2)	59.8 (29.9–90.3)	56.4 (24.4–81.6)	.30
Resting respiration rate, breaths/min	16.6 (1.3)	16.5 (1.3)	16.5 (1.3)	.70
Body mass index, kg/m^2	25.2 (4.7)	25.7 (4.6)	26.0 (5.2)	.011
Blood pressure				
Systolic, mm Hg	133.7 (18.4)	130.7 (19.9)	130.4 (19.4)	.007
Diastolic, mm Hg	78.4 (11.04)	77.6 (11.3)	78.9 (11.9)	.067
Heart or coronary disease (%)	3.6	4.9	5.7	.26
Chronic diseases, median no. (IQR)	0.0 (0.0–1.0)	0.0 (0.0–1.0)	1.0 (0.0–1.0)	<.001
Heart or blood pressure medication (%)	14.4	13.9	15.7	.58
Antidepressant use				
TCA (%)	0.2	2.1	4.5	<.001
SSRI (%)	0.4	14.8	21.3	<.001
SNRI (%)	0.0	3.6	7.0	<.001
Other psychotropic medication (%)	4.7	6.9	5.6	.23
IDS-SR score	6.4 (5.6)	12.7 (8.3)	24.7 (12.0)	<.001
BAI score	3.2 (4.0)	6.5 (6.2)	14.3 (9.4)	<.001
Current psychopathology				
Current MDD (%)	NA	NA	26.0	NA
Current anxiety (%)	NA	NA	39.2	NA
Current comorbid MDD and anxiety (%)	NA	NA	34.8	NA
Remitted psychopathology				
Remitted MDD (%)	NA	32.2	NA	NA
Remitted anxiety (%)	NA	19.2	NA	NA
Remitted MDD and anxiety (%)	NA	48.6	NA	NA
N-back task				
Reaction time, ms	576.9 (206.6)	588.1 (201.4)	588.9 (187.2)	.53
Accuracy, mean %	44.4 (20.2)	42.9 (19.1)	41.3 (19.0)	.020
Duration conditions[a]				
N-back rest, min	1.8 (0.5)	1.8 (0.5)	1.8 (0.6)	.14
N-back task, min	10.8 (2.1)	10.8 (2.0)	10.4 (2.0)	.001
General interview, min	26.2 (10.3)	31.9 (11.7)	36.7 (11.6)	<.001
Psychiatric interview, min	25.5 (12.8)	39.3 (20.6)	66.1 (22.7)	<.001

Values represent mean (standard deviation) unless otherwise indicated.

METhours/wk = multiple of resting metabolic rate times hours of physical activity per week; IQR = interquartile range; TCA = tricyclic antidepressant; SSRI = selective serotonin reuptake inhibitors; SNRI = selective serotonergic and noradrenergic reuptake inhibitors; IDS-SR = Inventory of Depressive Symptomatology; BAI = Beck Anxiety Inventory; MDD = Major Depressive Disorder; NA = not applicable.

[a] Comparison using analyses of variance (continuous variables) and χ^2 statistics (categorical variables).

use antidepressants, and had higher severity of depression (Inventory of Depressive Symptomatology score) and anxiety (Beck Anxiety Inventory score). Finally, these patients performed worse and took less time on the n-back task, and took more time on the general and psychiatric interview.

Table 2 describes the unadjusted means of ANS data during the n-back task and psychiatric interview stressor with their respective baseline and stress levels and the reactivity values for the three psychopathology groups. Results of the unadjusted and adjusted main and interaction effects of group and condition are shown in Table 3 (n-back task stressor) and Table 4 (psychiatric interview stressor).

Table 3 shows that mixed-model analyses resulted in significant main condition effects: higher HR and lower RMSSD, RSA, and PEP were seen for the n-back task compared with n-back rest (all p values < .001), indicating that the n-back task yielded the expected stress activation. Significant main psychopathology group effects were seen for HR, which was lower in both unadjusted and adjusted analyses for the remitted psychopathology group (range, p values = .001–.012) and the current psychopathology group ($p \leq .001$) as compared with controls. In addition, RMSSD was lower for participants with remitted psychopathology in the fully adjusted model ($p = .030$), and RSA was lower for patients with current psychopathology in the unadjusted ($p = .031$) and the first adjusted model ($p = .029$). However, as we expected based on earlier findings by Licht et al. (8–11), adjustment for antidepressants reduced many of these effects to nonsignificant, illustrating that there were, except for HR, not many general differences in ANS parameters across psychopathology groups. Importantly, highly significant results were found for the group by condition interaction effects (i.e., differences in stress reactivity across the groups). A lower HR reactivity was seen in the remitted ($p = .004$) and current psychopathology group ($p < .001$), and a lower reactivity of RMSSD ($p = .002$) and RSA ($p = .019$) in patients with current psychopathology than in controls. The fully adjusted significant interaction effects for n-back are illustrated in Figure 1. There were no significant interaction effects for PEP. When excluding the 450 antidepressant users from the analyses, the found effects remained significant and of similar magnitude.

