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Distress disorder histories predict HRV trajectories during and after stress

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ABSTRACT

Background: Breast cancer survivors face a number of physical health threats including cardiovascular disease, the leading cause of death among breast cancer survivors. Low heart rate variability (HRV) represents one well-established risk factor for poor cardiovascular health. Among physically healthy adults and breast cancer survivors, distress disorders may contribute to lower HRV, enhancing morbidity and mortality. This study examined how a distress disorder history altered survivors' HRV trajectories during and after an experimental stressor.
Methods: Breast cancer survivors (n = 178; mean age = 51.22) who finished treatment for stages 0-IIIa cancer within the past two years completed a diagnostic interview assessing lifetime presence of psychological disorders. They also participated in a Trier Social Stress Test (TSST). HRV data provided information on survivors' cardiovascular responses at baseline, during the TSST, and during recovery. HRV recovery data at 45 min and 120 min post-TSST was also collected. Survivors also completed questionnaires before and after the TSST assessing task performance, stress levels, ability to cope, and hopelessness. Covariates included body mass index, age, cancer stage, cardiovascular medications, exercise, menopause status, fatigue, current depressive and anxiety symptoms, and physical comorbidities.
Results: Women with a distress disorder history had significantly lower HRV before, during, and after the TSST compared to women without such a history. Survivors with distress disorders found the TSST to be more threatening, and reported feeling less control over their performance than those without distress disorders.
Conclusions: Breast cancer survivors with a distress disorder history may have lower autonomic flexibility before, during, and after stress exposure. Distress disorder histories also heighten several stress-related risk perceptions leading up to and following the TSST. These findings highlight distress disorder histories as a unique correlate of poorer cardiovascular function among survivors.

1. Introduction

Psychological distress represents a transdiagnostic experience that cuts across many forms of psychopathology, including mood and anxiety disorders (Watson, 2005). Distress influences people both with and without chronic health conditions. Distress disorders are a group of psychological disorders characterized by negative emotionality that includes major depressive disorder (MDD), persistent depressive disorder (PDD), generalized anxiety disorder (GAD), and post-traumatic stress disorder (PTSD) (Watson, 2005). Distress disorders follow a chronic and persistent course and typically do not remit without intervention (Tyrer and Baldwin, 2006). They also complicate the presentation and treatment of medical conditions throughout the lifespan, contributing to an increased risk for both cardiovascular disease and metabolic syndrome (Cohen et al., 2015; Hare et al., 2014). Theory and research highlight common phenomenological features among these disorders that distinguish them from other diagnostic groups (Watson, 2005). The distress disorder category of disorders therefore represents the field's growing push to examine transdiagnostic features (e.g., worry, rumination, intolerance of uncertainty, fatigue) rather than

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single diagnostic categories alone.

Distress disorders disproportionately affect cancer survivors (Niedzwiedz et al., 2019). Several factors influence distress among breast cancer survivors, including more advanced disease at diagnosis, chemotherapy treatment, being younger, unmarried, or of a lower socioeconomic status (Syrowatka et al., 2017). Approximately one in every two cancer patients experience high rates of psychological distress (Mehnert et al., 2018), and rates of depression and anxiety are higher among people with cancer compared to the general population (Niedzwiedz et al., 2019). Psychological distress is typically highest within the first year following cancer diagnosis, but cancer-related distress can remain elevated following treatment, impacting physical and psychological well-being (Bleiker et al., 2000; Buzaglo et al., 2016). A past history of a psychological disorder also predicts cancer-related distress at diagnosis and throughout treatment (O'Connor et al., 2011). However, the number of women who experience histories of distress disorders is not entirely clear, with rates ranging from 6% to 35% across previous studies (Gandubert et al., 2009; Kissane et al., 2004; O'Connor et al., 2011).

