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Psychological distress following marital separation interacts with a polymorphism in the serotonin transporter gene to predict cardiac vagal control in the laboratory

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Abstract

Marital separation is linked to negative mental and physical health; however, the strength of this link may vary across people. This study examined changes in respiratory sinus arrhythmia (RSA), used to assess cardiac vagal control, in recently separated adults ($N = 79$; M time since separation = 3.5 months). When reflecting on the separation, self-reported psychological distress following the separation interacted with a polymorphism in the serotonin transporter gene (*5-HTTLPR*) and a relevant single nucleotide polymorphism (SNP), rs25531, to predict RSA. Among people reporting emotional difficulties after the separation, those who were homozygous for the short allele had lower RSA levels while reflecting on their relationship than other genotypes. The findings, although limited by the relatively small sample size, are discussed in terms of how higher-sensitivity genotypes may interact with psychological responses to stress to alter physiology.

Descriptors: Divorce, Marital separation, Heart rate variability, Respiratory sinus arrhythmia, Single nucleotide polymorphism, Serotonin transporter gene (*5-HTTLPR*)

Marital separation and divorce are linked to a variety of negative physical health outcomes, including increased risk for all-cause mortality (Sbarra, Law, & Portley, 2011). The psychological stress of divorce, if chronic, can exert wear and tear on physiological regulatory systems that ultimately increase risk for cardiovascular and other morbidities (cf. McEwen, 1998; Sbarra, Hasselmo, & Nojopranoto, 2012; Stein & Kleiger, 1999; Treiber et al., 2003). As with many other negative life events, individual differences in the propensity toward poor emotion regulation in the face of stress are correlated with a range of negative outcomes following marital separation (e.g., Mason & Sbarra, 2012), including physiological responses that are health relevant. For example, recently separated men who reported emotional difficulty thinking about their relationship history evidenced the greatest blood pressure reactivity when asked to do so (Sbarra, Law, Lee, & Mason, 2009). Given that individual differences play a large role in shaping how people respond to stressful life events, including the end of a marriage, it is notable that no studies have examined whether specific candidate genes are associated with psychological and physiological responses to marital separation. In the current study, we investigate whether variability in a polymorphism of the promoter region (5-HTT linked polymorphic region or *5-HTTLPR*) of the serotonin transporter gene (5-HTT) is associated with separation-related psychological distress and heart rate variability (HRV) during a laboratory analogue task.

Respiratory sinus arrhythmia (RSA), the natural logarithm of the variance of the heart period within the frequency band-pass associated with respiration, is a frequently used measure of parasympathetic vagal influences on the heart (Beauchaine, 2001; Berntson et al., 1997; Berntson, Cacioppo, & Quigley, 1993; Porges, 1995). The vagus nerve has connections to the heart via the sinoatrial node and provides inhibitory control of the myocardium, moderates RSA withdrawal during tasks requiring attention and emotion, and may prepare the body to free metabolic resources for sympathetically driven coping responses (Frazier, Strauss, & Steinhauer, 2004; Movius & Allen, 2005; Rottenberg, Salomon, Gross, & Gotlib, 2005). Cardiovascular disease (CVD) is directly linked with vagal control through heart rate variability (Thayer & Lane, 2005), and low RSA is predictive of greater CVD risk, symptom severity, and increased mortality (Hayano et al., 1991; Kleiger, Miller, Bigger, & Moss, 1987). Furthermore, context-inappropriate changes in RSA are thought to index poor self-regulation (Porges, 1995, 1997) and are linked to a range of psychiatric disorders and comorbidities

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(Austin, Riniolo, & Porges, 2007; Beauchaine, 2001, Rottenberg et al., 2005; Thayer, Friedman, & Borkovec, 1996).

Although research examining genetic moderators of health is not without controversy (owed largely to issues of statistical power in small samples, see Dick et al., in press), a relatively consistent finding is that the polymorphic region of the 5-HTT gene plays an important role in shaping emotional responsivity to stress (Caspi et al., 2003; Karg, Burmeister, Shedden, & Sen, 2011; Vrshek-Schallhorn et al., 2013). A polymorphism in *5-HTTLPR* yields lower transcription of the serotonin transporter gene, SERT, resulting in differential availability and regulation of serotonin. This is caused by an insertion/deletion (ins/del), which results in 14 copies (the "short" or S allele), 16 copies (the "long" or L allele) or more, (the "extra long" or XL allele) of a repeat sequence of base pairs (Ehli, Hu, Lengyel-Nelson, Hudziak, & Davies, 2012; Lesch et al., 1996; Praschak-Rieder et al., 2007). The S variant shows decreases in serotonin transcription and reuptake (Lesch at al., 1996), and reduced serotonergic activity is associated with decreased functionality of the parasympathetic nervous system (Williams, 1994).