Table 4 shows that similar main condition effects were seen for interview as for n-back: HR was significantly higher for the psychiatric interview compared with the general interview, and RMSSD, RSA, and PEP were significantly lower (all p values < .001). Comparable to the results of the n-back conditions, significant group effects were found for HR, which was lower for participants with current psychopathology than for controls in both the unadjusted ($p = .03$) and adjusted models (range, p values = .001–.002). Compared with the controls, the remitted patients had a lower HR ($p = .02$), in addition to a shorter PEP ($p = .04$) only in the fully adjusted model. Again, we found highly significant group by condition effects for HR, RMSSD, and RSA. However, these interaction effects were in the complete opposite of the interaction effects found for the n-back task. Comparing the psychiatric interview to the general interview condition, a higher HR reactivity was seen for both the remitted and current psychopathology groups than for the control group ($p < .001$). In addition, a higher reactivity was seen for RMSSD ($p < .001$) and RSA ($p = .002$) in patients with current psychopathology than in controls. The fully adjusted significant interaction effects for the interview conditions are illustrated in Figure 1. Again, no significant interaction effects were found for PEP. Importantly, all of the results remained comparable after excluding antidepressant users from the analyses, suggesting that use of antidepressants was not the main driving factor of our findings.

DISCUSSION

This large-scale cohort study aimed to investigate the nature and direction of ANS stress reactivity dysregulation in psychopathology. Interestingly, compared with healthy controls, depressed and anxious participants showed a differential stress reactivity for HR, RMSSD, and RSA in opposite directions for two different stressors: a) a hyporeactivity for the n-back task, a cognitively challenging stressor, and b) a hyperreactivity for the psychiatric interview, a personal-emotional stressor related to the occurrence of symptoms of anxiety and depression. Both stress reactivity directions for the two stressors were also seen for participants with a remitted diagnosis but only for HR and with smaller effects. These results are interesting because previous studies have suggested both hyporeactivity (17–24) and hyperreactivity (12–16) in depression and anxiety. Those studies have focused on stress reactivity during mental and speech tasks, sometimes in combination with a cold pressure task or a postural challenge, but without unequivocal results on the effect of specific stressors on the ANS reactivity of people with psychopathology. However, no study has investigated both the effect of a cognitively challenging stressor and a personal-emotional stressor. The results of hyporeactivity during the n-back task led to the hypothesis that people with psychopathology who symptomatically show disengagement from commitments to difficult to reach goals (39,40) may consequently be less motivated (41,42) to perform well in comparison to healthy controls. This hypothesis is supported by the finding of a significantly worse performance on the n-back task by depressed and anxious patients (Table 1). Our findings are in line with research by Brinkmann and Gendolla (43), indicating that dysphoric participants showed lower systolic blood pressure reactivity than did nondysphoric participants when facing a difficult cognitive task. These authors also concluded that dysphoria is associated with a motivational deficit during difficult tasks. In contrast, requesting participants to describe depressing and anxious

TABLE 2. ANS Values During N-Back Task and Psychiatric Interview Stressor With Their Respective Baseline Condition and Stress Reactivity Values in Controls, Remitted Psychopathology, and Current Psychopathology