Distress disorders are difficult to treat, and, even following successful treatment, subthreshold symptoms can linger and the risk for recurrence is high. The scarring hypothesis suggests that histories of depression can result in cognitive, emotional, and behavioral changes, heightening emotional and physiological stress reactivity (Gunthert et al., 2007; Husky et al., 2009; Wichers et al., 2010). While these "scars" may not be permanent, individual differences (such as psychiatric diagnosis history) that confer risk for biological and emotional dysfunction at one time point can continue to confer future risk. Research has not assessed whether distress disorder histories may follow a similar course, and whether these findings replicate among breast cancer survivors—a group with notable health risks. Moreover, individuals with distress disorder histories may engage in perseverative cognition (e.g., worry and rumination), prolonging the emotional and physiological impact of a stressor (Brosschot et al., 2005). Therefore, even when an individual with a distress disorder history does not currently meet diagnostic criteria, stress exposure may highlight or widen physiological divergence from their peers without such a history. Moreover, recent research suggests that abnormally high or low physiological responses to stress predict future disease onset (Kiecolt-Glaser et al., 2020; Turner et al., 2020).

Psychological distress influences both emotional and physical well-being. Distress disorders disrupt biological processes including heart rate variability (HRV) (Chalmers et al., 2014; Koch et al., 2019). HRV represents the variation in beat-to-beat intervals of the heart (Appelhans and Luecken, 2006). Low HRV relates to an increased risk for hypertension, diabetes, high cholesterol, chronic systemic inflammation, and coronary calcification (Colhoun et al., 2001; Fagundes et al., 2011; Thayer et al., 2010). Collectively, these physiological changes are implicated in cardiovascular disease (CVD) onset. Coronary heart disease is the leading cause of death for breast cancer survivors (Patnaik et al., 2011). Low HRV occurs more commonly among breast cancer survivors than their physically healthy peers because of their cancer treatment, contributing to an increased risk of mortality (Caro-Moran et al., 2016; Giese-Davis et al., 2015). Accordingly, low HRV represents a risk factor for increased morbidity and mortality throughout breast cancer survivorship. Indeed, meta-analytic findings support the utility of HRV as a diagnostic and prognostic tool for cardiovascular disease among breast cancer survivors (Arab et al., 2016).

Among those early in survivorship who may not yet have developed CVD, phasic HRV measured throughout a laboratory visit or experimental stressor may sensitively capture clinically important differences between those with and without a distress disorder history that may not be evident at baseline. Fatigue, a common symptom of several distress disorders, is associated with lower HRV at baseline as well as throughout a social-evaluative threat task among breast cancer survivors across studies (Crosswell et al., 2014; Fagundes et al., 2011). In another study, depressed metastatic breast cancer patients had significantly lower HRV compared to their non-depressed peers at baseline and during the Trier Social Stress Test (TSST) (Giese-Davis et al., 2006). Given reliable relationships between HRV and psychological symptoms among physically healthy adults, examining how distress histories relate to both tonic and phasic HRV among breast cancer survivors, a group at heightened risk for cardiovascular disease, represents a worthwhile investigation.

We assessed whether having a distress disorder history corresponded to differential HRV trajectories in response to the TSST during an experimental study visit. We hypothesized that survivors with a distress disorder history would have significantly lower tonic and phasic HRV before, during, and after the TSST compared to women without such a history. Further, in order to assess if distress disorder histories influenced stress-related risk perceptions, we assessed the impact of distress disorder histories on perceived stress, threat, performance, hopelessness, and ability to cope with the TSST. Consistent with the scarring hypothesis, we hypothesized that women with distress disorder histories would report greater stress-related risk perceptions before and after the TSST compared to women without such histories.

2. Methods and materials

2.1. Participants

The baseline sample of a clinical trial (Kiecolt-Glaser et al., 2014) that addressed the potential benefits of yoga for breast cancer survivors provided the data for this study; the stressor was included at the baseline visit, but not at the end of the intervention because of financial constraints. Survivors (N = 178) were recruited through breast cancer clinics and media announcements. Eligible women had completed treatment for stage 0—IIIA breast cancer within the past two years and were at least two months post-surgery, radiation, or chemotherapy (whichever occurred last). Screening exclusions included a prior history of breast or any other cancer except basal or squamous cell, more than 5 h a week of vigorous physical exercise, participation in a current yoga practice, a body mass index (BMI) of 40 or greater, diabetes, chronic obstructive pulmonary disease, uncontrolled hypertension, evidence of liver or kidney failure, and symptomatic ischemic heart disease.

