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Effects of 5HTTLPR on cardiovascular response to an emotional stressor

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Abstract

Objective—To replicate a prior main effect of the 5HTTLPR genotype on cardiovascular reactivity (CVR), and explore caregiver stress as a potential moderator of 5HTTLPR effects on CVR. On the basis of prior findings, we hypothesized that the more transcriptionally active allele variants would be associated with increased CVR.

Methods—Expression of the serotonin transporter is affected by the genotype of the 5HTTLPR (S-short and L-long forms) as well as the genotype of the SNP rs25531 within this region. Based on the combined genotypes for these polymorphisms, we designated each allele as a Hi or Lo expressing allele according to expression—levels resulting in HiHi, HiLo, & LoLo groups. We examined the relationship between 5HTTLPR genotype and CVR in 164 caregivers and 158 non-caregivers. Main effects of 5HTTLPR on baseline adjusted blood pressure (SBP and DBP) and heart rate (HR) reactivity were examined, along with moderation by caregiving.

Results—The 5HTTLPR X Caregiver stress interaction moderated both SBP ($p < .02$), and HR ($p < .02$) reactivity. In controls the Hi activity allelic variants were associated with greater SBP and HR reactivity as compared to the Lo activity variants. In caregivers 5HTTLPR genotype was not associated with CVR.

Conclusions—Replication in this study's control group of our prior finding that 5HTTLPR alleles associated with Hi activity are associated with increased CVR to an emotion recall stressor strengthens the case that this association is real and could be partially responsible for the increased cardiovascular disease observed in persons carrying the 5HTTLPR L allele.

Keywords

5HTTLPR; Caregiving; Cardiovascular Reactivity; Emotion Recall

Introduction

Heightened cardiovascular reactivity (CVR) to stress has been associated with the development and course of cardiovascular disease (CVD) (1). Increased CVR to emotional tasks has been associated with increased development of carotid atherosclerosis (2), stroke incidence (3), insulin resistance (4), and blood lipid levels (5). Moreover, CVR to mental stress has been shown to predict increased risk of developing CVD in healthy groups, independently of resting BP and associations of CVR with the metabolic syndrome (6). The

moderation of CVR to stress by genetic factors is supported by heritability studies in twins. (7) Biologically plausible candidate genes have also been found to be associated with increased CVR to mental stress. (8). Identification of genetic variants that are associated with CVR to mental stress has the potential, therefore, to enable identification of persons at risk early in the pathogenic process, before even early tissue damage has been initiated, when preventive measures guided by the nature of the genetic variants identified could be instituted as part of a comprehensive program of personalized medicine.

There is now a growing consensus that a variety of stressors, ranging from uncontrollable and unpredictable aversive experiences to depression, act via increased serotonin release, to influence emotional experience (9), as well as functions of the HPA axis, the sympathetic and parasympathetic nervous systems with consequent effects on cardiovascular (CV) function (10–12). Not surprisingly, therefore, genes involved in serotonergic transmission have received considerable attention with regard to their influences on emotionally related health outcomes. The serotonin transporter is a major regulator, via reuptake of serotonin and termination of its effects on post-synaptic receptors, of serotonin function, and a functional polymorphism in the serotonin transporter gene promoter (5HTTLPR) has received extensive attention as a candidate gene regulating serotonin function and associated phenotypes. Williams et al. (13,14) found the higher activity 5HTTLPR L allele to be associated with increased CVR to emotion recall in a sample of healthy normal volunteers. This effect to increase CVR was independent of childhood SES which was also independently associated, additively with 5HTTLPR genotype, with CVR. Support for the hypothesis that the same 5HTTLPR L allele Williams et al. (13,14) found associated with increased CVR to mental stress could be contributing to higher CVD risk comes from three independent case-control studies – one from Japan (15) and two from Europe (16,17) – that found persons carrying the 5HTTLPR L allele to be at significantly higher risk of myocardial infarction than persons with the less active S allele.

