AUTONOMIC AND NEUROENDOCRINE RESPONSES TO MILD PSYCHOLOGICAL STRESSORS: EFFECTS OF CHRONIC STRESS ON OLDER WOMEN[1,2]

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ABSTRACT

We investigated autonomic and endocrine responses to acute stressors in 27 women who were or are presently caring for a spouse with a progressive dementia (high chronic stress) and 37 noncaregivers who were category matched for age and family income (low chronic stress). Measures were taken before (low acute stress) and in response to brief laboratory stressors (high acute stress). We replicated prior research showing that caregivers report greater stress, depression, and loneliness than the comparison groups, and acute stressors elevate autonomic and neuroendocrine activity. We also found that caregivers, relative to noncaregivers, exhibited shorter preejection periods and elevated blood pressure and heart rate, but the magnitude of autonomic and neuroendocrine reactivity to the experimental stressors was comparable across these groups. This pattern of autonomic differentiation replicates prior research showing that caregivers are characterized by higher sympathetic activation than noncaregivers and suggests that the effects of chronic stress on physiological reactivity may be a less robust effect in older adults.

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INTRODUCTION

Providing long-term care for a family member with a progressive dementia has a profound impact on the caregiver's life. The time course of progressive dementia such as Alzheimer's Disease (AD) is lengthy, with a modal survival time of 8 years after onset. Relatives who provide long-term care for a patient with progressive dementia report high levels of stress and dysphoria as they attempt to cope with patients' unpredictable, uncontrollable, and often difficult or embarrassing behaviors (1–3). Caregiving has been likened to exposure to multiple and severe long-term stressors (4,5). In addition, caregivers are characterized by higher levels of social isolation (6) than are comparison participants, which may contribute to adverse physiological (7) and health (8) outcomes. Not surprisingly in light of these findings, caregivers have a higher incidence of clinical depression than comparison participants (5,6,9–11).

Having served as a long-term caregiver for a relative with progressive dementia has physical health consequences as well. Spousal caregivers of dementia patients, relative to noncaregivers, report longer episodes of infectious illness, primarily reflecting upper respiratory tract infections (6). Caregivers of relatives with a progressive dementia, compared to noncaregivers, also are characterized by higher levels of IgG antibody titers to Epstein-Barr virus (EBV) capsid antigen reflecting dysregulation of cellular immunity to latent EBV (6), a lower response of natural killer (NK) cells in peripheral blood leukocytes (PBLs) to two cytokines that stimulate NK cell lysis (12), and a poorer antibody and virus-specific T-cell response to an influenza virus vaccination (13,14). Because AD typically strikes late in life, spousal caregivers of Alzheimer's patients are likely to be older individuals. Respiratory infections remain a major cause of morbidity and mortality among older adults; thus, the diminished immune response to infectious challenges in caregivers could have serious implications. Furthermore, the health consequences of the chronic stress of caregiving may extend beyond infectious diseases. Caregivers of relatives with a progressive dementia are also characterized by impaired wound-healing relative to a comparison group matched for age and family

income (15). The negative effects of caregiving on mental and physical health, although not universal, nevertheless affect a significant proportion of caregivers (16,17). These effects have been attributed largely to the chronic stress of caregiving (5).

Although many potential negative psychosocial and health consequences of chronic severe stress have been established, the mechanisms by which these effects occur are not yet well understood. Because of the possibility of exercising greater experimental control over acute than chronic stressors in humans, studies of the effects of short-term stressors have been pursued (e.g. 18–20). The extant research indicates that brief psychological stressors delivered in a laboratory setting (e.g. timed verbal arithmetic or speech tasks) can elevate heart rate (HR), systolic blood pressure (SBP), plasma adrenocorticotropic hormone (ACTH) levels, and plasma epinephrine (EPI) and norepinephrine (NEPI) levels (18,21–23). Much of the stress-induced change in HR can be abolished by beta-adrenergic blockade (24), suggesting that the effects of brief stressors may in large part be mediated by sympathetic activation. However, recent advances in the conceptualization of autonomic nervous system control have highlighted the importance of examining both sympathetic and parasympathetic contributions to functional outcomes (25). Research has shown that reductions in parasympathetic activity can account for a significant proportion of stress-induced increases in HR (26).

Investigations of the responses of caregivers to brief psychological stressors may be especially important because the stress of caregiving is thought to be attributable in part to the higher frequency of acute stressors to which caregivers are subjected (e.g. 5). Little research has been conducted to date, however, contrasting the autonomic and endocrinological reactions of caregivers and matched comparison participants to brief laboratory stressors. McEwen and colleagues (27,28) have demonstrated that repeated exposure to stressors alters hypothalamic–pituitary–adrenocortical (HPA) activation. McEwen and Stellar (27) coined the term "allostatic load" to refer to the cumulative strain on the body produced by repeated ups and downs of physiologic response as well as to the elevated activity of physiological systems under challenge. Interestingly, contemporary measures of allostatic load, which are thought to reflect the consequences of chronic stress, emphasize baseline differences in physiological functioning rather than differences in physiological reactivity (see review by 29).