2.2. Diagnostic interview data

The Structured Clinical Interview for DSM-IV (SCID-IV) assessed lifetime history of psychological disorders (First et al., 2002). A subset of modules from the full SCID were administered as part of this study. All mood disorders were assessed in addition to GAD, specific phobia, social phobia, and panic disorder. Research staff including trained post-doctoral fellows and clinical psychology graduate students completed the interviews. The diagnostic team recorded and reviewed each SCID-IV interview in consensus meetings to obtain diagnoses. Past diagnoses of major depressive disorder (MDD), dysthymic disorder, and generalized anxiety disorder (GAD) were collapsed to index whether or not the participant had a lifetime history of at least one distress disorder. Women who met criteria for a current distress disorder were excluded from analysis.

2.3. Heart rate variability

A continuous recording of HRV was collected non-invasively with the Polar s810 wristwatch and Wearlink belt band; the 1000 Hz sampling rate provides valid and reliable ECG data (Gamelin et al., 2006; Nunan et al., 2009). KUBIOS HRV analysis software was used to preprocess the raw interbeat intervals for artifacts prior to analysis (Tarvainen et al., 2009). For each time point, the KUBIOS software produced values for vagally mediated (parasympathetic) HRV using the time-domain method, square root of mean successive differences

(RMSSD) between R-Waves. RMSSD represents a time-domain specific HRV metric with a recommended minimum time frame for collection of five minutes (Shaffer and Ginsberg, 2017). It was selected due to its previously established relationships with anxiety and depression among physically healthy adults (Chalmers et al., 2014; Koch et al., 2019). RMSSD may also be less sensitive to the influence of respiration compared to other time-domain HRV metrics (Quintana et al., 2016; Shaffer and Ginsberg, 2017).

RMSSD is determined by calculating the differences between consecutive interbeat (RR) intervals before squaring and summing them. The values are then averaged and the square root obtained. Several steps were taken to clean the HRV data during processing. First, all segments were visually inspected and corrected for false or undetected R-waves, movement artifacts, and ectopic beats. The KUBIOS software also provides correction options on all data files ranging from none-very strong. The minimum correction level was always chosen. The percentage of beats changed was always kept at 10% or below to ensure that data were not overcorrected. Lastly, following artifact correction, value ranges were examined to ensure that all values fell within a plausible range (approximately 4–120 ms). Individual segments for a single participant were compared to one another to ensure that the data ranges were relatively consistent across timepoints.

2.4. Subjective stress variables

Prior to the stressor, women provided responses to two questions: "how threatening do you expect the upcoming task to be?", and "how well do you expect to be able to cope with the upcoming task?" Immediately following the stressor, survivors provided responses for, "How stressful did you find performing the speech and arithmetic tasks?", "How satisfied are you with your performance on the speech and arithmetic tasks?", "How much control did you feel you had during the speech and arithmetic tasks?", and "To what degree did you experience feelings of helplessness during the speech and arithmetic tasks?" Women provided responses on a 1–7 scale where 1 indicated 'not at all' and 7 corresponded to 'extremely'.

2.5. Covariates

All analyses controlled for age, cancer stage, menopause status, body mass index (BMI), fatigue, current depressive symptoms, current anxiety symptoms, use of cardiovascular and antidepressant medications, average hours of exercise, and medical comorbidities. The widely used Charlson Comorbidity Index, originally developed with breast cancer patients (Charlson et al., 1994), assigns weights to 19 medical conditions with higher scores equal to a greater comorbidity burden. The Multidimensional Fatigue Symptom Inventory (MFSI) measured fatigue (Stein et al., 1998). The Center for Epidemiological Studies Depression Scale (CESD) assessed current depressive symptoms (Radloff, 1977). Lastly, the Beck Anxiety Inventory (BAI) provided data on current anxiety symptoms (Beck et al., 1988). Previous research identified each of these as predictors of HRV or cardiovascular function.