To confirm that the more active 5HTTLPR L allele is indeed associated with the pathogenic mechanism of increased CVR to negative emotion induction, it will be necessary to replicate the earlier finding of an association between the L allele and increased CVR to emotion recall. To accomplish such replication, in the present study, therefore, we examined the association of 5HTTLPR genotype -- incorporating assessment of the single nucleotide polymorphism, rs25531 in the L allele that has been found to render its transcriptional activity similar to the S allele; (18) -- with CVR reactivity to an emotion recall protocol in a sample of caregivers for a relative with Alzheimer's Disease and age/race/sex/SES-matched controls. We hypothesized that increased CVR (SBP, DBP and HR) to an emotion recall stressor would be associated with the more transcriptionally active 5HTTLPR allele variant.

Consistent findings in prior research have demonstrated that the burden associated with providing care for a loved one suffering from dementia is a considerable environmental stressor (19), and has been associated with a number of negative health outcomes (20–22), and increased rates of early mortality, (23). We have also previously shown in participants from the present sample that caregiving is associated with increased symptoms of depression, poorer sleep quality, and increased glucose, as compared to non-caregivers (24,25). On the other hand, there is evidence that exposure to chronic stress may be associated with *reduced* CVR to a lab mental stress protocol in middle-aged adults (26). Thus, in the present study we examined the following: 1) replication of a prior genetic (5HTTLPR) main effect on CVR; 2) potential effects of caregiving status on CVR; and 3) the possibility that the two predictors might interact, such that genetic effects on CVR might be moderated by caregiver stress.

Methods

Sample

Individuals were recruited to be part of a study designed to examine the underlying genetic, biological, and behavioral mechanisms whereby stressful social and physical environments lead to adverse health outcomes. Persons who were the primary caregiver for a relative with Alzheimer's Disease or other major dementia were included as participants who were living in a stressful life situation. Controls were identified by asking each caregiver to nominate two to five friends who live in their neighborhood and are like them with respect to key demographic factors (e.g., age, race and gender). Cases and controls were matched within 5 years on age, race, gender and relationship to care recipient. The study was conducted at Duke University Medical Center, and all subjects gave informed consent prior to their participation in the study using a form approved by the Duke University Medical Center Institutional Review Board. Subjects were enrolled in the study between January 2001 and June 2004. Subjects enrolled in the study received \$250 for their participation. Individuals who were experiencing any acute major medical/psychiatric disorder were excluded, resulting in the exclusion of one individual who experienced a severe psychiatric problem. A questionnaire battery was given to participants during a home visit by a study nurse. The questionnaire battery was returned during the same week upon their visit to the General Clinical Research Center at Duke University Medical Center, during which they received a physical examination and blood was drawn for assessment of biological parameters. The full study sample consisted of 344 participants. A total of 22 individuals did not have valid data for one or more of the following constructs (5HTTLPR, education, or income); of these 22 individuals, 11 were caregivers and 11 were control participants. This resulted in a final sample of 322 (164 caregivers and 158 non-caregiving controls) in the present study.

Measures

Genotyping—As previously reported (27) the promoter region surrounding the 5HTTLPR and rs25531 polymorphisms was amplified and used to create a composite genotype reflecting the alleles of both polymorphisms. Briefly, the region was amplified and a portion of the PCR product was used for size separation to determine the “S” and “L” alleles, including the rare “XL” alleles. The remaining product was digested with Hpa II to determine the genotype at rs25531. The resulting genotypes from both procedures were used to create a composite genotype reflecting S, La, Lg, and XL alleles. These genotypes were then categorized as high or low expressing based on previous literature. The XL alleles were categorized with the L_A as Hi expressing. Additional quality control for all genotyping consisted of duplicate DNA's placed throughout the DNA plates in which 100% matching results were required. Laboratory technicians were blinded to the matching pattern of these duplicates. We also required greater than 95% efficiency on each genotyping protocol, i.e., no more than 5% of the samples processed could fail the assay.