	Participants			
ANS Data During N-Back Rest and N-Back Task	Control (n = 443)	Remitted Psychopathology (n = 808)	Current Psychopathology (n = 703)	p[a]
HR, beats/min				
N-back rest	69.0 (9.6)	67.9 (9.6)	67.6 (10.2)	.043
N-back task	73.1 (9.9)	71.3 (9.8)	70.7 (10.5)	<.001
Stress reactivity	4.1 (4.2)	3.5 (3.5)	3.1 (3.4)	<.001
RMSSD, ms[b]				
N-back rest	33.3 (27.3)	33.1 (29.2)	30.7 (24.8)	.038
N-back task	28.9 (21.5)	29.6 (24.1)	28.6 (20.9)	.48
Stress reactivity	−6.2 (14.5)	−5.4 (17.8)	−3.5 (15.4)	.013
RSA, ms[b]				
N-back rest	42.2 (31.0)	40.4 (28.4)	38.3 (28.2)	.033
N-back task	36.7 (23.7)	35.0 (21.9)	33.8 (20.6)	.26
Stress reactivity	−9.3 (17.0)	−7.4 (16.5)	−6.9 (15.0)	.044
PEP, ms				
N-back rest	123.9 (17.0)	122.1 (18.6)	123.0 (18.7)	.23
N-back task	121.1 (17.0)	119.6 (18.7)	120.6 (18.5)	.32
Stress reactivity	−2.8 (5.8)	−2.5 (5.0)	−2.4 (5.3)	.34
	Participants			
ANS Data During General Interview and Psychiatric Interview	Control (n = 454)	Remitted Psychopathology (n = 896)	Current Psychopathology (n = 791)	p[a]
HR, beats/min				
General interview	73.0 (9.6)	71.9 (9.5)	71.1 (10.3)	.005
Psychiatric interview	75.7 (9.6)	75.4 (9.8)	75.1 (10.4)	.59
Stress reactivity	2.7 (3.4)	3.5 (3.4)	4.0 (3.3)	<.001
RMSSD, ms[b]				
General interview	32.2 (25.0)	31.5 (24.7)	31.5 (27.1)	.77
Psychiatric interview	29.0 (22.9)	27.8 (22.4)	26.8 (22.7)	.062
Stress reactivity	−3.4 (12.2)	−4.1 (12.1)	−5.6 (11.8)	.004
RSA, ms[b]				
General interview	39.7 (24.6)	39.1 (22.6)	38.0 (23.7)	.32
Psychiatric interview	36.1 (22.9)	35.1 (20.9)	33.4 (21.3)	.038
Stress reactivity	−3.8 (8.1)	−4.3 (7.9)	−5.0 (7.9)	.028
PEP, ms				
General interview	122.1 (16.6)	120.5 (18.1)	121.2 (18.4)	.28
Psychiatric interview	120.0 (16.0)	118.1 (17.5)	119.0 (17.6)	.16
Stress reactivity	−2.1 (6.0)	−2.3 (5.9)	−2.2 (6.3)	.75

Values represent mean (standard deviation).

ANS = autonomic nervous system; HR = heart rate; RMSSD = root mean square of successive differences; RSA = respiratory sinus arrhythmia; PEP = preejection period.

Stress reactivity values represent averaged ANS values during the n-back task or psychiatric interview stressor minus their respective averaged baseline condition values.

[a] Comparison using analyses of variance.

[b] Values were ln-transformed for analyses and back-transformed for representation of the means.

events during a psychiatric interview may better capture the experiences of personal-emotional stress in daily life. This stressor evoked a reaction in controls, who also experienced some negative life events and anxious and depressing moments. However, it was probably more provocative for patients with psychopathology, and the heightened

TABLE 3. The Main and Interaction Effects on ANS of Group (Control, Remitted Psychopathology, and Current Psychopathology) and Condition (N-back Rest and N-back Task)

	Group effect[a]				Condition Effect[a]		Group by Condition Effect[a]			
	Remitted Psychopathology Versus Control		Current Psychopathology Versus Control		N-Back Task Versus N-Back Rest		Remitted Psychopathology by N-Back Task		Current Psychopathology by N-Back Task	
Variable	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*
HR, beats/min										
Unadjusted	−1.45	.012	−1.93	.001	3.48	<.001	−0.62	.004	−0.94	<.001
Adjusted[b]	−1.87	.001	−2.44	<.001	3.48	<.001	−0.62	.004	−0.94	<.001
Adjusted[c]	−1.94	<.001	−2.81	<.001	3.48	<.001	−0.62	.004	−0.94	<.001
RMSSD, ms[d]										
Unadjusted	0.01	.78	−0.05	.19	−0.10	<.001	0.03	.18	0.07	.002
Adjusted[b]	0.03	.38	−0.03	.44	−0.10	<.001	0.03	.18	0.07	.002
Adjusted[c]	0.07	.030	0.05	.14	−0.10	<.001	0.03	.18	0.07	.002
RSA, ms[d]										
Unadjusted	−0.03	.36	−0.08	.031	−0.14	<.001	0.03	.15	0.05	.019
Adjusted[b]	−0.02	.58	−0.06	.029	−0.14	<.001	0.03	.15	0.05	.019
Adjusted[c]	0.03	.28	0.02	.48	−0.14	<.001	0.03	.15	0.05	.019
PEP, ms										
Unadjusted	−1.66	.12	−0.66	.55	−2.52	<.001	0.34	.27	0.46	.15
Adjusted[b]	−1.32	.21	−0.43	.69	−2.52	<.001	0.34	.27	0.46	.15
Adjusted[c]	−1.58	.12	−0.27	.81	−2.52	<.001	0.34	.27	0.46	.15

