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Effects of childhood trauma exposure and cortisol levels on cognitive functioning among breast cancer survivors

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Abstract

Cognitive functioning difficulties in breast cancer patients receiving chemotherapy are common, but not all women experience these impairments. Exposure to childhood trauma may impair cognitive functioning following chemotherapy, and these impairments may be mediated by dysregulation of hypothalamic-pituitary-adrenal (HPA) axis function and cortisol slope. This study evaluated the association between childhood trauma exposure, cortisol, and cognition in a sample of breast cancer survivors. 56 women completed measures of trauma exposure (the Traumatic Events Survey), salivary cortisol, and self-reported cognitive functioning (the Functional Assessment of Cancer Therapy – Cognitive). We examined correlations between childhood trauma exposure and cognitive functioning, then used linear regression to control for factors associated with cognition (age, education, time since chemotherapy, depression, anxiety, and insomnia), and the MacArthur approach to test whether cortisol levels mediated the relationship between trauma and cognitive functioning. 57.1% of the sample had experienced at least one traumatic event in childhood, with 19.6% of the sample witnessing a serious injury, 17.9% experiencing physical abuse, and 14.3% experiencing sexual abuse. Childhood trauma exposure and cognitive functioning were moderately associated ($r=-0.29$). This association remained even when controlling for other factors associated with cognition; the final model explained 47% of the variance in cognitive functioning. The association between childhood trauma and cognitive functioning was mediated by steeper cortisol slope (partial $r=0.35$, $p=0.02$). Childhood trauma exposure is associated with self-reported cognitive functioning among breast cancer survivors and is mediated by cortisol dysregulation. Trauma should be considered, among other factors, in programs aiming to address cognition in this population.

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Keywords

Breast Cancer; Cortisol; HPA axis; Childhood Trauma; Cognitive functioning

Background

Breast cancer can have a pervasive impact on a woman's cognitive functioning (Fitch, Armstrong, & Tsang, 2008). Cognitive functioning difficulties in breast cancer patients receiving chemotherapy are well-documented in the research literature, and many women report concerns about experiencing cognitive difficulties during the breast cancer trajectory (Janelsins et al., 2016). Several theories have been proposed to explain the prevalence and onset of impaired cognitive functioning among breast cancer patients and survivors. Most commonly, either the direct effect of chemotherapy on the brain (Matsuda et al., 2005) or systemic inflammatory processes due to chemotherapy or radiation treatments are thought to underlie cancer-related impairments in cognitive functioning (Ahles & Saykin, 2007). Other research has shown that some cognitive functioning difficulties may begin even before the initiation of cancer treatments and could, therefore, be related to tumor pathophysiology (Adams, Packer, Palesh, & Kesler, 2016). However, not all women experience cognitive functioning difficulties during treatment, and not all women continue to report these impairments following the cessation of treatment (Christie et al., 2012; Fitch et al., 2008; Von Ah, Habermann, Carpenter, & Schneider, 2013). Much work still needs to be done in order to understand the mechanism of cognitive functioning difficulties in breast cancer patients. Identifying factors that can predict women at risk of cognitive functioning difficulties after breast cancer treatment would allow researchers and clinicians to develop and implement early interventions to improve long-term cognitive outcomes.

Early exposure to traumatic events could put women at risk of impaired cognitive functioning. In the population at large, exposure to traumatic events in childhood (before age 18) may result in persistent alteration of hypothalamic-pituitary-adrenal (HPA) activity (Heim, Newport, et al., 2000; Meinlschmidt & Heim, 2005; Shea, Walsh, Macmillan, & Steiner, 2005). A review by Lupien and colleagues (2009) suggests that depending on a person's age when exposed to trauma, he or she may develop long-term HPA suppression or hyperactivity, causing the HPA axis to be easily activated by stress and to continue to produce glucocorticoids even after a threat has passed (Lupien, McEwen, Gunnar, & Heim, 2009; McEwen, 1998). This overproduction of glucocorticoids, including cortisol, has a direct impact on cognitive functioning among people in general (McEwen, 1998; McEwen & Stellar, 1993) and in the specific context of cancer (Andreotti, Root, Ahles, McEwen, & Compas, 2015), indicating that exposure to childhood trauma may also put women at risk of cognitive functioning difficulties after breast cancer diagnosis and treatment.