The triallelic polymorphism did not deviate from Hardy Weinberg expectations in the entire data set ($p=0.16$), in the cases only ($p=0.76$) or in the controls only ($p=0.09$).

Cardiovascular Reactivity (CVR)—Minute to minute blood pressure (BP) and heart rate (HR) readings were gathered via a Dynamap XL 9300 (Johnson & Johnson Health Care System, Inc.), see e.g., (14) for similar use of this CVR protocol. Baseline systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate (HR) were represented by the mean of the last 5 minutes of a 10 minute resting baseline. Emotion recall periods were counter balanced (anger or sadness) and lasted 5 minutes with a 10 minute rest period between. Emotion recall blood pressure and heart rate measures were represented by the mean of the readings during each of the 5 minute recall periods. For the emotion recall

periods, participants were asked to think of an incident that made them very angry or very sad, and that still makes them experience that emotion right now when they think about it. They were then asked to visualize that experience in their mind, recalling in detail what happened. Next participants were asked to verbally recount the entire story, including how they felt at that time.

For the first minute, they were asked to visualize the emotional incident and then for the next four minutes they were asked to describe the situation. Blood pressures were taken throughout the five minute period; one during the first visualization minute and four during the telling of the episode. The first emotion induction period resulted in significantly higher reactivity levels for all measures (SBP $p < .03$; DBP $p < .001$, and HR $p < .001$), as compared to the second induction, leading us to use the reactivity measures from that period to reflect CVR. Per the instructions and tasks included for the full study protocol, no caffeine, nicotine, nor alcohol was consumed prior to the emotion recall task, which took place between 11:30 a.m. and 12:30 p.m. for all participants. With very few deviations all subjects had virtually the same level of physical activity during the morning prior to the reactivity protocol.

Adjustment Constructs—Gender, race (African American or white, based on self-report), and the stressor of caregiving were each coded as a dichotomous variables. Age and education were represented in years. Income was measured in 20 categories, beginning with less than \$10,000 and increasing by increments of \$4,999, and ending at \$100,000 or more. Smoking status was assessed with the following question, “Do you currently smoke cigarettes?” yes=1, no=0. Hypertension medication status was coded yes=1, no=0.

Analytic Plan

Multiple linear regression analyses were used to examine the hypotheses that allelic variation in 5HTTLPR (HiHi, HiLo, LoLo) is related to BP and HR reactivity; to test the stress of caregiving as a predictor of CVR; and to explore whether any 5HTTLPR effect will be moderated by the stressor of caregiving (caregiver versus control). Initially 3-way interaction terms (i.e., gender $\times$ stressor status $\times$ allele status; and race $\times$ stressor status $\times$ allele status), along with all appropriate univariate and 2-way product terms, were examined as predictors of CVR. Next, models were trimmed by removing any non-significant 3-way, and associated non-significant 2-way interaction terms. Analyses were carried out using SAS (Cary, NC). Separate models were estimated for each CVR outcome. In each model, 5HTTLPR allelic variation (HiHi, HiLo, LoLo) was examined as a predictor of SBP, DBP, or HR levels. Age, race, sex, education, income, hypertension medication status and corresponding baseline cardiovascular measures were included as covariates in all models. Thus, the parameter estimate for predictors in these models can be interpreted as the prediction of residualized change in BP and HR, independent of the effects of baseline BP or HR, and other covariates.

Results

Table 1 presents the 5HTTLPR allele frequency by group. Table 2 presents the sample characteristics by group. Caregivers were older ($p < .01$) and had higher baseline SBP ($p < .01$), as compared to controls. The two groups did not differ with respect to any other measures, including 5HTTLPR genotype frequencies

None of the 3-way interaction terms were significant. The 5HTTLPR $\times$ Caregiver status interaction term was significant for SBP reactivity ($F=4.01$, df 2, 321; $p < .02$), and for HR reactivity ($F=3.92$, df 2, 321; $p < .02$). Figures 1 and 2 depict the form of the interaction effects for SBP and HR reactivity. Among the control participants, SBP reactivity was larger

in participants with one or more copies of the Hi activity allele, as compared to those homozygous for the Lo activity alleles. In contrast, among caregiver participants, SBP reactivity was smaller than that of controls among carriers of the Hi activity allele. A similar pattern was seen for HR reactivity for controls, i.e., HR reactivity was larger in participants homozygous for the Hi activity allele, as compared to controls carrying the Lo activity alleles, as well as all caregivers regardless of genotype, among whom HR reactivity remained fairly stable across allele status.