ANS = autonomic nervous system; HR = heart rate; RMSSD = root mean square of successive differences; RSA = respiratory sinus arrhythmia; PEP = preejection period.

[a] Main effects of group and condition were analyzed in a mixed model separate from the interaction effect of group by condition.

[b] Adjusted for respiration rate, age, sex, education, body mass index, physical activity, smoking, alcohol use, heart disease, chronic disease, heart medication, and n-back task performance.

[c] Adjustment[b] + additionally adjusted for antidepressant use.

[d] Values were ln-transformed for analyses.

physiological reactivity most likely reflects a higher perceived stress level. We consider this to be representative for real-life situations where people with depression/anxiety are presumed to be more affected by recanting and sharing their daily situations and problems than people without mental disorder. Because only parameters controlled by the PNS were affected, the differences in stress reactivity between the psychopathology groups were probably caused by differences in vagal withdrawal during stressful situations.

Consistent with NESDA research conducted by Licht et al. (8–11), there were few group differences in overall ANS functioning after adjustment for confounding factors, including antidepressant medication. However, we did find main group effects for HR, which was lower in the current and remitted psychopathology groups than in controls during both n-back and interview conditions. These results are remarkable, because other studies indicate that HR is higher in patients with depressive and anxiety disorders (25,44–46). A possible explanation for this is the down-regulation of cardiac β-receptors due to prolonged activation of the SNS. There is indeed some evidence that depression and anxiety are associated with decreased β-adrenergic receptor responsiveness (47,48). Because HR, as opposed to RMSSD and RSA, is partly controlled by the SNS (27), it would be consistent with the theory of down-regulated β-receptors that we find lower values for HR, but not RMSSD and RSA, in our current and remitted psychopathology group. Correspondingly, prolonged activation of the SNS would be expected to increase cardiac contractility, but down-regulation of ventricular β-receptors would act to cancel this effect. This may also be an explanation as to why no group differences were seen in PEP. We note that others did find differences in SNS functioning in psychopathology. A study conducted by Salomon et al. (23) showed that people with MDD showed less PEP reactivity during a speech task than did controls. Light et al. (16) used both PEP and plasma norepinephrine (NE) as indicators of sympathetic activity. Plasma NE showed a significantly greater increase during a speech task, suggesting higher

TABLE 4. The Main and Interaction Effects on ANS of Group (Control, Remitted Psychopathology, and Current Psychopathology) and Condition (General Interview and Psychiatric Interview)

	Group Effect[a]				Condition Effect[a]		Group by Condition Effect[a]			
	Remitted Psychopathology Versus Control		Current Psychopathology Versus Control		Psychiatric Interview Versus General Interview		Remitted Psychopathology by Psychiatric Interview		Current Psychopathology by Psychiatric Interview	
Variable	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*	Estimate	*p*
HR, beats/min										
Unadjusted	−0.70	.21	−1.25	.030	3.52	<.001	0.81	<.001	1.30	<.001
Adjusted[b]	−1.04	.054	−1.75	.002	3.52	<.001	0.81	<.001	1.30	<.001
Adjusted[c]	−1.25	.020	−2.32	<.001	3.52	<.001	0.81	<.001	1.30	<.001
RMSSD, ms[d]										
Unadjusted	−0.03	.31	−0.05	.12	−0.14	<.001	−0.02	.12	−0.06	<.001
Adjusted[b]	−0.02	.59	−0.02	.44	−0.14	<.001	−0.02	.12	−0.06	<.001
Adjusted[c]	0.02	.61	0.04	.27	−0.14	<.001	−0.02	.12	−0.06	<.001
RSA, ms[d]										
Unadjusted	−0.02	.48	−0.06	.052	−0.11	<.001	−0.01	.18	−0.03	.002
Adjusted[b]	−0.01	.74	−0.04	.11	−0.11	<.001	−0.01	.18	−0.03	.002
Adjusted[c]	0.03	.20	0.03	.22	−0.11	<.001	−0.01	.18	−0.03	.002
PEP, ms										
Unadjusted	−1.75	.079	−0.90	.38	−2.24	<.001	−0.24	.49	−0.07	.84
Adjusted[b]	−1.59	.11	−0.85	.41	−2.24	<.001	−0.24	.49	−0.07	.84
Adjusted[c]	−1.99	.038	−0.88	.39	−2.24	<.001	−0.24	.49	−0.07	.84