Many studies examine the association between life stress, genotype, and mental health outcomes (e.g., Jenness, Hankin, Abela, Young, & Smolen, 2011; Karg et al., 2011; Vrshek-Schallhorn et al., 2013), but a smaller body focuses on the genetics of cardiovascular responding. The *5-HTTLPR* polymorphism explains about 5% of the variance in resting RSA, with carriers of the S allele (SS, SL) having lower resting vagal tone than homozygous carriers of the L allele (LL; Ellis, Beevers, Hixon, & McGeary, 2011). This finding may be limited by its exclusive focus on the ins/del polymorphism. A single-nucleotide polymorphism (SNP), rs25531, is embedded within the long allele of the gene and alters its transcription in an important way (Hu et al., 2006; Nakamura, Ueno, Sano, & Tanabe, 2000). Substitution of guanine for the adenine (A → G) found here results in a binding site for a transcription factor that decreases the transcription of the gene, reducing the output of the L_G allele to equal that of the S allele (Hu et al., 2006; Nakamura et al., 2000). This renders the locus triallelic, and including the SNP alters the distribution of the low and high transcription groups (Vulturar, Chis, Ungureanu, & Miu, 2012). It appears that the triallelic genotype provides a more conservative estimate of effects associated with variability at these loci.

In addition to the presence of this SNP, another complicating factor within the nascent genetic literature of HRV is that it is largely focused on main effects between genotype and vagal tone. In contrast, the psychological literature stresses Gene × Environment (G×E) interactions in which the effect of a past or present stressor on a health outcome is potentiated by genotype. In terms of physiological functioning, there is also reason to believe that any G×E interactions would exert their effects on task-relevant, cardiac vagal reactivity rather than resting vagal tone. This perspective is consistent with Coan, Allen, and McKnight's (2006) capability model of physiological responding, which posits that physiological responses associated with trait-level propensities are best evoked during state manipulations designed to assess the emotional system in question. Examining individual differences in frontal EEG asymmetry at rest and during an emotionally challenging task, Coan et al. (2006) found more prominent individual differences during the challenge task than while at rest; this finding serves as the foundation for their capability model, which posits that challenge tasks increase variability in outcomes of interest and make task engagement ideal for the study of individual differences. The current study applies this logic to investigate cardiac vagal tone at rest and while participants reflect over their relationship history and recent separation.

The research reported here combines the different lines of research reviewed above to examine if triallelic variability in *5-HTTLPR* genotype moderates the association between separation-related psychological distress and changes in RSA while participants think about their separation experience. Participants in this study were grouped into (a) homozygous carriers of the short variant (S′, or short variant equivalent using a triallelic specification, L_G) of the SERT gene, (b) those who were homozygous carriers of the long variant (L_A), and, (c) those who were heterozygous for a short variant and a long variant ($S'L_A$ or L_GL_A). Given that marital separation and divorce are among life's most stressful events, but that only a subset of people appear to be at risk for poor outcomes (Sbarra et al., 2012), we have chosen to align our hypotheses most squarely with the G×E life stress literature (see Caspi et al., 2003). From this perspective and that of the capability model (Coan et al., 2006), we hypothesized that adults reporting high separation-related psychological distress would evidence the greatest vagal withdrawal to our laboratory-analogue task when they are also homozygous for the low-expressing alleles of triallelic *5-HTTLPR* (i.e., $S'S'$, L_GL_G, $S'L_G$).

Method

Participants

Participants were 79 (24 men) community-dwelling adults (mean age = 41.19 years, *SD* = 9.21 years) who had been in a relationship with their partner for on average 170.73 months (*SD* = 88.8 months) and had recently experienced a marital separation (on average about 3.5 months before beginning participation in the study, *SD* = 2.4 months). Fifty-four percent of participants claimed to have initiated the separation from their partner. Seventy-six percent of the participants reported their ethnicity as Caucasian, 13.9% reported Hispanic, 2.5% were African American, and 2.5% were Asian, while 5.1% chose "other" as their ethnicity. These 79 participants were part of a follow-up study that initially collected data from a large sample of separated adults (*N* = 139; see Lee, Sbarra, Mason, & Law, 2011). These 79 follow-up participants did not differ significantly from the original sample on any of the following variables: age, race, sex, relationship length, time since separation, and reports of who initiated the divorce.

Measures

Separation-related psychological distress. Psychological distress following the separation event was assessed using the Impact of Events Scale–Revised (IES-R). The IES-R is a widely used measure of subjective responses to stressful events and assesses several dimensions of responding following a stressful event, including intrusive thoughts, hyperarousal, emotional numbing, avoidance, and total subjective distress (Weiss & Marmar, 1997). Respondents report on the degree of distress of a given symptom over the last 7 days on a scale from 0 = *not at all* to 4 = *extremely*. Sample items include statements such as "Any reminder brought back feelings about it" and "I thought about it when I didn't mean to." In the present study, two subscales were combined to form the hyperarousal-intrusion subscale, as a previous confirmatory factor analysis noted that a single factor of intrusion/hyperarousal provided the best fit to the data (Creamer, Bell, & Failla, 2003). These two subscales, composed of a total of 14 items, were averaged to create an individual IES-R score with a possible range of 0 to 4

(observed range = 0 to 3.86). Higher scores reflect greater self-reported emotional distress following the separation ($\alpha = .92$).