The interaction was not significant for DBP reactivity ($F=1.24$, $df\ 2, 321$; $p < .29$). With regard to 2-way interactions apart from 5HTTLPR X Caregiver status, there was a significant Race X Caregiver status interaction for SBP reactivity. African American (AA) caregivers had lower reactivity, as compared to all other groups ($F=6.32$, $df\ 1, 321$; $p < .01$). African American caregivers SBP mean reactivity = 8.6 (2.3), remaining groups SBP mean reactivity = 14.4 (1.6) to 15.4 (2.3). With regard to covariates, being female ($F=4.07$, $df\ 1, 321$; $p < .05$) and older ($F=7.30$, $df\ 1, 321$; $p < .01$) were associated with significantly increased SBP reactivity. Being older ($F=6.08$, $df\ 1, 321$; $p < .01$), African American ($F=4.30$, $df\ 2, 321$, $p < .05$), and on hypertension medication ($F=6.31$, $df\ 1, 321$; $p < .01$) were associated with less HR reactivity, whereas, being female ($F=11.32$, $df\ 1, 321$; $p < .01$) was associated with higher HR reactivity.

Discussion

The major finding of this study is the replication, only in the controls, of our primary hypothesis that 5HTTLPR alleles associated with increased activity would be associated with increased CVR. Exploratory analysis revealed that caregiver status did moderate our previously reported association of the 5HTTLPR L allele (represented in the present study by the more biologically accurate triallelic – La vs Lg and S – categorization) with increased CVR to stress. The expected association of the Hi activity (La) allele with increased CVR is found only in controls, suggesting that, somehow, the chronic stress of caregiving has reduced the effect of the Hi activity allele on CVR. In the present study the 3-way interactions (sex x genotype x caregiver status and race x genotype x caregiver status) were non-significant. This is consistent with our prior (14) finding that the 5HTTLPR genotype association with CVR is not moderated by race or sex.

The absence of a 5HTTLPR effect on CVR response in our stressed caregivers could be due to burnout in this group. Prior research (28) has shown that middle-aged persons with higher levels of chronic stress exhibit lower SBP and epinephrine responses to a lab mental stress protocol and lower levels of cortisol and norepinephrine during recovery. In addition we have also shown (29), in the present sample that, male caregivers with MAOA-uVNTR alleles associated with less transcriptional activity displayed a pattern of cortisol excretion that was suggestive of HPA axis blunting, as compared to non-caregivers and those caregivers with the more active alleles; suggesting that individuals with less active MAOA-uVNTR alleles who are under chronic stress may be at increased risk for exhaustion of the HPA.

In the present sample, females had higher levels of both SBP and HR reactivity to the emotional stressor, regardless of caregiver status. Similar gender differences have been found in other studies of CVR to stress (30,31). Not unexpectedly, individuals medicated for hypertension had significantly less HR reactivity, but effects of 5HTTLPR genotype on both SBP and HR reactivity were found when hypertensive medication use was controlled. In the current study being older was associated with significantly increased SBP reactivity and less HR reactivity. Results of a recent meta-analysis of age-related differences in CVR to laboratory tasks reported this same pattern of results to emotionally evocative tasks (32).