What effect might the stress of long-term caregiving for a spouse with dementia have on physiological functioning? The existing research has been mixed. Mills and colleagues (30), for instance, found that caregivers of Alzheimer's patients reported higher life stress and that higher resting plasma NEPI and higher stress ratings predicted greater β-adrenergic receptor sensitivity. A related study, however, found no differences between caregivers and noncaregivers in NK cell activity, catecholamines, or various pituitary hormones (31). Subanalyses revealed elevated ACTH levels in caregivers who were required to provide extensive care for the AD patient and who received little help or relief. Similarly, there is some evidence in humans that chronic stress can enhance reactivity (32,33), but null effects have also been reported (29,34). For instance, Benschop et al. (34), studying job stress among high school teachers, found no differences in the autonomic or endocrine reactivity to acute stressors in participants reporting high or low chronic job stress (see also 35).

Our primary goals in the current research were to explore the possible effects of long-term caregiving both on autonomic and neuroendocrine functioning at rest and on autonomic and neuroendocrine reactions to brief psychological stressors. To better understand autonomic processes, we measured variables that would allow us to differentiate between sympathetic and parasympathetic contributions to brief stress-related HR changes. These variables were cardiac preejection period (PEP) and respiratory sinus arrhythmia (RSA). Preejection period is the time interval between the onset of depolarization of the left ventricle and the opening of the aortic valve. Increased sympathetic activation of the cardiac muscle accelerates this process; hence, the duration of PEP is negatively related to the amount of sympathetic activation of the heart (36). Respiratory sinus arrhythmia is a rhythmical fluctuation in heart periods that is characterized by shortening and lengthening in a phase relationship with inspiration and expiration, respectively. This systematic variability is largely mediated by activity in the vagus nerve; hence, as parasympathetic input to the heart increases, RSA also increases (see review by 37,38). In addition to these cardiac variables, we also measured levels of the stress-related hormones EPI, NEPI, ACTH, and cortisol. Finally, to explore the psychosocial processes leading to stress-related change and to facilitate comparison with prior literature, we assessed several social psychological variables including participants' level of depression, satisfaction with life, loneliness, and perceived stress.

METHOD

Participants

Women who had been or currently were long-term caregivers for demented spouses (caregivers; $n = 27$) and women who were not caregivers (noncaregivers; $n = 37$) served as participants. Participants in the current study were a volunteer subset of individuals taking part in a multiyear study of the effects of caregiving on health. Women outnumber men in our larger spousal caregiver population by 3:1; given the preponderance of the former and the well-documented gender differences in endocrine function, we limited this sample to females. Similarly, to minimize extraneous variables, we chose to include caregivers only if they were or had been caring for a spouse (as opposed to caring for a parent or other relative) with progressive dementia (e.g. AD).

The sample for the larger study was recruited from a number of sources, including three local dementia evaluation centers in area hospitals, neurologists' referrals, the city's AD and Related Disorders Association (ADRDA) support groups, the monthly ADRDA newsletter, respite care programs, and governmental caregiver support programs. As in previous research (39), we define the primary family AD caregivers as those individuals who have major responsibility for providing the resources required by the AD patient or for coordinating those services (e.g. housekeeping, financial help, etc.). Caregivers had to be providing at least 5 hours of care per week at the time they were recruited. At the time of their participation in our study, eight of the caregivers were bereaved and thus no longer providing care for the AD patient. However, prior research suggests that the effects of caregiving for an AD patient often continue long after the patient has died (e.g. 40,41). Consistent with this prior literature, preliminary analyses revealed that the bereaved caregivers did not differ from the active caregivers. Consequently, analyses were conducted collapsing across these two caregiver groups.

Comparison participants were recruited from newspaper advertisements, notices posted in senior citizen centers, area newsletters, church groups, university alumni publications, and referral from other participants. Potential comparison participants who reported caregiving activities of any sort were excluded. Although not a randomly chosen sample, the participants in the caregiver and

comparison groups were similar on sociodemographic variables (see below).

All participants in the study were paid $75.00 for 3.5 to 4.0 hours of participation. The inclusion criteria were the following: Participants (a) were in good health; (b) were not taking beta-adrenergic receptor blockers; (c) consumed on average less than 10 alcoholic beverages per week; and (d) were not math, speech, or needle phobic. In preparation for the study, participants were asked to: (a) reschedule their appointment if they became ill; (b) not consume any alcohol or take any nonprescription medication (e.g. antihistamines) the day before the study; (c) refrain from exercise the day before the study; and (d) refrain from eating or drinking anything besides water from midnight until the time of their scheduled appointment the following morning.