Heart rate variability. Electrocardiograph (ECG) data was collected using a Biopac MP100 System and ECG amplifier, recorded using a standard lead II configuration (right clavicle and precordial site V6) with EL503 Ag/AgCl disposable electrodes (Biopac Technologies, Santa Barbara, CA). The signals received were digitized at 1,000 samples per second and amplified with the Biopac 100C system with a gain of 1,000. These signals were stored on a computer with Biopac's Acqknowledge physiological data acquisition software. Artifact detection and data cleaning of ECG interbeat interval (IBI) signals were then completed using the MindWare Technologies HRV 2.60 application (www.Mindwaretech.com, Westerville, OH). We used fast Fourier transforms (FFTs) for partitioning the total variance in IBIs into different spectral frequencies. RSA was calculated as the natural logarithm of the variance in the residual time series occurring within the frequency band-pass associated with respiration (0.12–0.40 Hz), which is an established proxy measure for estimating parasympathetic vagal influence on cardiac chronotropy (Allen, Chambers, & Towers, 2007). In addition, respiration was assessed using Biopac's respiratory effort transducer, and the breaths per minute, or respiratory rate (RR), was quantified using Mindware's HRV application. RSA and RR were determined for each minute epoch within a 4-min nature video and mundane events control tasks and the 7-min divorce-specific mental activation task; for each task, the minute-to-minute scores were averaged, yielding mean composite scores on each index for each of the three tasks (resting nature control task, mundane control task, and divorce-specific mental activation task).

Genotyping. After consenting to provide a sample of their DNA, participants submitted saliva samples. Genomic DNA was isolated from buccal cells by the University of Arizona Genomics Core per analytical methods described by Anchordoquy and colleagues (Anchordoquy, McGeary, Liu, & Krauter, 2003). The amplification method used was a modified method of Lesch et al. (1996). The primer sequences are: forward JP, 5′-6FAM-ATG CCA GCA CCT AAC CCC TAA TGT–3′, and reverse GR, 5′-GGA CCG CAA GGT GGG CGG GA–3′. To differentiate between L_A and L_G variants at rs25531 SNP, the full length PCR product was digested with the restriction enzyme MspI. The G allele at rs25531 creates an MspI restriction site (CCGG), which, when recognized and digested, yields a product of size 149 bp. The A allele here lacks the restriction site. A second MspI site 93 bp from the 3′ terminus of the amplicon provides a cutting site for the L_A and S alleles. The resulting polymorphic fragments were analyzed on an AB Prism 3730 Genetic Analyzer (Applied Biosystems), and digest products have the following approximate lengths: L_G allele 149 bp, S allele 278 bp, and L_A allele 321 bp.

Procedure

Adults who responded to the study advertisements were screened along several dimensions, and all respondents who reported that they were generally healthy, without a history of a psychotic disorder, and, for women, not pregnant were deemed eligible to participate. Participants were told that the purpose of the study was to understand "how adults adjust to marital separation and the ways in which your body responds when you think about and reflect on your separation experience." Prior to participants' scheduled laboratory visit, they were mailed a questionnaire packet that included a series of demographic questions, as well as self-report questionnaires (for example, the IES-R, and others not reported here) in order to reduce participant burden associated with laboratory physiology procedures. Participants were asked to refrain from tobacco and caffeine for at least 4 h prior to the study visit. At the laboratory visit, participants completed three physiological assessment tasks: a nature control task, a mundane control task, and a divorce-specific mental activation task (described below). Participants were seated in a physiological measurement chamber that included one speaker and two video cameras for communication between the participant and experimenter, who was located in the next room.

Study tasks. After equipment setup, participants were instructed to sit quietly and to relax during a 4-min neutral nature video, which served to acclimate them to the laboratory environment and as the first control condition (nature control task) for physiological comparisons.

Mundane events recall task (mundane control task). Following the nature control task, participants completed the mundane events recall task, which involved a 4-min reflection period asking four nonemotional questions presented on a computer screen one at a time in front of them. After each question was presented on the screen, a 1-min reflection period followed immediately before the next question appeared. Thus, for both the mundane control task and the divorce-specific mental activation task (described below), the 1-min reflection period was initiated the instant the question appeared on the computer screen and therefore included the time spent reading the question. Participants did not respond to the questions aloud; rather, they imagined and mentally reflected on their answers to the questions during each 1-min period. An example item from this task includes: "Please think about what you had for dinner last night, or the last time you ate dinner. Create a vivid image of that meal."

Divorce-specific mental activation task. The 7-min divorce-specific mental activation task asks participants to "spend some time thinking about yourself and your partner in a variety of different situations." Similar to the mundane control task, after a question was presented on the computer screen participants were asked to "concentrate on the question by letting any relevant thoughts, feelings, or images come to mind" for a 1-min period. Example items include: "Whose decision was it to end the relationship? Why? Please think about the events leading to the end of your relationship," and "What's been the worst part about this separation for you?"