2.6. Procedure

The Ohio State Biomedical Research Review Committee approved the project and all subjects provided written informed consent. Once they had eaten a standardized breakfast and completed questionnaires, they sat quietly in a chair for 20 min. A 10-minute period in the middle of this baseline relaxation period provided baseline HRV data. Next, women completed the Trier Social Stress Test (TSST) (Kirschbaum et al., 1993), a well-validated laboratory stressor that provokes reliable changes in autonomic functioning (Kudielka et al., 2004). After spending 10 min preparing a speech about why they were the best candidate for a job, a research assistant escorted them to a room where they saw a microphone, video camera, and an ''audience'' panel of two researchers wearing white laboratory coats. While seated, the survivors gave their 5-minute speech and then performed mental arithmetic serial subtraction tasks for 5 min in front of this panel. The time spent in front of the Trier panel provided the stress HRV data. After the TSST panel left the room (approximately 1 min), the next 10 min served as the HRV recovery period. Ten minutes of HRV data were collected 45 and 120 min following the TSST to provide data on continued HRV trajectories across the study visit. Survivors completed questionnaires relevant to the larger parent study following the TSST and prior to the 45-minute HRV assessment. Before the 120-minute HRV assessment, survivors completed additional questionnaires and the SCID interview to assess a lifetime history of psychological diagnoses.

2.7. Data analysis plan

SPSS Version 27 was used to conduct all analyses. HRV data underwent a natural log transformation to better approximate normality of residuals. Preliminary analyses examined correlations among the main study variables. Mixed linear models (MLMs) tested the primary hypothesis that distress disorder histories would influence HRV across the day and these histories would interact with time in predicting HRV. This modeling approach accounted for the non-independence in participants' data (i.e., the correlation between an individual's scores on the same variable over time) and maximized the use of existing data by including all participants in the analyses, regardless of missing data points (Brauer and Curtin, 2018). The mixed models used restricted maximum likelihood estimation, and a subject-specific random intercept captured the within-subject correlation. Within these models, time (baseline, pre-TSST, during TSST, recovery, 45 min post-recovery, and 120-minutes post-recovery) was treated as a categorical variable. This approach allowed for differences between any timepoints between and within groups to emerge. Independent sample *t*-tests tested the hypothesis that history of distress disorder was associated with perceived stress, threat, and ability to cope before and after the TSST.

Each model adjusted for physical comorbidities, age, fatigue, current depressive symptoms, current anxiety symptoms, average hours of exercise, cardiovascular medications (yes; no), antidepressant use (yes; no), post-menopausal status (yes; no), treatment type (surgery only; radiation and surgery; chemotherapy and surgery; and radiation, chemotherapy, and surgery) and cancer stage (0; I; II; IIIa) as time-invariant (level 2) covariates. Continuous covariates were grand-mean centered to improve interpretability of the intercepts.

3. Results

3.1. Participant demographics

Table 1 presents the sample demographics of survivors. Overall, 89 women (50.0%) endorsed a distress disorder history. Regarding specific diagnoses, 70 women met criteria for MDD, 12 for GAD, 6 for dysthymia, and one for a depressive disorder not otherwise specified. A total of 21 women had comorbid distress disorder histories, including 10 with comorbid MDD/dysthymia, 7 with comorbid MDD/GAD, 2 with comorbid GAD/dysthymia, and 2 with comorbid MDD, GAD, and dysthymia. There were no differences in HRV or key covariates between women with a single versus comorbid distress disorders ($ps > .14$).

Women with a distress disorder history ($M = 22.46$, $SD = 19.23$) reported greater fatigue compared to women without such a history ($M = 7.77$, $SD = 18.10$) $t(178) = -5.52$, $p < .01$. Survivors with distress disorder histories ($M = 14.01$, $SD = 8.88$) had higher levels of depressive symptoms compared to survivors without distress disorder histories ($M = 7.41$, $SD = 6.56$) $t(178) = -13.40$, $p < .001$. Similarly, women with distress disorder histories ($M = 12.26$, $SD = 7.52$) also experienced higher current anxiety symptoms than those without a history ($M = 7.89$, $SD = 5.80$) $t(178) = -10.34$, $p < .001$. Relative to women without a distress disorder history ($M = .06$, $SD = .37$), those with such a history

Table 1
Participant Demographics (N = 178).