ANS = autonomic nervous system; HR = heart rate; RMSSD = root mean square of successive differences; RSA = respiratory sinus arrhythmia; PEP = preejection period.

[a] Main effects of group and condition were analyzed in a mixed model separate from the interaction effect of group by condition.

[b] Adjusted for respiration rate, age, sex, education, body mass index, physical activity, smoking, alcohol use, heart disease, chronic disease, and heart medication.

[c] Adjustment[b] + additionally adjusted for antidepressant use.

[d] Values were ln-transformed for analyses.

SNS nerve spillover in people with depressive symptoms. This does not contradict down-regulation of β-receptors, as NE spillover, in contrast to PEP, should not be affected by β-receptor status.

Adjusting for confounding factors did not, to a large extent, change our results, nor did exclusion of antidepressant users. We conclude that, in contrast to studies by Licht et al. (8–11) that focused on general ANS activity, antidepressant use was not the main factor causing patient-control differences in the current study on ANS *re*activity during stress.

When interpreting these findings, we need to take some limitations into account. For instance, the psychiatric interview is not validated as a stress task in literature, and one limitation is that this stressor is more susceptible to interpersonal variability. This limitation is illustrated by the large differences in interview duration between individuals and between groups, which may have influenced some of the differences in ANS functioning between groups. In addition, the general interview might not have been a neutral reference condition for the psychiatric interview, because it also contains some questions (e.g., somatic health and disease) that might have caused arousal. However, because all groups showed a stress response from our chosen baseline condition to our chosen stress condition, we can assume that the psychiatric interview was generally more stress evoking compared with the general interview. It should be mentioned that multiple statistical comparisons were performed without prespecified hypotheses or statistical adjustments, increasing the chance of false positives. In addition, compared with a meta-analysis published in 2004, suggesting a moderate effect size for the relationship between depressive symptoms and stressor-evoked cardiovascular reactivity (15), we found only small differences in ANS reactivity. However, strong associations are rare in the field of biological psychiatry, as has been shown for immunoinflammatory and hypothalamic-pituitary-adrenal axis dysregulations (3), and the absence of large effect sizes does not necessarily mean that the findings are immaterial. Smaller studies might have found larger effect sizes, but these studies are prone to error from possibly testing atypical samples, whereas our