The mundane control task was used in the reactivity analyses to account for RSA changes associated with deploying attention and other information processing resources to mentally reflect on each question. Thus, changes in RSA from the mundane control task to the divorce-specific mental activation task are presumed to be specific to the content of the tasks and not due to a general physiological-orienting response or to the physiological demands of sustained attention.

Immediately after the divorce-specific mental activation task, participants completed a set of task appraisal items designed to serve as a manipulation check. Participants were asked to fill out a set of 7-point Likert scale appraisal items to determine if their thought process during the task paralleled their thinking in daily life and to assess how realistic they found the divorce-specific mental activation task. On average, participants reported 5.57 out of

Table 1. *Correlations Among and Descriptive Statistics for Relevant Study Variables*

	1	2	3	4	5	6	7	8	9	10	11	12	13	14
1. Nature IBI	–													
2. Mundane IBI	.83**	–												
3. DMAT IBI	.88**	.85**	–											
4. Nature RR	−.04	−.06	−.09	–										
5. Mundane RR	−.01	−.05	−.03	.76**	–									
6. DMAT RR	.02	.00	.04	.62**	.74**	–								
7. Nature RSA	.42**	.25*	.28*	−.25*	−.25*	−.26*	–							
8. Mundane RSA	.42**	.35*	.32**	−.25*	−.40**	−.33**	.88**	–						
9. DMAT RSA	.42**	.37**	.35**	−.24*	−.33**	−.34**	.86**	.93**	–					
10. Age	.06	.04	.10	−.13	−.01	.04	−.33**	−.36**	−.41**	–				
11. Sex	−.12	−.15	−.2	.26*	0.30**	.33**	.02	−.04	−.10	−.08	–			
12. C1	.14	−.02	.08	−.05	−.05	−.09	.06	.11	.02	−.14	.00	–		
13. C2	−.10	−.05	−.15	.11	.18	.07	−.01	−.07	−.04	−.00	.04	−.23*	–	
14. IES-R	.03	−.04	−.01	−.04	.01	.00	.04	−.10	−.10	.03	.04	.11	−.05	–
M	856.69	845.69	846.58	12.17	13.77	12.66	5.77	5.63	5.69	41.19	.68	−.39	.37	1.42
SD	117.28	131.21	117.55	3.76	4.16	3.89	1.20	1.27	1.14	9.21	.47	1.21	.82	.88

Note. Nature = nature control task; IBI = interbeat interval; Mundane = mundane control task; DMAT = divorce-specific mental activation task; RR = respiratory rate; RSA = respiratory sinus arrhythmia; Sex = coded 0 for male, 1 for female; C1 = S′S′ vs. S′L′ + L′L′ (carriers of two shorts vs. all other genotypes); C2 = S′L′ vs. L′L′ (carriers of one long allele vs. two long alleles); IES-R = Impact of Events Scale–Revised.
*$p < .05$; **$p < .01$.

7.00 that they felt they were able to focus on the task demands (*SD* = 1.15). When asked about the divorce-specific mental activation task's realism, participants rated their experience at a 4.95 out of 7 (*SD* = 1.39), suggesting they indeed found the task to be a realistic expression of their everyday thoughts about the separation event, and they were engaged in considering the questions posed during the task. After a 4-min recovery period, the physiological equipment was removed and participants were debriefed about the overall nature of the study.

The buccal swab samples, used for DNA extraction, were collected an average of 4.5 years (*SD* = 10 months) after the psychophysiological and questionnaire assessments. The original sample of participants was recontacted to see if they would consider participating in a follow-up study, which involved the collection of DNA samples. Contact with all members of the initial sample was attempted by both mail and phone over the course of several months, and all sample members who responded positively and were available to participate were included.

All aspects of this study were approved by the University of Arizona Human Subjects Protection Program.

Statistical Analysis

We used linear regression analysis to examine our primary hypothesis, which states that the possession of two copies of the short allele of the serotonin transporter gene will increase vagal withdrawal during a separation-related reflection task among people experiencing distress while adjusting to their separation. We computed orthogonal linear contrasts (see Judd, McClelland, & Culhane, 1995) that coded the presence or absence of a *5-HTTLPR* allele in different ways. All contrasts resulted in dichotomous grouping variables (for the genotype data) that were included in the regression analyses. Because people can be homozygous for the short or long variants or heterozygous, the three genotype combinations allow for only two orthogonal contrasts. The contrasts (C) were established as follows: (C1) compared S′S′ carriers to all other genotypes (S′L′ and L′L′), and (C2) compared S′L′ carriers to L′L′ carriers.

To test the primary hypothesis of interest, we interacted the first planned contrast (C1) with psychological distress (as determined by the IES-R) when predicting RSA during the nature control task and during the divorce-specific mental activation task. For the reactivity analyses, we first examined whether the interaction predicted RSA during the divorce-specific mental activation task after accounting for a series of relevant covariates (age, sex, RR, and RSA during the nature control task, RR and RSA during the mundane control task, and RR during the divorce-specific mental activation task) as well as the main effects of interest. We accounted for participants' sex and age, the main effects of interest, then examined the Psychological Distress × Genotype (contrast-coded) interaction.