Caregivers and noncaregivers did not differ in age (M = 67.2), weight (M = 156.4 lb), or body mass index (weight in kg/squared height in m; M = 27.5; all $ts < 1.5$). Nor did they differ in terms of education (70% with some college), income (81% over $15,000/yr), marital status (61% married, 11% divorced, 28% widowed), racial composition (17% Black, 83% White), or usage of estrogen replacement therapy (33% current users). Indeed, the only statistical difference that emerged from these preliminary tests was that caregivers in our sample were shorter than noncaregivers ($M_{\text{caregivers}}$ = 63.1 in., $M_{\text{noncaregivers}}$ = 64.5 in., $t(61) = 2.33, p < .05$).

Procedure

Participants were tested at approximately the same time in the morning. When a participant arrived, the tasks and measures were reviewed, any questions were answered, and informed consent was obtained. An occluding cuff of appropriate size was placed over the brachial artery of the participant's arm for blood pressure measurements, a strain-gauge respirometer was placed around the lower thorax, and spot electrodes for impedance cardiography were attached by a female experimenter to the participant's chest and back. Because our primary interest was in heart period time series (for calculation of RSA) and systolic time interval measures (particularly the PEP) and because spot electrodes are more convenient and comfortable than band electrodes for older participants, we used the spot electrodes in the configuration presented by Sherwood, Royal, Hutcheson, and Turner (42). Sherwood et al. (42) compared impedance measures recorded using spot versus band electrodes and reported comparable data and reliabilities for systolic time interval measurements.

Following the placement of the electrodes, the participant was placed in a supine position and a 20-gauge catheter was inserted into an antecubital vein on the arm without the occluding cuff. To allow adaptation to the setting, the participant rested in a supine position while a set of questionnaires, listed below, were verbally administered for approximately 30 minutes. After this adaptation period, the participant was placed in an upright position and asked to sit quietly and relax for approximately 5 to 8 minutes while the equipment was adjusted. To assess baseline neuroendocrine function, a blood sample was collected. Following the blood draw, baseline cardiovascular and respiratory measures were recorded for 6 minutes. Cardiovascular measures were recorded using the Cortronics 7000 blood pressure monitor and an IFM Minnesota Impedance Cardiograph (Model 304B), and respiration was recorded using a EPM Systems (Midlothian, VA) strain gauge and amplifier.

Following the baseline measures, participants received instructions for the two psychological tasks they would be performing and any questions about the stressors were answered. The tasks consisted of a math task and an evaluated speech task; the second stressor immediately followed completion of the first, and the order of the stressors was counterbalanced across participants to allow examination of the separate effects of time and type of stressor. Cardiovascular and respiration measures were collected continuously throughout each 6-minute task. In addition, blood samples were collected for endocrine assays immediately following each of the stressors.

Math Stressor: Participants were asked to perform serial subtraction for six 1-minute epochs. Participants were instructed that any error they made would be corrected by the experimenter and that they should continue from the correct number. The minuend (starting number from which the other number was subtracted) for Minute 1 was 297, for Minute 2 was 688, for Minute 3 was 955, for Minute 4 was 593, for Minute 5 was 1,200, and for Minute 6 was 1,741. The subtrahend (number being subtracted) in Minute 1 was 3. Results from prior research on mental arithmetic in older adults indicated that participants average approximately 10 serial subtractions per minute (18). To maintain maximal task involvement and moderate task difficulty (i.e. approximately 10 correct answers per minute), the subtrahend specified for each subsequent minute was contingent on the participant's performance (gauged by the number of attempted problems and the number of errors) during the preceding minute (see 18). Better performance led to more difficult math problems (e.g. subtracting 7 or 9 rather than 3 or 4 from each result). Participants were asked to work as quickly and as accurately as possible, and they were prompted to speed up their responses at the beginning of minutes 2, 4, and 6.

Speech Stressor: The speech task was based on the speech stressor developed by Saab et al. (22). Each participant was asked to imagine that she was being harassed by an obnoxious bill collector who insisted she had not paid a large medical bill that had, in fact, been paid. She was instructed to prepare a 3-minute speech to deliver to the bill collector's supervisor, covering the following points: (a) her side of the story (what actually happened), (b) what the bill collector did that was wrong and why the bill collector may have suspected her of not paying the bill, (c) how she could prove she did pay the bill, (d) what should happen to the bill collector for the mistake, and (e) a summary of her points. Participants were given 3 minutes to prepare and 3 minutes to present their speeches. They were further instructed to give intelligent and well thought out answers because their speeches would be recorded and compared with the speeches of others.

Following the completion of the second stressor, participants were asked to rate the tasks and their responses to the tasks on several dimensions (see below).