Childhood trauma may have a pervasive impact on cognitive functioning because glucocorticoid receptors are found throughout the brain, including the hippocampus. The hippocampus is particularly vulnerable during childhood as this brain area is developing. Prolonged excessive secretion of glucocorticoids in the hippocampus, especially during childhood, may lead to a reduction of hippocampal volume, and thereby restrict capacity for

learning and memory formation (Lupien et al., 1998; Sapolsky, Krey, & McEwen, 1986). Multiple studies have shown that memory and learning are impaired in survivors of childhood trauma (Bremner & Narayan, 1998; Charney & Manji, 2004; Weniger, Lange, Sachsse, & Irle, 2009), and that reduced hippocampal volume in trauma survivors is associated with increased arousal under stress (Gilbertson et al., 2002). The nature of the glucocorticoid response when exposed to stress, however, has yet to be fully characterized in medically ill populations who have been exposed to trauma. Some studies examining cortisol slopes in medical and psychiatric illness (Heim, Ehlert, & Hellhammer, 2000; McEwen, 1998; Sephton, 1998), including trauma (Heim, Ehlert, et al., 2000; Yehuda, 1997), have shown that flatter slopes, indicating a blunted stress response, are likely to emerge after longstanding exposure to stress. However, some studies have found a steeper cortisol slope, indicating a more pronounced stress response, in individuals experiencing health and illness related anxiety (Edwards, Hucklebridge, Clow, & Evans, 2003; Ferguson, 2008). For example, previous studies have indicated that steeper diurnal cortisol slopes were significantly related to increased anxiety about nonspecific health symptoms in healthy adults (Ferguson, 2008) and to increased awareness of one's medical symptoms (Edwards et al., 2003). Similarly, another study among 274 women with breast cancer found that steeper diurnal cortisol levels predicted greater fatigue and depression (Palesh, 2009).

Given that hippocampal degeneration has also been found in cancer patients following chemotherapy (Christie et al., 2012), exposure to early childhood trauma could predispose cancer survivors to experience increased stress-related arousal and poorer cognitive functioning in the context of cancer treatment. Breast cancer patients who experienced childhood trauma may have dysregulated HPA axis function; their cortisol secretion patterns may have already been dysregulated by early life stress and could be further dysregulated by the introduction of inflammatory chemotherapies to their vulnerable neurocognitive systems. At present, few studies have explored the link between childhood trauma exposure, cancer treatment, dysregulation of HPA axis and cortisol secretion, and cognitive functioning among women with breast cancer. The current study addresses this gap. Our hypotheses are:

H1: Exposure to one or more traumatic events in childhood will be associated with greater impairment in cognitive functioning following breast cancer treatment. This relationship will remain even after controlling for type of breast cancer treatment, time since treatment, depression, anxiety, and sleep disturbance.

H2: Greater impairment in cognitive functioning will be mediated by dysregulation in cortisol levels in those patients who were exposed to one or more traumatic events in childhood.

Methods

Participants

This was a secondary analysis of data collected in the context of a randomized clinical trial. Participants were recruited between March, 2011 and April, 2012 through the Stanford Cancer Center and Love/Avon Army of Women (AOW), an online recruitment resource designed to partner women with the breast cancer research community (Stanton et al., 2013).