The mechanism(s) responsible for the 5HTTLPR Hi activity allele's association with increased CVR to stress cannot be stated with certainty at present. Given that the Hi activity allele is associated with increased expression of the 5HT transporter (18), persons with this allele would be expected to have less synaptic 5HT – due to increased reuptake – following any stimulus that caused 5HT release. One mechanism whereby such reduced synaptic 5HT could cause increased CVR would involve effects of the reduced levels of 5HT on 5HT_{1A} receptors in the CNS. Stimulation of 5HT_{1A} receptors in the rostral ventrolateral medulla has been shown to inhibit sympathetic outflow with a consequent decrease in blood pressure (33). In contrast, stimulation of 5HT_{1A} receptors in brain nuclei containing cardiac vagal preganglionic neurones (nucleus ambiguus and dorsal vagal nucleus) has been shown to increase parasympathetic outflow to the heart (33). It is possible, therefore, that a more rapid clearance of synaptic 5HT in persons with the Hi activity 5HTTLPR allele results in decreased stimulation of CNS 5HT_{1A} receptors that mediate decreased sympathetic outflow and increased parasympathetic outflow, thereby resulting in increased sympathetic and decreased parasympathetic outflow and, consequently, increased CVR to stress. We would be the first to acknowledge that this potential mechanism is speculative and selective, in that it ignores the reported effects of stimulation of CNS 5HT₂ receptors to cause increased sympathetic outflow and increased blood pressure.

We are aware of only one prior study of 5HTTLPR genotype effects on CVR (34). This study found no effects of 5HTTLPR on SBP or DBP reactivity, with sex moderating HR reactivity such that in women they found SS associated with increased HR reactivity but with decreased HR reactivity (similar to our finding in both our prior study (14) and the current study) in men. Given the different stressors – cognitive in McCaffery et al. vs negative emotion-eliciting in both our studies – it is not possible to compare their results directly with ours. As we note in our prior study's (14) discussion of the McCaffery et al (2003) study, "replication studies will be required to determine the effect of 5HTTLPR genotype on CVR to stress." And that is what the current study has successfully done: replicated the finding of association, in middle-aged persons not subjected to chronic stress of caregiving, between the 5HTTLPR Hi activity allele and increased CVR to stress.

Certain study limitations should be noted. Although we examined 3-way interactions with respect to gender and race, failure to detect such associations may have been due to the fact that the present sample was underpowered with regard to detection of potential race and gender effects. However, it should be noted that we also failed to find race or gender moderation of the effects of 5HTTLPR genotype on CVR to emotion recall in our prior study (14), suggesting that this effect is not moderated by race or gender. We did not perform genomic control in this study, thus there is the possibility that cryptic population stratification may exist in the present sample. We did not include ratings of self-reported emotion in the present study. However, in two other studies (14,35) we have used this emotional induction task, and in those studies we have measured pre and post emotional responses. We have consistently seen the expected emotional changes in sadness and anger pre to post task, and thus have been assured of the effectiveness of the task. Given these prior results and our desire to decrease subject burden we did not include pre and post task emotional ratings in the current study. In the present study we are limited in our ability to distinguish emotional and physiological responses. Thus, it is possible that the caregivers may have had a different emotional response to the laboratory stressor, as compared to the controls, and that the differences in reactivity may be, in part, attributable to differences in emotional reactivity.

In conclusion, the replication of our earlier finding of increased CVR among controls carrying the 5HTTLPR higher activity allele strengthens the case that increased CVR to emotional stress is one mechanism that is contributing to the previously reported (15–17)

association between the 5HTTLPR L allele and increased risk of myocardial infarction. Our major finding is that the Hi activity allele is associated with increased SBP and HR reactivity, but that further research will be required to determine whether the apparent differences in the pattern of association – Hi dominant for SBP, Lo dominant for HR – are real. The strongest support will come from research currently under way by our group to evaluate the association between the 5HTTLPR higher activity allele and development of CVD in a large healthy cohort and the course of CHD in a large sample of patients with angiographically documented CAD. If such support is forthcoming, it will contribute significantly to the development of personalized/prospective medicine, whereby persons at high risk for CVD can be identified very early in the development of pathogenesis and targeted for interventions to reduce expression of pre-disease endophenotypes – in the case of 5HTTLPR higher activity allele carriers, increased CVR to emotional stress.