Psychosocial Measures

Participants completed a number of scales throughout the course of the study to determine if there were differences between the caregivers and the comparison participants in terms of demographic, life-style, or various personality dimensions. Some general psychosocial measures were completed during the acclimation period; others were completed as part of an annual interview that is a component of the larger, multiyear study. Finally, as noted above, immediately following the second stressor, participants completed scales assessing their reactions to and perceptions of the tasks. The questionnaires given at the annual evaluation, which were generally administered several months prior to the current study, included the following:

Hamilton Depression Rating Scale: The Hamilton Depression Rating Scale (43) is an interviewer-rated instrument and consists of 24 items that assess the presence of various depressive symptoms such as feelings of guilt, depressed mood, and insomnia. Possible scores range from 0 to 87, with higher scores indicating greater depression.

Older Americans' Resources and Services Multidimensional Functional Assessment Questionnaire (OMFAQ): The modified version of the OMFAQ (44) used here includes single-item measures, on scales of 0 to 2, to assess: (a) perceived changes in mental or emotional health over the past 5 years, (b) life excitement, and (c) life satisfaction.

New York University Loneliness Scale (NYUL): We used an abbreviated (3-item) version of the NYUL to assess the frequency and extent of loneliness (45). Possible scores range from 0 to 18, with higher scores indicating greater loneliness.

The questionnaires given during the acclimation period prior to baseline monitoring included the following:

Life-Style and Health Questionnaire: Participants completed a straightforward questionnaire assessing basic life-style variables (e.g. exercise habits, caffeine consumption).

Positive and Negative Affect Schedule (PANAS): The PANAS assesses the extent to which the participant has experienced various positive (e.g. enthusiasm, pride) and negative (e.g. distress, guilt) states and emotions over the past week (46). Possible scores range from 10 to 50 for negative emotions and from 10 to 50 for positive emotions, with higher scores indicating greater presence of the emotions.

Perceived Stress Scale (PSS): The PSS assesses how often in the past month the participant has felt stressed or unable to cope (47). Possible scores range from 0 to 40, with higher scores indicating greater distress.

Interpersonal Support Evaluation List (ISEL): The short version of the ISEL consists of six questions that assess the perceived availability of social support (48). Possible scores range from 6 to 24, with higher scores indicating greater perceived social support.

Spielberger State–Trait Anxiety Inventory (STAI): The trait portion of the STAI asks participants to indicate the extent to which they generally feel tense and worried (49). Possible scores range from 1 to 4, with higher scores indicating greater trait anxiety. In addition to the trait version of the scale, the state version was used to assess the extent to which participants felt anxious at baseline and in response to the psychological tasks (see below).

To determine if caregivers and comparison participants differed initially in ways that might affect their psychological reactions to the tasks, measures of state anxiety, fear of math, fear of public speaking, and fear of needles were taken during the baseline period. Participants' reactions to the tasks were also assessed following the tasks. Participants responded to a series of questions that assessed how they had felt during the tasks and their perceptions of the tasks. They were asked to evaluate the tasks on several dimensions, including how effortful they were, how unpleasant they were, and whether they had induced feelings of helplessness. The state version of the STAI was also administered following the tasks, and participants were asked to indicate how anxious they had felt during the tasks. Possible scores on the STAI range from 1 to 4, with higher numbers indicating greater state anxiety.

Autonomic Measures

As described elsewhere (18), the Minnesota Impedance Cardiograph (Model 304B) was used to measure the electrocardiogram (ECG), thoracic impedance (Z_0), and the first derivative of the impedance signal (dZ/dt). The ECG data were monitored during collection and bandpass filtered (1 Hz to 10,000 Hz) to reduce artifacts prior to digitization (12-bit A/D converter, 500 Hz). The digitized data (ECG and dZ/dt) were ensemble averaged within 1-minute epochs, and each heartbeat waveform was examined for artifacts and verified or edited before analyses.

Using custom software, PEP was quantified as the time interval in milliseconds from the onset of the ECG Q-wave to the B-point of the dZ/dt wave. For RSA, beat-by-beat heart period data were transformed to a 500 msec interval time series. Respiratory sinus arrhythmia was derived with a Porges–Bohrer filter and confirmed using spectral analysis (.12–.40 Hz) (see 18 for details).

Respiration was monitored using an EZ-AMP amplifier and strain gauge (EPM Systems, Midlothian, VA). The signal was bandpass filtered (.12–.40 Hz) using an interpolated finite impulse response filter, digitized, and then edited to eliminate movement artifacts.

Systolic blood pressure and diastolic blood pressure (DBP) were recorded using the Cortronics 7000 blood pressure monitor, the accuracy of which was verified periodically against standard sphygmomanometer readings by nurses. When valid data from the Cortronics 7000 were unavailable but measurements from the nurses were available, the latter were used.

Mean HR, PEP, RSA, respiration, SBP, and DBP values were calculated for each minute for each participant. To increase reliability, these minute-by-minute means were averaged over the 6-minute baseline and each 6-minute stressor, yielding baseline, Task 1, and Task 2 values.