Participants were approached, recruited, and consented into a study of acupuncture for treatment of insomnia in breast cancer survivors. In order to be eligible for this study, participants had to: 1) be diagnosed with breast cancer but not currently undergoing cancer treatment (with the exception of hormonal treatment), 2) have completed their last cancer treatment ≥ 2 weeks prior to screening, 3) have a habitual sleep phase between 9:00 pm and 11:00 am, 4) meet DSM-IV criteria for insomnia with duration ≥ 1 month, 5) have a Karnofsky Performance Status scale score ≥ 70, 6) have an Insomnia Severity Index (ISI) score ≥ 8, 7) be at least 21 years of age, 8) be able to understand written and spoken English, and 9) be able to travel to the study site. Participants could not: 1) have an unstable medical or psychiatric illness (determined by the Mini-International Neuropsychiatric Interview; Sheehan et al., 1998) within the last 5 years, 2) have had exposure to acupuncture within six months prior to screening, 3) be using sleep aids (e.g., over-the-counter, prescription, naturopathic), 4) be currently pregnant or nursing, 5) have history of substance abuse or meet criteria for current alcohol abuse or dependence, 6) have a Center for Epidemiological Studies Depression Scale (CES-D) score >27 (Hann, Winter, & Jacobsen, 1999), 7) meet DSM-IV criteria for restless legs syndrome, Circadian Rhythm Sleep Disorder, or probable sleep apnea, or 8) have had major surgery within four weeks prior to first acupuncture treatment. A total of 68 participants were screened and found eligible to participate in the parent study. Of these, 12 opted not to complete measures of trauma and could not be included in the current study. The 12 women who opted not to complete the measure of trauma did not differ in demographic characteristics from the 56 who did. The final sample for the current study consisted of 56 women with breast cancer.

Design

Participants in the study were randomized by a study statistician to receive either real (N=34) or sham (N=34) acupuncture. Participants and study staff were blinded to the randomization arm. Participants completed assessments at baseline (prior to any intervention procedures), 3 weeks (mid-treatment), 6 weeks (end of acupuncture or sham treatment), and 10 weeks (follow-up). Because we were interested in associations between childhood trauma exposure and perceived cognitive function in the current study, we only used data from the baseline assessment period from the 56 women who completed the measure of trauma exposure before any intervention procedures. All study procedures were approved by the Stanford University Institutional Review Board.

Measures

Demographics and medical variables—Demographic information and medical history were obtained by self-report measures as well as extraction from medical records

Childhood trauma exposure—Exposure to traumatic events in childhood was assessed with the Traumatic Events Survey (TES; Briere, Woo, McRae, Foltz, & Sitzman, 1997; Elliott & Briere, 1992). The TES is a face-valid measure that is widely accepted and utilized in the field of trauma psychology. See Briere (1997) for a detailed examination on psychological measures used to assess posttraumatic states, including a thorough description of the TES. This survey assesses a range of traumatic experiences in both childhood and adulthood. Of the 30 traumatic experiences assessed, 10 are specifically childhood traumas:

experienced natural disaster, had a life-threatening illness, witnessed serious injury to someone else, witnessed someone being killed, witnessed someone being sexually assaulted, was physically assaulted, been sexually assaulted, was victim of a violent crime, was tortured or witnessed torture, was kidnapped or held captive. For each traumatic event, participants are asked how many times the event happened, who perpetrated the event (for interpersonal traumas), and how helpless and horrified the participant felt during the event. We calculated childhood trauma exposure as a count of the number of traumatic events experienced in childhood (range: 0–10) and also dichotomized exposure as experienced any trauma vs. experienced no trauma to account for the relatively low base rate of childhood trauma.

Self-reported cognitive functioning—Cognitive functioning was assessed using items from Version 3 of the Functional Assessment of Cancer Therapy – Cognitive (FACT-Cog; Wagner, 2009). In the current study, at the recommendation of the measure's publisher, we used a subset of 29 items organized into three subscales: perceived cognitive abilities (18 items; e.g., concentration, verbal and nonverbal memory, verbal fluency), perceived cognitive impairment (7 items; e.g., cognitive deficits in daily activities), and impact of cognitive impairment on quality of life (4 items). Items are rated on a 0–4 scale of severity. Subscale scores were added together to create a sum score, representing overall cognitive functioning; higher scores on each subscale and on the sum scale indicate better cognitive functioning. The FACT-Cog has excellent psychometric characteristics in general, and has been psychometrically validated with a sample of 204 cancer patients undergoing chemotherapy (Wagner, 2009). The sum score created for this study similarly displayed excellent internal consistency (α=0.88).