Results

Table 1 presents the descriptive statistics and correlations for the predictor and outcome variables. In addition, to facilitate a meaningful interpretation of the physiological variables, Table 1 includes the IBI data from each of the study tasks even though these variables are not used in the focal analyses presented below. In addition, paired samples *t* tests were conducted on IBI, RR, and RSA across all three study conditions. These tests revealed significant differences between mean RR during the nature control task and the mundane control task, $t(78) = -5.09$, $p < .001$, as well as for RR between the mundane control task and the divorce-specific mental activation task, $t(78) = 3.40$, $p = .001$, and finally in RSA between the nature control task ($M = 5.77$, $SD = 1.20$) and the mundane control task, $t(78) = 2.10$, $p = .05$). All other comparisons were nonsignificant.

Genotype Comparisons

The allele frequencies of S′ and L′ were .49 and .51, respectively. The distribution of the *5-HTTLPR* ins/del and rs25531 genotypes was as follows: 10 SS (12.8%), 1 L_GL_G (1.3%), 5 SL_G (6.4%), 4 L_AL_G (5.1%), 42 SL_A (53.8%), 16 L_AL_A (20.5%), and 1 L_AXL (1.3%). On the basis of the triallelic *5-HTTLPR*, the genotypes were categorized into 16 carriers of two low-expressing alleles (i.e., SS, L_GL_G, SL_G), labeled S′S′ for simplicity, 46 carriers of one low-expressing allele (i.e., L_AL_G, SL_A), labeled S′L′, and 17 carriers of two high-expressing alleles (i.e., L_AL_A, L_AXL), labeled

Table 2. *Unstandardized Regression Coefficients from the Model Predicting Respiratory Sinus Arrhythmia and from the Model Predicting Residualized Respiratory Sinus Arrhythmia during the Divorce-specific Mental Activation Task from Genotype*

Parameter	B	*SE*	*p*
Intercept	1.59	.50	.00
Nature RR	−.01	.02	.61
Mundane RR	.04	.02	.08
DMAT RR	−.03	.02	.08
Nature RSA	.17	.09	.06
Mundane RSA	.66	.09	.00
Age	−.01	.01	.06
Sex	−.20	.10	.05
C1	.09	.07	.20
C2	−.01	.06	.78
IES-R	−.04	.05	.43
C1 × IES-R	−.10	.04	.01

Note. Nature = nature control task; Mundane = mundane control task; RR = respiratory rate; DMAT = divorce-specific mental activation task; RSA = respiratory sinus arrhythmia; Sex = coded 0 for male and 1 for female; C1 = S′S′ vs. S′L′ + L′L′ (carriers of two short alleles vs. all other genotypes); C2 = S′L′ vs. L′L′ (carriers of one long allele vs. two long alleles); IES-R = Impact of Events Scale–Revised; Model 1 = genotype and IES-R predicting RSA during DMAT.

L′L′. These genotypes were in Hardy–Weinberg equilibrium, $\chi^2 = 2.14$, *n.s.*

Prior to conducting any of the planned analyses, we examined whether psychological distress was associated with participants' genotype. Scores on the IES-R were unrelated to the C1 genotype (i.e., S′S′ vs. S′L′ + L′L′) variable, $r = .35$, $p = .10$.

Nature Control Task Analyses

Vagal tone while watching the nature video was first predicted by age, nature control task RR, psychological distress in response to the separation (as assessed by IES-R scores), and the two orthogonal genotype contrasts and their interaction effects. There were no significant main effects for any of the aforementioned genotype contrasts predicting RSA during the nature video (all $ps \geq .10$), nor were there any significant main effects of psychological distress (all $ps \geq .52$). There were also no significant interaction effects between psychological distress and any of the genotype contrasts when predicting vagal tone during the nature video (all $ps \geq .15$). Nature control task RR and age were significant (all $ps < .007$, and $ps < .001$, respectively) predictors in each analysis, and were thus included in the subsequent analyses.

RSA Reactivity

A repeated measures analysis of variance (ANOVA) revealed there are no significant differences for mean RSA change from the mundane control task to the divorce-specific mental activation task by *5-HTTLPR* genotype (S′S′ $M = -.16$, $SD = .43$; S′L′ $M = .13$, $SD = .52$; L′L′ $M = .08$, $SD = .32$), $F(2,76) = 2.24$, $p = .11$. Furthermore, Levene's test of homogeneity of variances revealed no significant group differences between RSA variances during each of the described tasks, nature control task, mundane control task, and the divorce-specific mental activation task, $F(1,77) = .52$, $p = .47$; $F(1,77) = .87$, $p = .35$; $F(1,77) = .03$, $p = .86$. Taken together, these results suggest that any RSA changes detected from the mundane control task to the divorce-specific mental activation task are not due merely to differences in variance within genotypes.