Neuroendocrine Measures

Assays for EPI, NEPI, ACTH, and cortisol were performed using plasma from the blood samples drawn at baseline, after the first stressor (midstress), and after the second stressor (poststress) using procedures described in Malarkey et al. (50). Plasma catecholamine levels were determined by high performance liquid chromatography using a Waters system with an electrochemical detector. The sensitivity of this system for EPI is 10 pg/ml and for NEPI is 20 pg/ml. The assay has intra- and inter-assay coefficients of variation of 12% for EPI and 7% for NEPI. Plasma ACTH levels were measured using an immunoradiometric method (Nichols Institute, Capistrano, CA). This assay has intra- and inter-assay coefficients of variation of less than 10% and the sensitivity is 1 pg/ml. Plasma cortisol levels were tested using a fluorescent polarization technique (TDX-Abbott Lab, Chicago, IL). This assay has intra- and inter-assay coefficients of variation of less than 10%.

Data Analysis

The effects of caregiving were evaluated using *t*-tests on psychosocial variables and on baseline values of the physiological variables. The effects of the laboratory stressors were evaluated using reactivity measures that reflect change from baseline. Thus, for each measure representing autonomic or endocrine activity, a participant's mean baseline value was subtracted from her mean value of the measure during the tasks. To determine whether the

law of initial values influenced the results, analyses using residualized change scores were also performed (26). The results were not altered in these analyses, so we report simple change scores here.

Preliminary analyses also showed that the pattern of responses did not vary as a function of type of stressor or the order of the stress tasks. Kamarck (51) reviews evidence that the psychometric properties of cardiovascular measures are enhanced considerably by aggregation over repeated measures within measurement periods (e.g. pretask baseline, task) and across psychological stressors. Therefore, analyses were conducted collapsing across stressors to increase reliability and to obtain a more general measure of the effects of brief psychological stressors.

Finally, the degrees of freedom in all analyses were adjusted for measures in which technical problems resulted in incomplete data.[3] One-tailed tests were used to test a priori hypotheses where appropriate to maximize statistical power. Based on the prior literature, for instance, we hypothesized that chronic stress would be associated with heightened physiological activity and reactivity. The power to detect moderate effect sizes (i.e. d = .50) in the current study ranged from 50% to 62%.

RESULTS

Psychosocial Variables in Relation to Caregiver Status

Prior research has shown that caregivers are relatively dysphoric and experience greater levels of stress and depression than do their noncaregiving counterparts (1,2). Given the difficulties that caregivers frequently encounter, we anticipated that caregivers and noncaregivers in our sample would differ on affective and social measures. Cell means for psychological states and traits are summarized in Table 1.

Consistent with the prior literature, analyses revealed that caregivers, relative to noncaregivers, expressed higher levels of depression, $t(62) = 2.17, p < .04$, greater negative affect over the prior 2 weeks, $t(61) = 2.29, p < .03$, and higher levels of perceived stress, $t(62) = 3.23$, $p < .01$. Analyses also indicated that caregivers, in contrast to noncaregivers, described their mental health as having declined more over the prior 5 years, $t(62) = 2.88$, $p < .01$, found life less exciting, $t(62) = 4.17$, $p < .001$, and expressed less satisfaction with life generally, $t(62) = 3.31$, $p < .01$. Caregivers and noncaregivers did not differ in the levels of positive affect experienced over the prior 2 weeks or in their trait anxiety ($ts < 1.5$; see Table 1). Prior research has also shown that caregivers are more isolated than noncaregivers (6). Consistent with this research, we found caregivers reported feeling lonelier, $t(62) = 2.23, p < .03$, than the comparison group. Caregivers and noncaregivers did not differ in terms of their perceived social support, however ($t < 1.5$).

TABLE 1
Psychosocial Means and Standard Errors (SEM) for Caregiver and Noncaregiver Participants

	Group			
	Noncaregivers		Caregivers	
Measure	*n*	Mean (SEM)	*n*	Mean (SEM)
Depression*	37	4.51 (0.98)	27	7.70 (1.08)
Negative affect*	37	15.24 (0.95)	26	18.62 (1.12)
Perceived stress**	37	9.92 (1.11)	27	15.43 (1.29)
Self-rated mental health changes[a]**	37	2.22 (0.12)	27	1.48 (0.25)
Excitement about life***	37	1.68 (0.08)	27	1.15 (0.10)
Satisfaction with life**	37	1.84 (0.07)	27	1.44 (0.10)
Positive affect	37	35.97 (0.92)	26	35.12 (1.10)
Trait anxiety	37	1.72 (0.08)	26	1.84 (0.07)
Loneliness*	37	6.76 (0.46)	27	8.37 (0.57)
Perceived social support	37	21.70 (0.45)	27	21.00 (0.49)

[a] Smaller values indicate greater perceived decline.
* $p < .05$.
** $p < .01$.
*** $p < .001$.

In sum, the psychosocial measures replicate and extend prior research in showing that caregivers, relative to noncaregivers, experience chronic stress but remain able to find positive events in their lives.