Cortisol—We assessed cortisol as a marker of HPA axis function and stress response (Clow, Hucklebridge, Stalder, Evans, & Thorn, 2010; Evans et al., 2011). Participants were asked to collect their saliva three times a day (T1: waking, before getting out of bed; T2: 30 minutes after waking; T3: at 9:00 pm) for two days. Immediately after participants collected their saliva, samples were frozen at −20° C. Following completion of two days of saliva collection, the samples were transported to a −70° C freezer. Salivary cortisol was analyzed in duplicates using an enzyme immunoassay (Salimetrics, PA, USA). The minimal level of sensitivity to distinguish from zero cortisol is 0.007 μg/dL and average intra- and inter-assay coefficients of variation are 4.6% and 6% respectively. The following seven variables were considered as mediators: Log Cortisol at T1, Log Cortisol at T2, Log Cortisol at T3, Slope (LogT1–T2), Slope (LogT2–T3), Slope (LogT1–T3), and area under the curve (LogT1,T2,T3).

Mental health covariates—As participants were selected into the parent study on the basis of insomnia scores, we used these scores as control variables in our analyses. Insomnia was assessed using the total score on the Insomnia Severity Index questionnaire (ISI), a well-validated measure of sleep that has been found to be reliable and valid in cancer patients and survivors (Savard, Savard, Simard, & Ivers, 2005). The ISI has acceptable internal consistency (Cronbach's alpha = 0.74) and moderate item-total correlations with sleep diaries (correlations ranging from 0.35 – 0.38 for the domains of early morning

awakenings, sleep onset latency, and wake time after sleep onset; Bastien, Vallieres, & Morin, 2001). Both depression and anxiety are associated with cognitive functioning; accordingly, we controlled for both anxiety and depression in our analyses. Depression was assessed using the Center for Epidemiological Studies – Depression scale (CESD), a commonly-used 20 item measure of depression (Hann et al., 1999). The CESD has been shown to be a valid and reliable measure with cancer patients. Internal consistency is good (Cronbach's alpha > 0.85) and test-retest correlations range from 0.51 – 0.57. Furthermore, the CESD has been found to correlate well with other tests of depression (Hann et al., 1999). Anxiety was assessed with the State-Trait Anxiety Inventory (STAI) – State subscale, a 20-item measure of anxiety with good internal consistency, reliability, and convergent validity (Spielberger, Sydeman, Owen, & Marsh, 1999).

Statistical Analyses

We examined descriptive statistics for sample demographic characteristics, childhood trauma exposure, and self-reported cognitive functioning. Given that most individuals with exposure to childhood trauma experienced only one traumatic event, we categorized individuals into two categories: those with one or more childhood trauma exposures (trauma) and those without childhood trauma exposure (no trauma). To test associations between trauma exposure and cognitive functioning, we used t-tests to assess mean differences between those with trauma and no trauma in baseline self-reported cognitive functioning, looking both at the FACT-Cog sum score and at the subscale scores. We also examined mean differences between those with trauma and no trauma in mental health covariates, and correlations between cognitive functioning and mental health covariates. Finally, we regressed cognitive function onto childhood trauma exposure while controlling for insomnia, depression, anxiety, and demographic variables such as age and education that have been associated with cognitive functioning in previous literature (e.g., Hayat et al., 2016).

For hypothesis 2, we theorized that childhood trauma exposure affects HPA axis functioning, operationalized as elevated salivary cortisol levels and a dysregulation in diurnal cortisol slope. Under this theoretical framework, although our data are cross-sectional, we assume that childhood trauma exposure precedes change in cortisol and change in cortisol precedes change in cognitive functioning. Assuming this temporal precedence, we explored the mediating role of cortisol patterns using the MacArthur approach for mediator analysis (Kraemer, Kiernan, Essex, & Kupfer, 2008). All cortisol measures were log-transformed before the analysis. Using a two-sample t-test, we first compared individuals with and without trauma in terms of cortisol patterns. Cortisol variables that showed significant group differences, meeting the eligibility criteria for mediators, were then examined in a subsequent linear regression analysis to identify potential mediators. In this second step of mediation analysis, trauma exposure, cortisol variables and the interaction between the two were modeled as predictors of self-reported cognitive functioning. Mediators were centered at their means and trauma exposure was centered at +0.5 and −0.5. In line with the analytical criteria for mediators in the MacArthur approach, a cortisol variable that showed a significant main effect or an interaction effect on cognitive functioning was identified as a potential mediator (Kraemer et al., 2008). Regression coefficients for these analyses were standardized and therefore each predictor's coefficient can be interpreted as correlation

conditional on the other predictors in the model. We used SPSS version 22 to conduct analyses.