We next examined RSA reactivity from the mundane control task, which asked participants to recall mundane events, to the divorce-specific mental activation task, which asked participants to reflect over their relationship history and separation experience. As our main study hypothesis focused on the Psychological Distress × Genotype interaction, we initially regressed divorce-specific mental activation task RSA on the relevant RSA covariates (RRs for the mundane control task, the nature control task, and divorce-specific mental activation tasks, as well as RSA from the mundane and nature control tasks) in addition to sex, age, psychological distress, and the contrast of interest (C1) comparing homozygous S′ carriers to other genotypes (S′S′ vs. S′L′ + L′L′). We also included the second genotype contrast (C2), comparing individuals carrying any copy of the L′ allele (S′L′ vs. L′L′), as a main effect in this model (see Table 2). After accounting for the main effects of the C1 genotype and psychological distress, which were nonsignificant ($p = .20$ and $p = .43$, respectively), as well as the other covariates, the Psychological Distress × Genotype interaction was a significant predictor of RSA during the divorce-specific mental activation task, $B = -.10$, $SE = .04$, $p = .01$, 95% CI [−.17, −.02]. Importantly, in a model including only the main effects and their interaction (as well as the nature and mundane control task RSA values), the G×E effect was a significant predictor of RSA during the divorce-specific mental activation task, B = -.08, $SE = .04$, $p = .03$, 95% CI [−.16, −.009]. This analysis bolsters confidence that the interaction is not emerging as the result of a suppression effect.

As shown in Figure 1, a simple slope decomposition of the interaction revealed that, among people carrying two copies of the S′ allele (either by virtue of having the short allele at the insertion/deletion or the required SNP at rs25531), those who reported having a more difficult time adjusting to their separation on the IES-R evidenced significantly lower RSA when asked to reflect over their separation experience relative to people who reported less difficulty adjusting to the separation, $B = -.24$, $SE = .09$, $p = .01$ (see Figure 1a). In contrast, for people who were heterozygous or homozygous long carriers (S′L′ + L′L′) there was no significant difference in RSA levels during the divorce-specific mental task across levels of psychological distress, $B = .06$, $SE = .06$, $p = .36$. When we treated psychological distress as the moderator (to test RSA differences within each genotype; see Figure 1b), we observed that significant differences in the two genotypes emerge at a score of 1.74 on the IES-R, which is slightly above the mean, $B = -.08$, $SE = .04$, $p = .05$.[1]

In the next model, we tested whether the interaction effect remained significant in a contrast that included people who were either heterozygous or homozygous for the short allele (S′L′ + S′S′ vs. L′L′). Accounting for the same set of variables included in the original analysis (substituting the contrast accounting for S′L′ vs. L′L′ with one comparing S′S′ vs. S′L′), the Psychological

1. Due to concerns with the limited sample size, we ran a second, similar analysis using the residualized RSA during the divorce-specific mental activation task, accounting for nature control RR and RSA, mundane control task RR and RSA, and divorce-specific mental activation task RR; using the residualized divorce-specific mental activation task RSA allowed us to include fewer variables in the overall prediction model. Controlling for the main effects of genotype, psychological distress, and participants' age (all of which were nonsignificant), and the main effects of sex ($p = .03$), the Psychological Distress × Genotype interaction was a significant predictor of residualized RSA reactivity during the divorce-specific mental activation task, $B = -.08$, $SE = 04$, $p = .04$, 95% CI [−.15, −.004].