	Mean (SD)	Number (%)
Age	51.36 (9.02)	–
BMI	27.78 (5.80)	–
Fatigue	16.19 (20.69)	
Physical comorbidities	.13 (.46)	–
Exercise over past week (hours)	6.24 (5.05)	
Current depressive symptoms	10.87 (8.52)	
Current anxiety symptoms	10.17 (7.10)	
Race		
White	–	155 (87.1%)
Black	–	17 (9.6%)
Asian American	–	5 (2.8%)
Native American	–	2 (1.1%)
Other		3 (1.7%)
Cancer stage		
0	–	17 (9.6%)
I	–	77 (43.3%)
II	–	68 (29.2%)
IIIa	–	16 (9.0%)
Cancer treatment		
Surgery only	–	23 (12.9%)
Radiation and surgery	–	46 (25.8%)
Chemotherapy and surgery	–	42 (23.6%)
Radiation, chemotherapy, and surgery	–	67 (37.6%)
On Endocrine Therapy		67 (37.6%)
No longer menstruating	–	134 (79.8%)
Cardiovascular medication use	–	48 (27.0%)
Antidepressant use		53 (29.8%)

Note: SD = standard deviation; BMI = body mass index. Current depressive symptoms were measured using the Center for Epidemiological Studies Depression Scale. Current anxiety symptoms were measured using the Beck Anxiety Inventory. Physical comorbidities represent values based on the Charlson Comorbidity Index. The Multidimensional Fatigue Symptom Inventory measured fatigue.

($M = .20$, $SD = .56$) had more physical comorbidities $t(178) = -2.27$, $p = .02$ and were more likely to be post-menopausal X^2 (1, $N = 178$) = 4.37, $p = .04$. Lastly, survivors with versus without a distress disorder history differed in terms of cancer treatment X^2 (1, $N = 178$) = 8.79, $p = .03$. Women with distress disorder histories were more likely to receive chemotherapy and radiation, rather than one of these treatments alone, compared to women without such a history. There were no differences between groups regarding age, BMI, cardiovascular medication use, exercise, race, cancer stage, or marital status (*ps* > .12). Table 2 presents correlations among study variables.

When comparing HRV between women who were prescribed antidepressants, took cardiovascular medications, received chemotherapy, identified as white, or were post-menopausal, independent samples *t*-tests revealed no significant differences between groups (*ps* range = .08–.95).

3.2. Pre- and post-TSST ratings

Table 3 presents results from the independent samples *t*-tests examining differences in subjective stress, coping, and threat pre- and post- the TSST. Results indicated that survivors with distress disorder histories reported greater threat prior to the TSST. These women also experienced less perceived control and lower satisfaction with their performance relative to women without distress disorder histories.

3.3. Distress disorder histories' influence on HRV

Table 4 presents the unadjusted HRV means and standard deviations at each time point for the two groups of survivors. Unadjusted models demonstrated a significant relationship between distress disorder histories and HRV across the day ($b = 5.81$, SE = 1.77, $p = .001$, $\beta = .21$).

When covariates were added to the models, results indicated a significant main effect of time, as HRV significantly differed across each time point (*ps* = <.001–.01, βs = .11–.22). A distress disorder history

Table 3
Comparisons of pre- and post-TSST subjective ratings based on distress disorder history.

	No Distress Dx Hx ($n = 89$)		Distress Dx Hx ($n = 89$)		
	M	SD	M	SD	t
Pre-Threat	3.58	1.56	4.11	1.54	-2.15*
Pre-Cope	4.65	1.30	4.35	1.32	1.44
Post-Stress	4.77	1.50	5.10	1.32	-1.49
Post-Satisfaction	3.71	1.38	3.10	1.45	2.67**
Post-Control	4.10	1.32	3.62	1.53	2.09*
Post-Helpless	3.67	1.70	3.98	1.76	-1.12

Note: *$p < .05$; **$p < .01$, Dx = diagnosis, Hx = history, M = mean, SD = standard deviation, pre-threat = how threatening survivors feel the TSST is, pre-cope = how well survivors anticipate they can cope with the TSST, post-stress = how stressful survivors perceived the task to be, post-satisfaction = how satisfied survivors are with their performance on TSST, post-control = how much control survivors felt they had on TSST performance, post-helpless = how helpless survivors felt as a result of the TSST.