Results

Participant characteristics

Of the 332 patients who were assessed for eligibility, 84 were eligible and consented to the study, 68 were randomized, and 12 opted not to respond to the Traumatic Events Survey. The mean age of the final sample of 56 breast cancer patients was 54 years. The modal level of education was 4 year college or university (39.3%, n = 22), modal yearly household income was over $100,000 (62.5%, n=35), and the majority were married (78.6%, n=44) and non-Hispanic White (94.6%, n=53). In subsequent analyses, we dichotomized education into college education or higher (76.8%, n=43) or less than college education (23.2%, n=13). The modal breast cancer stage was Stage II (41.1%, n = 23). See Table 1 for demographic factors for the sample.

Childhood trauma exposure and cognitive functioning

In total, 57.1% (n=32) of the sample had experienced at least one traumatic event in childhood; 41.1% (n=23) had experienced only one event, 10.7% (n=6) had experienced two, 3.6% (n=2) had experienced three, and one participant had experienced four events. The most commonly experienced event was witnessing a serious injury (19.6%, n=11), followed by experiencing physical abuse (17.9%, n=10), and experiencing sexual abuse (14.3%, n=8).

The mean self-reported cognitive functioning score at baseline as measured by the FACT-Cog sum score was 74.62 (standard deviation = 20.63). Individuals with childhood trauma exposure had significantly lower FACT-Cog sum scores than those without childhood trauma ($t=2.09$, $p=0.04$). Individuals with childhood trauma exposure had significantly lower FACT-Cog subscale scores for perceived cognitive abilities ($t=-2.09$, $p=0.04$) and between-group differences approached significance for perceived cognitive impairments ($t=-1.87$, $p=0.06$). Individuals with and without trauma did not differ on mental health covariates. However, self-reported cognitive functioning was significantly negatively correlated with insomnia as measured by the Insomnia Severity Index ($r=-0.50$, $p<0.001$) and anxiety as measured by the STAI-State subscale ($r=-0.45$, $p<0.001$).

Modeling perceived cognitive functioning

To test hypothesis 1, we regressed the FACT-Cog sum score onto the dichotomous variable for childhood trauma exposure, controlling for age, college education or higher (dichotomous), time since last chemotherapy treatment, depression, anxiety, and insomnia. Childhood trauma exposure was significantly associated with self-reported cognitive functioning as measured by the FACT-Cog sum score in this multivariate model ($\beta=-0.22$, $p=0.04$). Anxiety and insomnia were also independently associated with cognitive functioning, while age, education, time since chemotherapy treatment, and depression were not significantly associated with cognitive functioning.

In an exploratory analysis, we tested for moderation of the effect of exposure to traumatic events in childhood by education, anxiety, or insomnia, using interaction terms. None of the interactions between other factors and exposure to traumatic events in childhood were significant.

To test hypothesis 2, we examined the sample statistics of individuals with and without childhood trauma exposure and compared differences in cortisol patterns. Among the seven cortisol-related candidate mediators, the two groups showed statistically significant differences in waking cortisol (Log cortisol T1: d=0.75, p=.010) and in the cortisol slope between morning and evening (SlopeLogT1T3: d=0.68, p=.019). We additionally examined college education, anxiety, depression and insomnia as possible mediators. Among these, only college education showed difference between those with and without trauma (χ^2=4.30, p=0.04). As these three candidate mediators (waking cortisol, cortisol slope between morning and evening, college education) met the eligibility criteria for mediators, we proceeded with the next step of mediation analysis.

To conduct mediation analysis in line with the MacArthur approach, we used a linear regression model treating self-reported cognitive functioning as the outcome (Kraemer et al., 2008). We tested log-transformed waking cortisol, the diurnal slope between the waking and evening time cortisol, and college education (dichotomous yes/no) as potential mediators of the effect of childhood trauma on cognitive functioning. These models were run independently, in keeping with the MacArthur approach (Kraemer et al., 2008). We also included trauma and the interaction between trauma and the candidate variables in the model as predictors. In this final model, only the cortisol slope between morning (waking) and evening (9:00 pm) was identified as a potential mediator. The estimated correlation between cognitive functioning and the cortisol slope between morning and evening (with the outcome conditional on the other predictors in the model) was significant (partial r=0.35, p=0.02), meaning that the cortisol slope meets the analytical criteria for a mediator assuming that temporal precedence holds.