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ABBREVIATIONS

CVR	Cardiovascular Reactivity
SBP	Systolic Blood Pressure
DBP	Diastolic Blood Pressure
HR	Heart Rate
CVD	Cardiovascular Disease
CAD	Coronary Artery Disease
SES	Socioeconomic Status

References

1. Treiber FA, Kamarck T, Schneiderman N, Sheffield D, Kapuku G, Taylor T. Cardiovascular reactivity and development of preclinical and clinical disease states. *Psychosom Med.* 2003; 65:46–62. [PubMed: 12554815]
2. Barnett PA, Spence JD, Manuck SB, Jennings JR. Psychological stress and the progression of carotid artery disease. *J Hypertens.* 1997; 15:49–55. [PubMed: 9050970]
3. Everson SA, Lynch JW, Kaplan GA, Lakka TA, Sivenius J, Salonen JT. Stress-induced blood pressure reactivity and incident stroke in middle-aged men. *Stroke.* 2001; 32
4. Moan A, Nordby G, Rostrup M, Eide I, Kjeldsen SE. Insulin sensitivity, sympathetic activity, and cardiovascular reactivity in young men. *Am J Hypertens.* 1995; 8:268–75. [PubMed: 7794576]
5. Burkner EJ, Fredrikson M, Rifai N, Siegel W, Blumenthal JA. Serum lipids, neuroendocrine, and cardiovascular responses to stress in men and women with mild hypertension. *Behav Med.* 1994; 19:155–61. [PubMed: 8032118]
6. Matthews KA, Zhu S, Tucker DC, Whooley MA. Blood pressure reactivity to psychological stress and coronary calcification in the Coronary Artery Risk Development in Young Adults Study. *Hypertension.* 2006; 47:391–5. [PubMed: 16446400]
7. Boomsma DI, Snieder H, de Geus EJ, van Doornen LJ. Heritability of blood pressure increases during mental stress. *Twin Res.* 1998; 1:15–24. [PubMed: 10051353]