Basal Physiological Function in Relation to Caregiver Status

Cell means for the physiological measures are summarized in Table 2. Analyses of the autonomic data suggested that caregivers, relative to noncaregivers, were characterized by elevated resting HR, $t(44) = 1.73, p < .05$ (one-tailed). The analyses of PEP and RSA as markers of the sympathetic and vagal control of cardiac chronotropy, respectively, indicated that caregivers, relative to noncaregivers, were characterized by shorter PEPs, $t(44) = 3.15$, $p < .01$, but comparable respiration and RSA, $t < 1$. These data suggest that the higher basal HR in caregivers may be due to higher tonic sympathetic activation in caregivers than in noncaregivers. Further evidence for this difference was suggested by the results for blood pressure. Caregivers were characterized by higher SBP, $t(56) = 1.87, p < .05$, and higher DBP, $t(56) = 3.13, p < .01$ (one-tailed), levels. Together, these results are consistent with prior work suggesting higher levels of activation of the sympathetic nervous system in caregivers.

Analyses of plasma catecholamine levels at baseline suggested that differences in sympathetic tonus between caregivers and noncaregivers did not extend to the sympathetic adrenomedullary system, as no differences in EPI or NEPI were found, $ts < 1$. Caregivers did exhibit higher levels of plasma ACTH, $t(58) =$

[3] Incomplete data occurred in the following instances: values were not recorded for one caregiver for some demographic data (weight, height, body mass index, income) and some questionnaire data (negative affect, positive affect, trait anxiety, fear of public speaking, fear of needles); HR and PEP data from 15 participants were missing due to technical problems with the impedance cardiograph; RSA data from 8 participants were missing due to technical problems with RSA collection or due to unscoreable RSA data; blood pressure data were missing due to problems with the blood pressure equipment (baseline data from 3 participants, reactivity data from 7 participants); problems with the respiration belt resulted in missing data for 5 participants; problems with blood collection resulted in missing data on EPI and NEPI values (baseline data from 2 participants, reactivity data from 3 participants), on ACTH values (baseline data from 4 participants, reactivity data from 6 participants), and on cortisol values (reactivity data from 1 participant). Further, 3 participants were excluded from all of the cardiovascular analyses because their data revealed that they had mitral value prolapse, which would make it difficult to interpret their data. These missing data reduce power to detect effects but appeared to be unsystematic.

TABLE 2

Baseline Physiologic Means and Standard Errors (SEM) for Caregiver and Noncaregiver Participants

	Group			
	Controls		Caregivers	
Measure	*n*	Mean (SEM)	*n*	Mean (SEM)
Heart rate† in beats/min	26	62.81 (1.52)	20	68.03 (2.82)
Preejection period** in ms	26	103.12 (3.37)	20	84.75 (5.00)
Respiratory sinus arrhythmia in log units	31	5.19 (0.18)	22	5.07 (0.19)
Systolic blood pressure† in mm Hg	31	137.13 (3.16)	27	146.22 (3.72)
Diastolic blood pressure†† in mm Hg	31	77.00 (2.07)	27	85.63 (1.75)
Respiration in breaths/min	32	15.39 (0.41)	24	14.48 (0.69)
Epinephrine in pg/ml	35	21.80 (1.37)	27	24.41 (2.94)
Norepinephrine in pg/ml	35	610.23 (43.18)	27	568.04 (40.03)
Adrenocorticotropic hormone** in pg/ml	34	9.75 (1.00)	26	16.59 (2.21)
Cortisol in μg/dl	37	10.51 (0.60)	27	10.36 (0.73)

* $p < .05$.
** $p < .01$.
† $p < .05$, one-tailed.
†† $p < .01$, one-tailed.

TABLE 3

Reactivity[a] Physiologic Means and Standard Errors (SEM) for Caregiver and Noncaregiver Participants

	Group			
	Controls		Caregivers	
Measure	*n*	Mean (SEM)	*n*	Mean (SEM)
Heart rate reactivity in beats/min	26	9.04 (1.09)	20	10.45 (1.18)
Preejection period reactivity in ms	26	−7.67 (2.16)	20	−6.20 (1.80)
Respiratory sinus arrhythmia reactivity in log units	31	−0.37 (0.14)	22	−0.59 (0.15)
Systolic blood pressure reactivity in mm Hg	29	−1.38 (2.22)	25	−0.14 (2.17)
Diastolic blood pressure reactivity in mm Hg	29	3.86 (1.96)	25	−0.44 (1.12)
Respiration reactivity in breaths/min	32	2.97 (0.39)	24	2.93 (0.71)
Epinephrine reactivity in pg/ml	34	8.51 (2.12)	27	8.09 (1.79)
Norepinephrine reactivity in pg/ml	34	−41.53 (20.57)	27	−18.65 (14.69)
Adrenocorticotropic hormone reactivity in pg/ml	32	3.78 (1.07)	26	5.65 (1.42)
Cortisol reactivity* in μg/dl	36	0.91 (0.49)	27	2.84 (0.80)

[a] Reactivity is the value of the variable during the task minus the value of the variable during baseline; that is, reactivity represents the amount of change from baseline to the task.
* $p < .05$.