Table 2
Correlations among study variables.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1. Base HRV	–														
2. Distress Dx	-.20**	–													
3. Fatigue	-.08*	.40*	–												
4. Comorbid	-.06	.19*	.13*	–											
5. BMI	-.10*	.08*	.17*	.16*	–										
6. Age	-.27*	.06	-.08*	.08**	.08**	–									
7. Menopause	-.19**	.21**	.12**	.10**	.14**	.53**	–								
8. Cancer Tx	.04	.10**	.03	-.10	-.08*	-.21**	-.05	–							
9. Stage	-.01	.12**	.15**	.05	.02	-.05	.09**	.44**	–						
10. Current dep	-.01	.39**	.77**	.09**	.13**	-.13**	.08*	.08*	.15**	–					
11. Current anx	-.08*	.31**	.69**	-.02	.19**	-.02	.10**	.06	.15**	.71**	–				
12. Exercise	.03	-.02	-.16**	-.06*	-.001	.17**	.05	.02	-.09**	-.06	-.04	–			
13. Cardio Med	-.09**	.04	.06*	.23**	.20**	.29**	.18**	-.06	-.02	.02	-.01	.06	–		
14. Antidepress	-.17**	.41**	.24**	.09**	-.02	.06*	.20**	.17**	.15**	.16**	.15**	.01	-.02	–	
15. Post-Stress	.12**	.18**	.20**	.14**	-.04	.01	.18**	-.02	.02	.15**	.05	-.13**	.11**	.08*	–

Note: *$p < .05$; **$p < .01$, Base HRV = baseline heart rate variability; Distress Dx = history of a distress disorder diagnosis; Comorbid = physical comorbidities as measured by the Charlson Comorbidity Index, BMI = body mass index; Cancer Tx = cancer treatment type, Current dep = current depressive symptoms as measured by the Center for Epidemiological Studies Depression Scale, Current anx = current anxiety symptoms as measured by the Beck Anxiety Inventory, Exercise = average hours of exercise in the past week, Cardio Med = use of cardiovascular medications, Antidepress = antidepressant medication use, Post-Stress = how stressful survivors perceived and reported the Trier Social Stress Test to be.

Table 4
HRV means and standard deviations across the day.

	No Distress Disorder Hx ($n = 89$)	Distress Disorder Hx ($n = 89$)
Baseline	29.03 (16.82)	23.45 (15.71)
Pre-TSST	20.60 (15.91)	14.65 (10.49)
During TSST	19.27 (14.38)	14.28 (10.01)
After TSST	24.09 (16.42)	16.58 (8.97)
45 m Post-TSST	20.55 (10.43)	16.68 (10.13)
120 m Post-TSST	25.91 (14.10)	20.92 (14.96)

Note: M = mean, SD = standard deviation, TSST = Trier Social Stress Test, 45 m Post-TSST = 45 min following the TSST, 120 m Post-TSST = 120 min following the TSST.

was related to HRV across the day ($b = 5.77$, SE = 2.29, $p = .01$, $\beta = .20$), indicating that for survivors with a distress disorder history, HRV was lower before, during, and after the TSST compared to women without a distress disorder history. Fig. 1 displays HRV trajectories before, during, and after the TSST based on distress disorder history status. Time did not interact with a distress disorder history ($p = .44$), indicating that the difference observed in HRV trajectories between women with versus without a distress disorder history did not differ as a function of different points throughout the study visit.

Older age was associated with lower HRV among breast cancer survivors ($b = .29$, SE = .13, $p = .03$, $\beta = .01$), but HRV was not associated with physical comorbidities, BMI, fatigue, current depressive symptoms, current anxiety symptoms, cardiovascular medication use, antidepressant use, exercise, cancer stage, treatment type, or menopausal status (all $ps > .21$).

3.4. Alternative models

Given that many survivors with a distress disorder history reported past MDD, we re-ran all models with MDD history as the predictor rather than distress disorder history. Results remained significant when using MDD history to predict HRV across the day instead of distress disorder history ($b = 5.91$, SE = 2.06, $p = .01$, $\beta = .21$). Further, previous research has indicated significant effects of fatigue on HRV among breast cancer survivors (Crosswell et al., 2014; Fagundes et al., 2011). We therefore ran a mediational model to test whether fatigue exerted an indirect effect on the relationship between distress disorder histories and HRV. However, there was not a significant indirect effect of fatigue on this relationship ($b = -.06$, SE = .37, *95% CI* = −.78, .68).