Discussion

In this present study we found a significant relationship between exposure to childhood trauma and self-reported cognitive functioning in a sample of breast cancer survivors following treatment. In addition to childhood trauma, education, anxiety, and insomnia were also significantly related to cognitive functioning. The relationship between childhood trauma and cognitive functioning remained significant even after controlling for age, education, time since chemotherapy treatment, insomnia, anxiety, and depression. These results suggest that childhood trauma may play an important role in cognitive functioning experienced after cancer treatments and should be taken into consideration in developing interventions and support services for this population.

The present study is novel in its examination of cortisol as an explanatory mechanism for the effects of childhood trauma on cognitive functioning in breast cancer survivors. Results of our study suggest that those who had experienced trauma had significantly higher morning cortisol levels and steeper cortisol slopes than those who had not experienced trauma. In

regression analyses predicting cognitive scores, steeper diurnal cortisol slopes found in the trauma group were significantly related to poorer self-reported cognitive functioning. As such, our data suggest that traumatic experiences during childhood may result in changes in cortisol response that continue into adulthood, which may in turn be associated with more significant perceived cognitive difficulties.

Our findings of a significant association between poor self-reported cognitive functioning and stress in early life are consistent with previous literature suggesting that trauma experienced during childhood can be detrimental to neurological development and, thereby, impact cognitive functioning (Lupien et al., 2009), even in non-clinical samples of healthy adults (Majer, Nater, Lin, Capuron, & Reeves, 2010). Interestingly, in this sample of breast cancer survivors, the relationship between trauma and cognitive functioning was mediated by a *steeper* diurnal cortisol slope. Such findings are in contrast to previous research studies that implicated *flatter* cortisol slopes in populations exposed to trauma (Heim, Ehlert, et al., 2000; Yehuda, 1997). This finding is consonant, however, with research showing that a steeper cortisol slope indicates a more pronounced stress response in the context of medical illness (Edwards et al., 2003; Ferguson, 2008). The inconsistent link between cortisol slope, stress, and trauma has been the subject of scientific discussion for decades (Abercrombie et al., 2004; Heim, Ehlert, et al., 2000; Lupien et al., 2009; Yehuda, 1997). Part of the difficulty in establishing a consistent base of evidence regarding cortisol can be attributed to lack of consistency in measurement methods used (e.g., blood, saliva, or urine), interpretation of data, and implications of findings (Levine, Zagoory-Sharon, Feldman, Lewis, & Weller, 2007; Pollard, 1995). Conceivably, cognitive functioning difficulties may not be attributable directly to the steepness or flatness of the cortisol slope, but instead to how the overall system responds to a particular endogenous or exogenous challenge. The findings of the current study on cortisol in the context of cancer should be replicated to better assess the impact of stress response on cognitive function among cancer survivors exposed to childhood trauma.

Though the lack of longitudinal data makes causal relationships impossible to determine, the relationship between dysregulated diurnal cortisol slopes and impaired cognitive functioning following cancer diagnosis and treatment may be the result of a preexisting vulnerability due to exposure to childhood trauma (Lupien et al., 2009; Miller, Chen, & Zhou, 2007). In that regard, trauma should be considered, among other factors, in treatments aiming to address difficulties with cognitive functioning in cancer population. Future research should assess mechanisms leading from trauma exposure to cognitive functioning difficulties and possible intervention approaches. For example, interventions may place greater emphasis on enhancing cancer survivors' coping strategies (specifically using cognitive behavioral techniques). Such interventions have been shown not only to effect psychological and emotional well-being in breast cancer patients, but also to alter physiological functioning, including HPA functioning (Luecken & Compas, 2002). Such interventions may also be beneficial for cancer survivors who have experienced childhood trauma.