3.06, $p < .01$, than the comparison group, replicating subanalyses by Irwin et al. (31).

Basal Physiological Function in Relation to Psychosocial Function

Pearson correlation coefficients reflecting the relations between the physiological parameters and psychosocial variables across both groups of participants provided mild support for higher sympathetic tonus in participants reporting a less favorable psychosocial climate. Most relevant were the findings that HR was positively and PEP was negatively correlated with negative affect over the prior 2 weeks ($r = .30$ and $r = -.32$, respectively; both $ps < .05$), as would be expected if negative affect was associated with the tonic activation of the sympathetic nervous system. In addition, SBP was negatively correlated with positive affect over the past 2 weeks ($r = -.35$, $p < .01$), and DBP was negatively correlated with life satisfaction ($r = -.37$, $p < .01$). With regard to the HPA axis, both ACTH and cortisol were negatively correlated with finding excitement in life ($r = -.34$, $p < .01$; and $r = -.25$, $p < .05$, respectively). These latter correlations should be interpreted cautiously, however, given the number of tests conducted.

Stress Reactivity

State anxiety was assessed at baseline and following the stressors as a manipulation check. Consistent with expectations, the acute stress tasks led to increased state anxiety, $t(63) = 13.91$, $p < .001$. Participants were selected to be low in fear of math, public speaking, and needles; analyses confirmed that caregivers and noncaregivers reported equivalent levels of baseline state anxiety and comparably low levels of fear of math, speech, and needles (all $ts < 1$). Furthermore, the tasks were designed to be comparably engaging and threatening for caregivers and noncaregivers and, accordingly, caregivers and noncaregivers reported similar psychological reactions to the tasks. Specifically, caregivers did not differ on posttask anxiety (as measured by the STAI), mental effort, unpleasantness, arousal, uncertainty, helplessness, or control associated with the tasks; all $ts < 1$ with the exceptions of uncertainty, $t(62) = 1.76$, $p = .08$, and control $t(62) = 1.76$, $p = .08$.

Cell means for the physiological measures of stress reactivity are summarized in Table 3. Analyses of autonomic responses to the stressors revealed that the laboratory tasks elevated HR, $t(45) = 12.09$, $p < .001$, shortened PEP, $t(45) = 4.88$, $p < .001$, reduced RSA, $t(52) = 4.48$, $p < .001$, had no effect on systolic blood pressure, $t(53) = .520$, or diastolic blood pressure, $t(53) = 1.56$, and increased respiration rate, $t(55) = 7.87$, $p < .001$. Analyses of the neuroendocrine data similarly revealed that the stressors elevated plasma levels of ACTH, $t(56) = 5.32$, $p < .001$, cortisol, $t(62) = 3.81$, $p < .001$, and EPI, $t(60) = 5.90$, $p < .001$.[4]

Despite the laboratory stressors having the intended psychological and physiological effects, caregivers and noncaregivers did

[4] A significant decrease in NEPI was also found. The NEPI data are anomalous but may reflect the postural change that preceded the laboratory stressor by approximately 5 minutes. This is long enough for EPI, HR, and blood pressure to return to normal after a postural change. Norepinephrine is less likely than EPI to have returned to normal levels within that time frame because it reaches a higher blood level than EPI during a change in posture.

not differ in their autonomic reactivity to the acute stressors (see Table 3). Caregivers did show larger increases in plasma cortisol, but in all other regards, the stress reactivity of the two groups was comparable. The differences in stress-related cortisol activation, therefore, require replication before they can be taken as evidence that the stress of caregiving alters HPA reactivity.

DISCUSSION

The development of progressive dementia is unpredictable, irreversible, and devastating to social relations. Although there are notable exceptions (17), many long-term caregivers for a spouse with a progressive dementia live in strained relationships. Accordingly, caregivers are more likely to report depressive symptoms than noncaregivers (5,9,11). The present research replicated and extended this work by showing that caregivers differ from a category-matched comparison group on autonomic and neuroendocrine measures, adding to the evidence that the chronic psychological stress carries physiological as well as psychological costs. Additionally, this study provides some evidence for a relation between measures of chronic strain and baseline physiological status.

Allostatic load refers to the cumulative strain on the body produced by repeated ups and downs of physiologic response as well as to the elevated activity of physiological systems under challenge (27,29). The present results are in accord with caregiving taking a toll in terms of allostatic load. Specifically, measurements obtained during a resting baseline revealed that caregivers, relative to age and gender-matched noncaregivers, exhibited shorter PEP and elevated blood pressure and HR. Research using autonomic blockade in humans has shown that individuals with shortened PEPs were also characterized by heightened sympathetic activation of the heart (see 36). This pattern of autonomic differentiation suggests that caregivers show greater activation of the sympathetic branch of the autonomic nervous system than noncaregivers. Furthermore, the fact that caregivers and noncaregivers showed equivalent PEP responses to the acute psychological stressors suggests that the observed differences in tonic control of the heart were not secondary to abnormal cardiac function in caregivers. It is unlikely that individuals with short PEPs were any more likely to become spousal caregivers than were those with long PEPs. The shorter PEPs may therefore be a consequence of the chronic stress on caregiving and reflect elevated cardiac sympathetic activation in caregivers compared to noncaregivers. This possibility might best be explored in future research using prospective longitudinal designs and/or autonomic blockades.