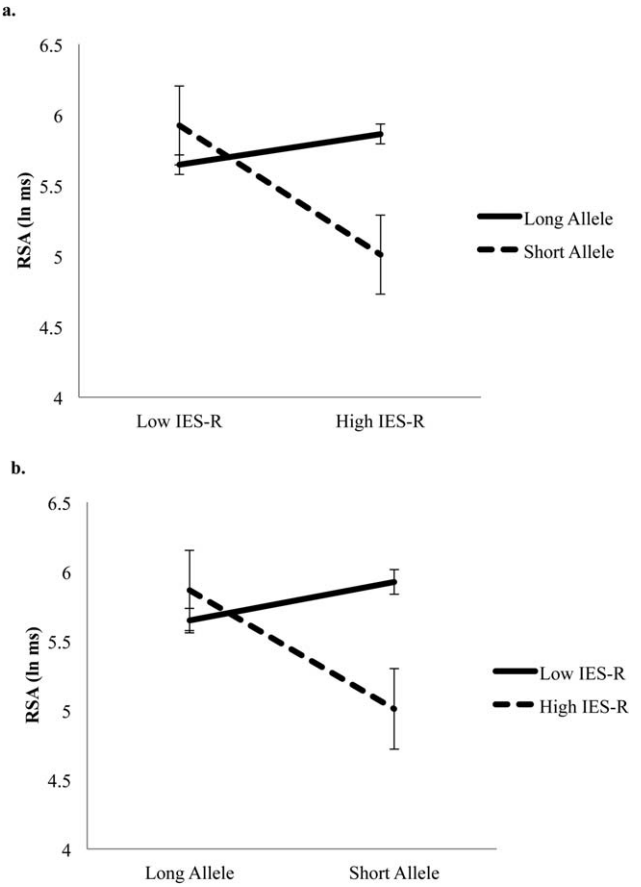

Figure 1. Simple slope decomposition of the interaction between genotype and IES-R (after accounting for relevant covariates) predicting RSA levels during the divorce-specific mental activation task. a: RSA when considering genotype as the moderator of interest. b: Reverses the comparison and treats IES-R scores as the moderator. Short Allele = homozygous S′ carriers, Long Allele = S′L′ + L′L′ carriers; RSA = respiratory sinus arrhythmia; IES-R = Impact of Events Scale–Revised. Simple slope decompositions are illustrated for people scoring 1 *SD* ± from the mean on the IES-R.

Distress × Genotype interaction was not a significant predictor of RSA during the divorce-specific mental activation task, B = .08, *SE* = .04, *p* = .06, 95% CI [−.16, .003].

Given the heterogeneity of our sample and the known variability in allele frequencies for the various races included in the sample (Gelernter, Kranzler, & Cubells, 1997), we conducted a separate analysis using only individuals of European descent. We found similar results among this subsample (*n* = 60); the Psychological Distress × C1 Genotype interaction remained significant for the analysis, B = -.12, *SE* = .04, *p* = .002, 95% CI [−.19, −.04], as did the conditional effects of having two copies of the short allele, B = -.27, *SE* = .09, *p* = .004.

Discussion

This study examined the interplay of adults' psychological responses to marital separation, physiological functioning, and a polymorphism in the serotonin transporter gene, *5-HTTLPR*. Consistent with our primary hypothesis, participants with (a) two copies of the low-expressing allele, and (b) who reported a more difficult time adjusting to their separation experience evidenced lower levels of RSA when asked to reflect over their relationship history and separation experience (presumably reflecting greater vagal withdrawal from the control to separation-specific tasks) relative to participants who were not experiencing psychological difficulty adjusting to their separation or who were not homozygous for the short allele. In addition, while assessing triallelic variability in *5-HTTLPR*, we found no genetic main effects on RSA during the nature video or the mundane events recall task control conditions. This observation helps provide confidence that the observed RSA changes are due to the effects elicited by the separation-related condition, as opposed to the efforts required to perform the mundane control task or the physiological responses activated by the nature video alone.

Genotype was unrelated to psychological distress, which is not surprising given that an allele's main effects on psychological functioning are likely quite trivial (Caspi et al., 2003; Moffitt, Caspi, & Rutter, 2006). The genes that are implicated in conferring susceptibility to psychopathology are generally widespread, normal variants of alleles (like the S′ allele, in the case of SERT), and do not produce decrements to vital functions, nor do they exert their effects free from the influence of many other genetic, molecular, and environmental processes. These dynamic cellular and environmental phenomena render a single gene's influence on any one outcome, for example, psychopathology, to be generally small (see Dick et al., in press).

Given the small sample size and low power of this study, these results should be considered preliminary. Nevertheless, even when viewed tentatively, the findings can help shed light on the ways in which the short serotonin transporter allele is associated with an increased sensitivity to social influences, and particularly how it interacts with psychological distress to shape physiological responding following marital separation. When we approach questions of G×E interactions, we must also be cautious of passive Gene × Environment correlation (rGE; Plomin, DeFries, & Loehlin, 1977), and the idea that the putative consequences of marital separation are explained by individual differences that select some people out of marriage is consistent with a G×E correlation (Sbarra, Emery, Beam, & Ocker, 2013). In our sample, there were no main effects linking genotype to either psychological or physiological responding, but it is likely that G×E correlation operates beyond the serotonin transporter gene alone.

Consistent with classic diathesis stress models (cf. Monroe & Simons, 1991), carriers of the low-expressing allele who reported having difficulty adjusting to their separation experience demonstrated the greatest vagal withdrawal during the divorce-specific mental activation task. Importantly, our results show limited cross-task change in RSA among people who report high levels of separation-related psychological distress without a corresponding S′S′ allele genotype. We evaluated the possibility that people who were heterozygous for the short allele (S′L′) might show a corresponding decrease in RSA during the divorce-specific mental activation task when they reported high levels of psychological distress; the effect was nonsignificant. In addition, there was only limited cross-task change in RSA among S′S′ allele carriers who were not experiencing at least mean levels of separation-related psychological distress. Conceptually, this finding is consistent with results reported by Sbarra et al. (2013), who demonstrated that the greatest risk for a depressive episode following divorce was only observed among people who reported clinically significant depression prior to the separation. Thus, for a prescribed set of psychological and physiological indicators, it appears that the worst outcomes are observed among people who carry more than one risk factor.