4. Discussion

This study was the first to address the relationship between HRV and a distress disorder history among breast cancer survivors, a group at considerably increased risk for cardiovascular disease and subsequent early mortality. Moreover, we tested this relationship at baseline, during, and after the TSST to examine both tonic HRV and phasic HRV trajectories across the day. Understanding breast cancer survivors' HRV is especially important given its link to cardiovascular disease – the leading cause of death among stage I survivors (Arab et al., 2016; Patnaik et al., 2011). Consistent with our hypotheses, results indicated that survivors with distress disorder histories had lower HRV before, during, and after the task. Overall, this study identified differences in HRV between these two groups of breast cancer survivors at baseline and throughout the TSST – indicating that a distress disorder history, not just a current distress disorder, is relevant to breast cancer survivors' cardiovascular disease risk.

Consistent with the scarring hypothesis of depression, a lifetime history of distress disorders predicted differences in HRV among survivors in this study, highlighting the influential role that distress diagnoses can have on cardiovascular function, even years following remittance. This relationship was robust, as controlling for current anxiety and depressive symptoms did not alter the results. The non-significant interaction between group and time indicated that survivors with distress disorder histories had significantly lower HRV across the day compared to survivors without such a history. Although the TSST was perceived to be stressful for all survivors, future research may benefit from utilizing a more contextually salient laboratory-based stressor. Findings from this study extend one related work examining HRV reactivity during a TSST among depressed breast cancer survivors (Giese-Davis et al., 2006).

Results from this study advance previous findings by utilizing a transdiagnostic approach to assessing disorder histories. Our findings extend previous research in healthy samples which demonstrated a significant influence of distress disorders on HRV (Chalmers et al., 2014; Koch et al., 2019). While fear-based disorders, including social anxiety disorder, specific phobia, and panic disorder, influence HRV, this influence may be most prominent during engagement with the fear-based stimuli (Hu et al., 2016; Madison et al., 2021). Further, assessing diagnosed psychological disorders, rather than symptoms alone, highlights how clinically significant distress can affect HRV even if the symptoms are not current. The prevalence of distress disorder histories in our sample was 50%, with rates of MDD and GAD histories in previous studies ranging from 6% to 35% (Gandubert et al., 2009; Kissane et al., 2004; O'Connor et al., 2011). Interestingly, alternative models highlighted similar results when the analysis was limited to those with

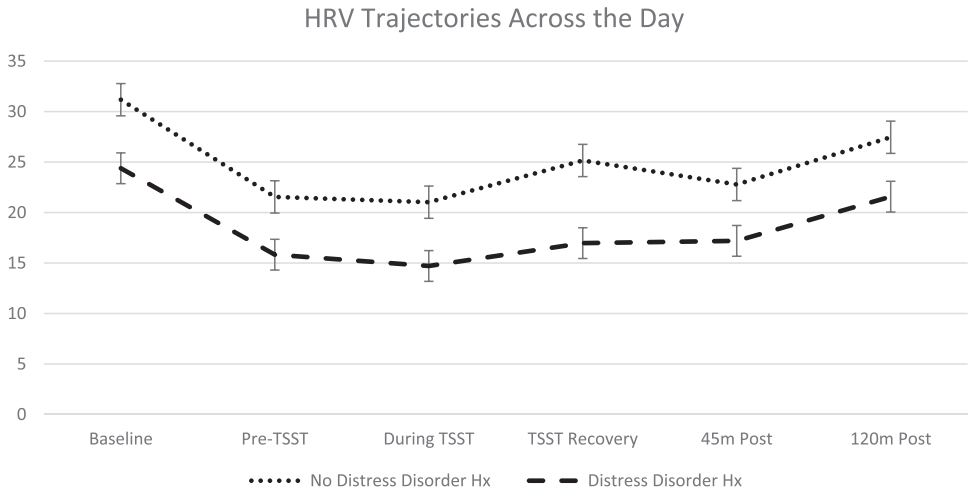

Fig. 1. Estimated marginal means of non-transformed HRV trajectories, measured by RMSSD, before, during, and after the Trier Social Stress Test based on distress disorder history status. Results indicated that women without a distress disorder history had higher HRV at each time point compared to women with a distress disorder history ($b = 5.77$, SE = 2.29, $p = .01$, $\beta = .20$). The time points graphed on this figure represent baseline (1), pre-Trier (2), during Trier (3), immediately post Trier (4), 45 min post Trier (5), and 120 min post Trier (6).