8. Uemura K, Kohara K, Nakura J, Miki T. Deletion polymorphism of the ACE gene is associated with higher blood pressure after hospitalization in normotensive subjects. *Hypertens Res.* 2000; 23:201–5. [PubMed: 10821127]
9. Whitaker-Azmitia PM, Peroutka SJ. The neuropharmacology of serotonin. *Ann N Y Acad Sci.* 1990; 600:1–718.
10. Dinan TG. Serotonin and the regulation of hypothalamic-pituitary-adrenal axis function. *Life Sci.* 1996; 58:1683–94. [PubMed: 8637392]
11. Lowry CA. Functional subsets of serotonergic neurons. Implications for control of the hypothalamic-pituitary-adrenal axis. *J Neuroendocrinol.* 2002; 14:911–23. [PubMed: 12421345]
12. Williams RB. Neurobiology, cellular and molecular biology, and psychosomatic medicine. *Psychosom Med.* 1994; 56:308–315. [PubMed: 7972613]
13. Williams RB, Marchuk DA, Gadde KM, Barefoot JC, Grichnik K, Helms MJ, Kuhn CM, Lewis JG, Schanberg SM, Stafford-Smith M, Suarez EC, Clary GL, Svenson IK, Siegler IC. Central nervous system serotonin function and cardiovascular responses to stress. *Psychosom Med.* 2001; 63:300–5. [PubMed: 11292279]
14. Williams RB, Marchuk DA, Siegler IC, Barefoot JC, Helms MJ, Brummett BH, Surwit RS, Lane JD, Kuhn CM, Gadde KM, Ashley-Koch A, Svenson IK, Schanberg SM. Childhood socioeconomic status and serotonin transporter gene polymorphism enhance cardiovascular reactivity to mental stress. *Psychosom Med.* 2008; 70:32–39. [PubMed: 18158371]
15. Arinami T, Ohtsuki T, Yamakawa-Kobayashi K, Amemiya H, Fujiwara H, Kawata K, Ishiguro H, Hamaguchi H. A synergistic effect of serotonin transporter gene polymorphism and smoking in association with CHD. *Thromb Haemost.* 1999; 81:853–856. [PubMed: 10404755]
16. Fumeron F, Betoulle D, Nicaud V, Evans A, Kee F, Ruidavets JB, Arveiler D, Luc G, Cambien F. Serotonin transporter gene polymorphism and myocardial infarction. *Circulation.* 2002; 105:2943–45. [PubMed: 12081984]
17. Coto E, Reguero JR, Alvarez V, Morales B, Batalla A, Gonzalez P, Martin M, Garcia-Castro M, Iglesias-Cubero G, Cortina A. 5-Hydroxytryptamine 5-HT_{2A} receptor and 5-hydroxytryptamine transporter polymorphisms in acute myocardial infarction. *Clin Sci.* 2003; 104:241–5. [PubMed: 12605580]
18. Hu XZ, Lipsky RH, Zhu G, Akhtar LA, Traubman J, Greenberg BD, Xu K, Arnold PD, Richter MA, Kennedy JL, Murphy DL, Goldman D. Serotonin transporter promoter gain-of-function genotypes are linked to obsessive-compulsive disorder. *Am J Hum Genet.* 2006; 78:815–26. [PubMed: 16642437]
19. Schulz R, O'Brien AT, Bookwala J, Fleissner K. Psychiatric and physical morbidity effects of dementia caregiving. Prevalence, correlates, and causes. *The Gerontologist.* 1995; 35:771–791. [PubMed: 8557205]
20. Baumgarten M, Battista RN, Infante-Rivard C, Hanley JA, Becker R, Gauthier S. The psychological and physical health of family members caring for an elderly person with dementia. *J Clin Epidemiol.* 1992; 45:61–70. [PubMed: 1738013]
21. Kiecolt-Glaser JK, Dura JR, Speicher CE, Trask J, Glaser R. Spousal caregivers of dementia victims. Longitudinal changes in immunity and health. *Psychosom Med.* 1991; 53:345–362. [PubMed: 1656478]
22. Vitaliano PP, Russo J, Niaura R. Plasma lipids and their relationships with psychosocial factors in older adults. *Journal of Gerontology Psychological Sciences.* 1995; 50B:18–24.
23. Schulz R, Beach SR. Caregiving as a risk factor for mortality. The Caregiver Health Effects Study. *JAMA.* 1999; 282:2215–2219. [PubMed: 10605972]
24. Brummett BH, Siegler IC, Rohe WM, Barefoot JC, Vitaliano PP, Surwit RS, Feinglos MN, Williams RB. Neighborhood characteristics moderate effects of caregiving on glucose functioning. *Psychosom Med.* 2005; 67:752–758. [PubMed: 16204434]
25. Brummett BH, Babyak MA, Siegler IC, Vitaliano PP, Ballard EL, Gwyther LP, Williams RB. Associations among perceptions of social support, negative affect, and quality of sleep in caregivers and non-caregivers. *Health Psychol.* 2006; 25:220–225. [PubMed: 16569114]