If caregivers differed from noncaregivers in sympathetic tonus, why might we not have found similar group effects on our measures of plasma catecholamines? Epinephrine and NEPI are powerful neurotransmitters with widespread effects on central and peripheral sites. Physiological processes are in place to minimize long-lasting elevations of the catecholamines, at least in normal, healthy individuals. Future research might examine metabolites, such as uric acid level, for traces of elevated sympathetic activation in caregivers (52). In addition, McEwen and Seeman (29) recommend overnight (12-hour) measures of urinary catecholamines rather than single plasma measures to better index tonic sympathetic activation. Future research, therefore, might benefit from measuring overnight urinary catecholamine levels.

Caregivers were also characterized by significantly higher basal levels of plasma ACTH than the comparison group. Altered HPA functioning has been shown to result from high allostatic loads (29), so the difference in ACTH (which is less constrained by regulatory feedback than is cortisol) raises the possibility that the activity in the hypothalamic or pituitary arm of the HPA axis was elevated in caregivers relative to noncaregivers. This should be considered only a hypothesis at this juncture, however, because neuroendocrine activity is pulsatile in nature and we measured basal neuroendocrine activity at only one point in time. Having said this, the present results replicated those of Irwin and his colleagues (31), who found elevated ACTH levels in caregivers who were required to provide extensive care for their spouses. Indeed, as in Irwin et al.'s (31) subanalyses, the caregivers in the current study were and/or had long been the primary caregiver for their spouse with dementia.

As noted, the physiological effects of the stress of caregiving were more apparent in basal functioning than in stress reactivity. All of our tonic cardiovascular measures that were at least in part sympathetically controlled revealed caregivers to have higher levels of activation than noncaregivers. No differences were observed on any autonomic measure of stress reactivity, however, and the effect sizes for these comparisons were quite small. These results, too, are in accord with McEwen and colleagues' emphasis on basal measures rather than reactivity measures in older adults to index allostatic load (29).

In two previous studies by Uchino and colleagues (53,54), cross-sectional analyses revealed that basal blood pressure increased with age, but that these age-related increases tended to be seen in subjects with low but not with high levels of perceived social support. Uchino et al. (53,54) also found no differences between the high and low support groups in reactivity to acute stress. Social support has been shown to buffer the effects of chronic psychosocial stress (see review in 55). It follows, therefore, that individuals with low social support may be viewed as living more chronically stressed lives relative to those with high social support. From this viewpoint, our current results are similar, as we found evidence in the chronically stressed of higher basal sympathetic tone, but no enhancement in reactivity.

The comparable autonomic reactions shown to acute stressors by caregivers and noncaregivers cannot be attributed to a floor effect in this study because, as in prior research (e.g. 18,56–58), these acute stressors evoked significant autonomic and neuroendocrine responses. An isolated significant difference was observed between caregivers and noncaregivers on the measure of cortisol reactivity, but this result requires replication with multiple measures of neuroendocrine activity prestress and poststress. When the results as a whole are considered, they suggest that the stress of caregiving elevates homeostatic set points rather than arousability per se. A possible mechanism for this result is a downregulation of adrenergic receptors in long-term caregivers.

Schulz et al. (17) found that caregivers tend to have lower income, be less educated, have more functional limitations, and engage in poorer health behaviors (e.g. more smoking, less exercise) than noncaregivers—factors that they noted are independently associated with health outcomes. To avoid confounding that might render the interpretation of autonomic or neuroendocrine effects equivocal, participants in the current study were selected based on stringent health criteria (e.g. no history of chronic illness of immunological or endocrinological nature; no cancer within the past 5 years). If our sample of caregivers represents a healthier, more active, and more resilient group than a random sample of caregivers from the population, the finding that caregivers are characterized by greater sympathetic tonus than are noncaregivers is all the more remarkable, and the effect sizes observed in this study may underestimate the strength of these effects in the

population. Despite the conservative selection of caregivers in this study, we also replicated psychosocial differences between caregivers and comparison groups reported previously in the literature. For instance, we found that our sample of caregivers reported higher levels of stress and loneliness, scored higher on depression, expressed less satisfaction with life generally, found life more boring, and described their mental health as having deteriorated more over the preceding 5 years than did a category-matched comparison group. Together, then, our results suggest that the stress of caregiving produces a long-term tonic activation of the sympathetic branch of the autonomic nervous system.

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