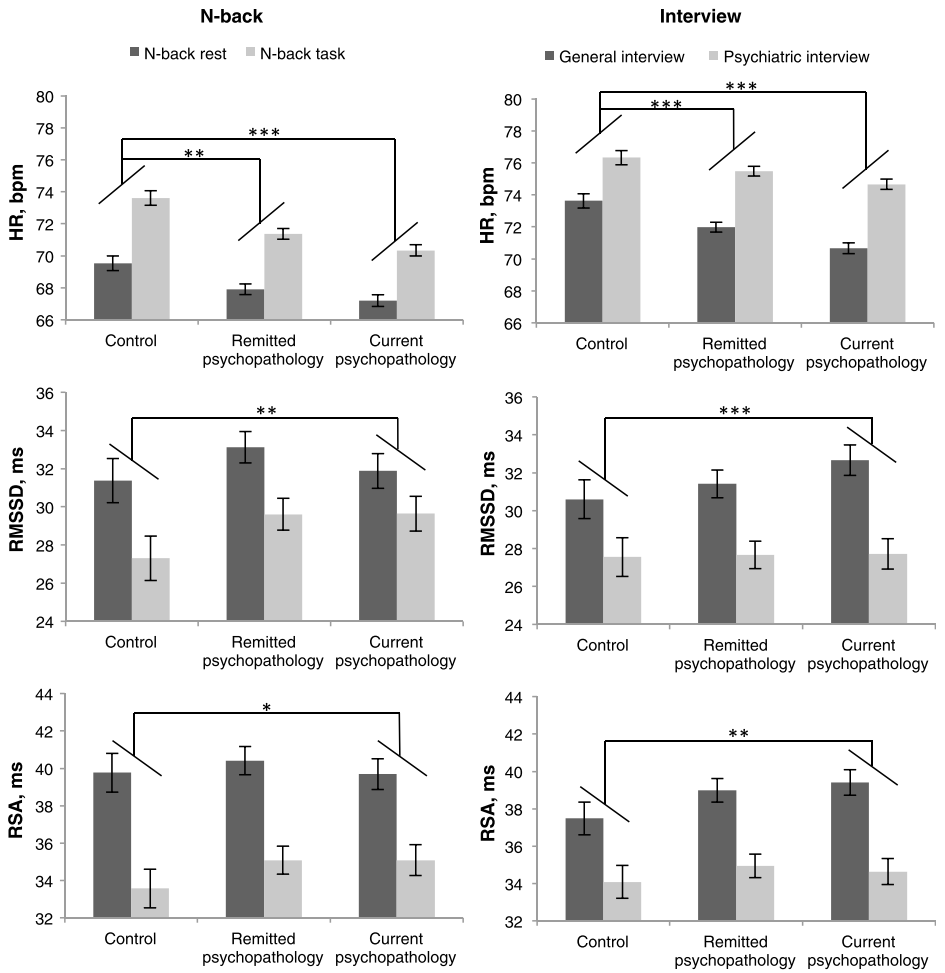

FIGURE 1. Mean HR, RMSSD, and RSA during n-back task or psychiatric interview stressor and their respective baseline condition values in controls, remitted psychopathology, and current psychopathology. Values were adjusted for respiration rate, age, sex, education, BMI, physical activity, smoking, alcohol use, heart disease, chronic disease, heart medication, and antidepressant use. For analyses of the n-back task stressor, values were also adjusted for n-back task performance. * $p < .05$, ** $p < .01$, *** $p < .001$; p values were derived from linear mixed-model analyses and represent a significantly different stress reactivity of the remitted or current psychopathology group compared with controls. HR = heart rate; RMSSD = root mean square of differences between successive interbeat intervals; RSA = respiratory sinus arrhythmia; BMI = body mass index; bpm = beats/min.

results are much more replicable to larger studies. Also, our short-term stressors clearly induced a proportionally mild stress reactivity compared with the more chronic and intense stress that people experience in daily life. This is a limitation, but we note that our aim was to examine potential biological pathways linking psychopathology to cardiovascular health, as opposed to providing a clinically useful marker of dysfunctional stress reactivity at the level of individual participants. Furthermore, our cohort was relatively young with few cardiovascular health problems and we cannot rule out that psychopathology has larger effects on ANS functioning in older, less healthy populations. Another limitation concerns the potential heterogeneity in the type and severity of psychopathology which can be a crucial source of variability in biological dysregulation (3,49), and perhaps even crucial in determining blunted or exaggerated autonomic responses to stress (50,51). For the current study, we chose to merge data of patients with depression and anxiety because preliminary analyses showed very similar results for both psychopathologies on ANS activity. However, we have not examined heterogeneity within anxiety diagnosis (e.g., panic disorder, social phobia, and/or generalized anxiety disorder) or severity of psychopathology. Although earlier research did not reveal large basal ANS differences across different anxiety patients (11), it would be interesting to study such influence of disease character on ANS stress reactivity more in depth during further research. Finally, the cross-sectional nature of our data makes it difficult to infer causality from the found relationships. Therefore, it remains unclear whether altered ANS reactivity is a vulnerability factor for developing psychopathology, whether having depression and anxiety changes stress reactivity, or

whether there is a common mechanism that influences both the ANS and depressive symptoms.

Despite the limitations, this study has a number of strengths: the findings of altered ANS reactivity were robust in our large study sample and inclusion of many key confounding factors did not change this. We used stable and reliable indicators of both SNS and PNS activity, and we used two types of stressors that showed an intuitively appealing discrepancy in reactivity levels between patients with psychopathology compared with healthy controls.

In conclusion, ANS stress reactivity, specifically cardiac vagal reactivity, is dysregulated in psychopathology. The results imply a hyporeactivity for people with depression and anxiety in response to cognitively challenging stressors and a hyperreactivity in response to stressors evoking personal-emotional stress. If the interview stressor has captured the response of patients with psychopathology to the affective afflictions they are confronted with in daily life, it may be a more ecologically valid means of testing ANS stress reactivity in people with depression and anxiety compared with the predominantly used laboratory stressors.

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