26. Matthews KA, Gump BB, Owens JF. Chronic stress influences cardiovascular and neuroendocrine responses during acute stress and recovery, especially in men. *Health Psychol.* 2001; 20:403–10. [PubMed: 11714181]
27. Brummett BH, Muller CL, Collins AL, Boyle SH, Kuhn CM, Siegler IC, Williams RB, Ashley-Koch A. 5-HTTLPR and Gender Moderate Changes in Negative Affect Responses to Tryptophan Infusion. *Behavior Genetics.* 2008; 38:476–83. [PubMed: 18661222]
28. Matthews KA, Gump BB, Owens JF. Chronic stress influences cardiovascular and neuroendocrine responses during acute stress and recovery, especially in men. *Health Psychol.* 2001; 20:403–10.
29. Brummett BH, Boyle SH, Siegler IC, Kuhn C, Surwit RS, Kail ME, Züchner S, Collins A, Ashley-Koch A, Williams RB. HPA axis function in male caregivers. effect of the monoamine oxidase-A gene promoter (MAOA-uVNTR). *Biol Psychol.* 2008; 79:250–5. [PubMed: 18639608]
30. Schmaus BJ, Laubmeier KK, Boquiren VM, Herzer M, Zakowski SG. Gender and stress. differential psychophysiological reactivity to stress reexposure in the laboratory. *Int J Psychophysiol.* 2008; 69:101–6. [PubMed: 18453025]
31. Bloor LE, Uchino BN, Hicks A, Smith TW. Social relationships and physiological function. the effects of recalling social relationships on cardiovascular reactivity. *Ann Behav Med.* 2004; 28:29–38. [PubMed: 15249257]
32. Uchino BN. Are older adults less or more physiologically reactive? A meta-analysis of age-related differences in cardiovascular reactivity to laboratory tasks. *J Gerontol B Psychol Sci Soc Sci.* 2010; 65B:154–62. [PubMed: 20054015]
33. Ramage AG. Central cardiovascular regulation and 5-hydroxytryptamine receptors. *Brain Research Bulletin.* 2001; 56:425–439. [PubMed: 11750788]
34. McCaffery JM, Bleil M, Pogue-Geile MF, Ferrell RE, Manuck SB. Allelic variation in the serotonin transporter gene-linked polymorphic region (5-HTTLPR) and cardiovascular reactivity in young adult male and female twins of European-American descent. *Psychosomatic Medicine.* 2003; 65:721–8.
35. Brummett BH, Boyle SH, Kuhn C, Siegler IC, Williams RB. Positive Affect is Associated with Cardiovascular Reactivity, Norepinephrine Level, and Morning Rise in Salivary Cortisol. *Psychophysiology.* 2009; 46:862–869. [PubMed: 19470128]

Figure 1.

Study 1: 5HTTLPR X Group: SBP reactivity. SBP change refers to the difference in SBP from baseline to post-recall task, with adjustment for baseline SBP, age, race, sex, education, income, hypertension medication status.

Figure 2.

Study 2: 5HTTLPR X Group: HR reactivity. HR change refers to the difference in HR from baseline to post-recall task, with adjustment for baseline SBP, age, race, sex, education, income, hypertension medication status.

Table 1**5HTTLPR Distribution by Group**

Characteristic			
5HTTLPR Allele Frequency	Lo/Lo	Hi/Lo	Hi/Hi
Caregivers n = 164 (50.9%)	33 (20.1%)	87 (53.1%)	44 (26.8%)
Controls n = 158 (49.1%)	34 (21.5%)	91 (57.6%)	33 (20.9%)
Whites n = 232 (72.0%)	47 (20.3%)	126 (54.3%)	59 (25.4%)
African Americans n = 90 (28.0%)	20 (22.2%)	52 (57.8%)	18 (20.0%)

* Percentages columns 2–3 represent those for each row total.

Table 2

Sample Characteristics by Group

Characteristic	Caregivers n = 164	Non-caregivers n = 158
Age, mean (SD) *	60.8 (13.6)	55.5 (14.5)
Gender, n (%) male	41 (25.0)	37 (23.4)
Race, n (%) African American	44 (26.8)	46 (29.1)
Education, n (%) > 12 years	133 (81.1)	132 (83.5)
Income, median range	\$50,000 – 54,999	\$55,000–59,999
Currently Smoke, n (%)	21 (12.8)	12 (7.6)
On Hypertension Medication, n (%)	63 (38.4)	47 (30.0)
Baseline SBP, mean (SD) *	125.0 (20.7)	119.5 (16.5)
Baseline DBP, mean (SD)	67.8 (9.7)	68.3 (9.7)
Baseline HR, mean (SD)	68.4 (11.3)	69.8 (11.4)
Years served as primary caregiver, mean (SD)	5.4 (3.4)	N/A

* denotes significant difference ($p < .05$) between caregivers and controls