Limitations

There are several limitations to the study. First, the structure of the original study from which these data were drawn limits both generalizability and power. Our relatively small sample size of breast cancer survivors was selected on the basis of insomnia symptoms and may be different from breast cancer survivors in general. While we are unable to state, given our data, whether these results might be replicated in a population without any sleep problems, current research suggests that sleep problems are ubiquitous in this population, with over two-thirds of breast cancer survivors suffering from chronic sleep disturbance (Palesh et al., 2013; Palesh et al., 2012). Our small sample size also limits our power to detect statistically significant associations between exposure to childhood trauma and other psychological outcomes, such as depression and anxiety. We were unable in this dataset to measure the impact of particular types and dosages of chemotherapy on cognitive functioning. Participants also self-reported both their trauma history and their cognitive functioning. Recall bias may impact self-report of trauma experiences, particularly self-report of childhood trauma by adults. Our measure of cognitive functioning was derived from a subset of items from the FACT-Cog, and so may not match established norms and is best treated as a general indicator of cognitive functioning. Standardized and objective measures of cognitive functioning would allow for a more nuanced assessment of various domains of cognition, and should be implemented in other studies in this area.

Although is impossible to draw causal inferences in this research, our hypotheses are based on plausible findings from previous research studies in non-cancer populations. The results of the current study should be cautiously interpreted as initial support for our hypothesis that childhood trauma affects cortisol secretion, and that this physiological dysregulation is associated with lower cognitive functioning. Future research should use temporal precedence and repeated measures of cortisol and cognitive functioning to more accurately determine longitudinal relationships. Furthermore, researchers should replicate current findings with cortisol data collected throughout a 24-hour time period, as our cortisol samples were only collected during the daytime. Cortisol can behave differently throughout the day and night, and thus collecting samples throughout a 24-hour day on multiple occasions will strengthen the accuracy of cortisol test data.

Overall, the current study indicates that childhood trauma exposure is uniquely associated with self-reported cognitive functioning among breast cancer survivors. Future studies should further investigate the complex relationship between trauma and HPA axis dysregulation and explore interventions that could address exposure to childhood trauma in this patient population. This study could serve as a stepping stone for future observational research and treatment studies to consider exposure to childhood trauma as a potential marker for poor cancer-related outcomes among breast cancer survivors.

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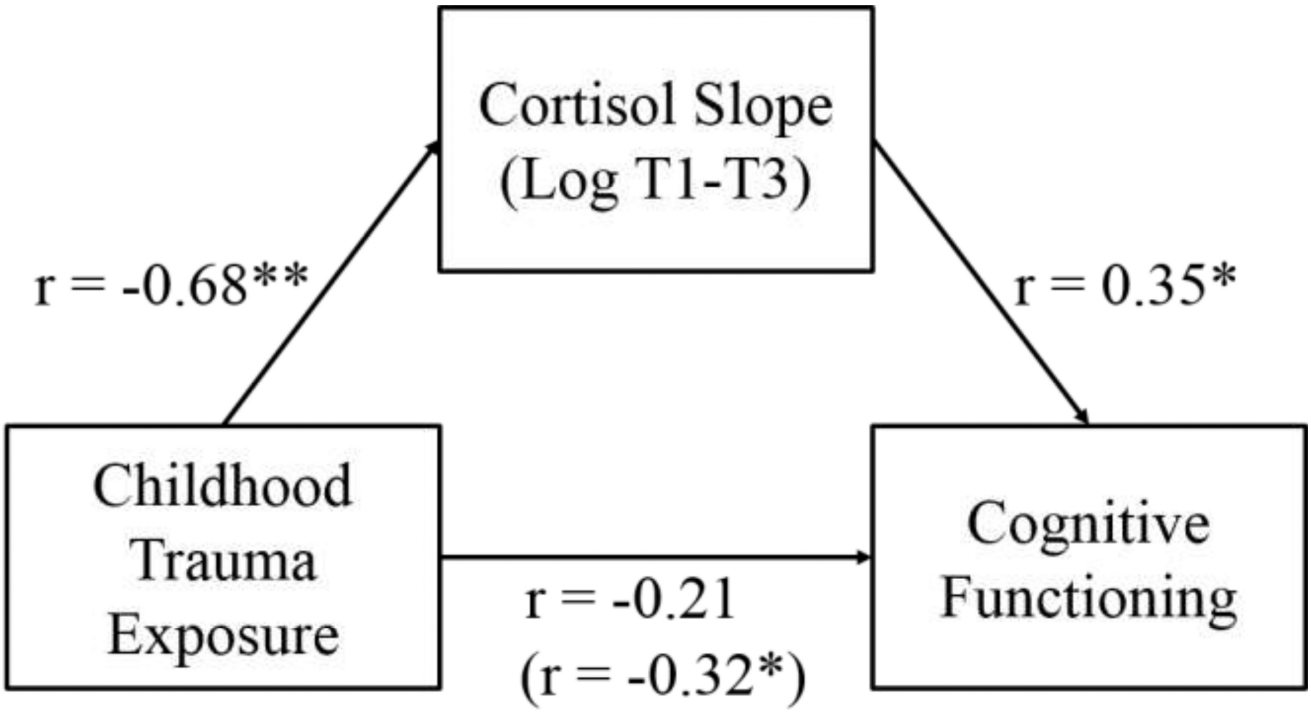