Among people carrying the S′S′ genotype, we observed significant differences in RSA across levels of psychological distress—

people reporting few symptoms of separation-related emotional distress evidence higher levels of RSA during the divorce-specific mental activation task, whereas the opposite was found for people reporting higher levels of distress in response to their separation. One relevant question is whether these findings are also consistent with a model of differential susceptibility (Belsky & Pluess, 2009), which holds that people carrying a putative risk genotype may show negative outcomes in aversive environments, but may in fact show positive outcomes in ideal contexts. Evidence for this argument comes from a range of sources. For example, Taylor et al. (2006) found a significant G×E effect indicating people who were homozygous carriers of the short SERT genotype were at increased risk for depressive symptoms in a high-stress current environment, whereas in a supportive environment this same genotype yielded a protective effect. Furthermore, previous studies of married couples found similar links between the *5-HTTLPR* polymorphism and couple-relevant factors like positive and negative emotions (Schoebi, Way, Karney, & Bradbury, 2012) and behaviors (Hasse et al., 2013). All of these authors concluded that the crossover interaction they observed may suggest that the lower-expressing variant of the *5-HTTLPR* gene is not simply a "risk" factor for pathology, but an indicator of sensitivity to environmental context. For the current findings, it is unclear whether low scores on the IES-R (our measure of separation-related psychological distress) reflect a positive response to the end of marriage or a context in which people with an S′S′ genotype may be buffered against adverse outcomes. This question awaits further inquiry.

Another question emerging from this study is whether the RSA differences observed here have any degree of health relevance. Marital separation and divorce are associated with poor distal physical health outcomes (see Sbarra et al., 2012), and RSA is studied as an index of both emotional responding and as a health-relevant biomarker (cf. Sbarra & Coan, 2013). Minimally, we can conclude that people carrying two copies of the risk allele (as determined by both the alleles themselves and the pertinent SNP) and who experience greater psychological distress evidence greater emotion-related physiological changes when reflecting on their separation, potentially indexing a biological preparedness for task demands (Porges, 1995, 2007; Thayer & Lane, 2005). To the extent that these responses become chronic, long-term excessive vagal withdrawal can exert downstream health effects. For example, Gianaros et al. (2005) found HRV changes in a sample of postmenopausal women from a baseline condition to a speech stressor condition (mean difference = .29 ln units) comparable to our own difference between homozygous carriers of the short allele and carriers of a long allele (mean difference = .34 ln units). In the Gianaros et al. (2005) study, the RSA decrease was associated with increased coronary artery calcification.

Further evidence of the health correlates of RSA includes a study conducted by Masi and colleagues of 220 older adults where RSA was found to be a significant predictor of hypertension (high blood pressure) after accounting for traditional risk factors like age, body mass index, diabetes, cigarette smoking, and total cholesterol (Masi, Hawkley, Rickett, & Cacioppo, 2007). RSA was negatively associated with hypertension, which is a significant predictor of coronary artery disease, stroke, and diseases of the cardiovascular system. Low levels of HRV at rest and excessive vagal withdrawal are associated with metabolic abnormalities (Brook & Julius, 2000) and immune dysfunction and inflammation (O'Connor, Motivala, Valladares, Olmstead, & Irwin, 2007; Sgoutas-Emch et al., 1994), including health-relevant biomarkers like interleukin (IL)−6 and C-reactive protein (CRP; von Kanel, Carney, Zhao, & Whooley, 2012). A critical challenge for future research will be to calibrate changes in RSA that have direct relevance for health. Furthermore, other health-relevant systems should be explored, specifically, the G×E's effects on measures of cardiac sympathetic activity (e.g., pre-ejection period) and blood pressure responses as well.

The results of this study should be considered in light of several limitations. First, as noted above, the sample size is small relative to many other G×E studies in the literature (Luan, Wong, Day, & Wareham, 2001), and the results must be considered preliminary. At the same time, however, it would be difficult to collect an exceptionally large sample of participants in this detailed, laboratory-based psychophysiological study of separating adults. Thus, in weighing the merits of this study, the loss of statistical power must be considered against the uniqueness of study design and sample. Second, it is possible sex differences exist in the observed pattern of responding (Williams et al., 2003). The number of men was not adequate to probe these potential differences, as the study sample was about 70% female ($n = 24$ men). Finally, although the divorce-specific mental activation task presents the opportunity to study how participants respond physiologically when thinking about their separation, we have no objective measure of what these people actually thought about—almost all participants reported that the task is similar to how they think about the separation outside the laboratory, but this fact alone does not ensure compliance with task directions.

Conclusions

This study demonstrated that, following marital separation, participants who were homozygous carriers of the short variant (or short-variant equivalent using a triallelic specification) of the SERT gene *and* who reported greater separation-related psychological distress evidenced greater vagal withdrawal when asked to reflect over their relationship history and separation experience. Epidemiological data suggest that divorce is associated with increased risk for poor long-term health among people who are especially vulnerable to prolonged emotional distress when their marriage comes to an end. To the extent that separation-related distress becomes chronic, the findings reported here identify a group of higher-risk people (i.e., short allele carriers who report high levels of emotional distress) who may be particularly vulnerable to poor outcomes by virtue of less long-term parasympathetic inhibition of cardiac control.

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