histories of MDD rather than distress disorders broadly. Using a transdiagnostic category such as distress disorders can therefore provide information about how several diagnostic groups HRV respond to stress rather than a single group alone. These results also complement previous findings emphasizing a relationship between HRV and fatigue among breast cancer survivors both cross-sectionally and during the TSST (Crosswell et al., 2014; Fagundes et al., 2011). Among the diagnoses within the distress disorder category, fatigue is one common symptom, but examining fatigue alone may not provide a comprehensive picture of psychological distress' relationship to HRV. This study therefore expands our currently available understanding about how distress disorder histories relate to HRV in the context of breast cancer survivorship.

In addition to the physiological impact that our study showed, survivors with distress disorder histories also perceived the TSST to be more threatening, felt as if they had less control following the task, and felt less satisfied with their performance compared to women without such histories. These results highlight how distress histories heighten stress-related risk perceptions. Given that HRV may serve as one proxy for emotional responding (Appelhans and Luecken, 2006), higher stress-related risk perceptions for women with a distress disorder history likely contributes to lower HRV among these women. In contrast, although women with distress disorder histories had higher post-TSST stress, this value was not significantly different compared to survivors without such a history, highlighting a discrepancy between subjective reporting and HRV responding.

Low HRV, high inflammation, and increased pain and fatigue all represent consequences of breast cancer diagnosis and treatment – all of which influence quality of life and overall health. Psychological interventions can help offset the psychological and biological consequences associated with breast cancer survivorship (Cramer et al., 2012; Tatrow and Montgomery, 2006). Further, these results underscore benefits of screening for current *and* past distress disorders in breast cancer survivors. This is in line with recommendations from the American Society of Clinical Oncology and accreditation standards for cancer facilities set forth by the American College of Surgeons Commission on Cancer (Andersen et al., 2014; CoC, 2019). Brief, evidence-based interventions offer the potential to improve physical and psychological health among survivors. However, barriers to psychological treatment among cancer survivors include limited screenings for distress and referral resources, access, appointment burden, and financial considerations (Rankin et al., 2015).

This study has several notable strengths and limitations. Examining the relationship between distress disorder histories and both tonic and phasic HRV provides a more comprehensive understanding of this relationship than examining one type of HRV alone. Looking at both tonic and phasic HRV on a day where survivors experience stress provides an understanding of how stress influences and interrupts normal autonomic function for these women, thus enhancing disease risk. Although RMSSD was selected because it is less susceptible to respiratory effects than other HRV metrics, there is a possibility that respiration, particularly during the TSST while participants were completing the speech task, may have influenced HRV data. Analyses also controlled for several important covariates, including current depressive and anxiety symptoms. However, the BAI primarily measures physiological anxiety and we did not include a self-report measure of current GAD symptoms. Further, replication of the findings from these studies in more diverse samples is important to increase generalizability of these results. Examining behavioral and cognitive mediators is warranted in future research. Individuals with distress disorders also are more likely to engage in risky behaviors (Clancy et al., 2016), such as smoking tobacco, consuming greater quantities of alcohol, living a more sedentary lifestyle, and eating an unhealthier diet than those without such a history (Strine et al., 2008). Further, these individuals are also likely to engage in perseverative cognition such as worry and rumination, which could last well beyond diagnostic remission (Brosschot et al., 2005). Given that a subset of SCID modules were administered in this study, we were unable to assess lifetime histories of several potential comorbidities including substance use, psychotic, and eating disorders. Lastly, PTSD was not assessed in this study and many survivors reported MDD histories, limiting the ability of the study to examine HRV in the context of each type of distress disorder diagnosis.

5. Conclusion

Findings from this study showed that breast cancer survivors with distress disorder histories experienced lower HRV before, throughout, and following the TSST compared to survivors without such a history. Distress disorder histories also heightened stress-related risk perceptions leading up to and following the TSST. Results from this study highlight distress disorder histories as unique risk factors associated with reduced cardiovascular function via diminished HRV among breast cancer survivors.

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Conflict of interest statement

The authors have no conflicts of interest to report.

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