Figure 1.

Mediation of the relationship between childhood trauma exposure and cognitive functioning by cortisol slope (n=56).

Note: All standardized associations are presented as correlations. * statistically significant at the 0.05 level; ** statistically significant at the 0.01 level.

Table 1

Survivor demographics at baseline (n=56).

Age, M (SD)	53.6 (9.8)
Education, n (%)	
Graduate training	21 (37.5%)
Standard college/university	22 (39.3%)
Partial college or less	13 (23.2%)
Household income, n (%)	
<$20,000–$59,999	7 (12.5%)
$60,000–$99,999	13 (23.2%)
>$100,000	35 (62.5%)
Missing	1 (1.8%)
Employment status, n (%)	
Disability Leave	1 (1.8%)
Retired	16 (28.6%)
Employed	16 (28.6%)
None of the above	23 (41.1%)
Marital status, n (%)	
Married & living with spouse	44 (78.6%)
Divorced	6 (10.7%)
Widowed	1 (1.8%)
Long-term committed relationship	3 (5.4%)
Single	2 (3.6%)
Race, n (%)	
White	53 (94.6%)
Asian/Asian American	2 (3.6%)
Other	1 (1.8%)
Ethnicity, n (%)	
Hispanic or Latino	2 (3.6%)
Not Hispanic or Latino	54 (96.4%)
Stage, n (%)	
DCIS	9 (16.1%)
I	11 (19.6%)
II	23 (41.1%)
III	9 (16.1%)
IV	2 (3.6%)
Missing	2 (3.6%)
Weeks since chemotherapy, M (SD)	235 (225)

Table 2

Sample means (and standard deviations) of study measures by childhood trauma exposure (n=56).

Variable	Total (n=56)		Trauma (n=32)		No Trauma (n=24)		t-test	Cohen's d
Cognitive functioning (FACT-Cog)	74.13	(20.57)	68.80	(21.90)	80.79	(16.93)	p=0.03	−0.60
Insomnia (ISI)	13.70	(3.83)	13.72	(3.93)	13.67	(3.77)	p=0.96	0.01
Depression (CES-D)	8.27	(7.51)	7.91	(7.86)	8.75	(7.15)	p=0.68	−0.11
Anxiety (STAI)	30.32	(8.91)	30.84	(10.08)	29.63	(7.20)	p=0.62	0.14
Log Cortisol T1	−1.41	(0.55)	−1.24	(0.53)	−1.63	(0.49)	p=0.01	0.75
Log Cortisol T2	−1.10	(0.59)	−1.01	(0.46)	−1.22	(0.73)	p=0.26	0.34
Log Cortisol T3	−3.48	(0.59)	−3.55	(0.60)	−3.39	(0.58)	p=0.33	−0.28
Slope (LogT1–T2)	0.57	(1.03)	0.44	(0.78)	0.74	(1.29)	p=0.35	−0.28
Slope (LogT2–T3)	−0.18	(0.05)	−0.18	(0.05)	−0.17	(0.05)	p=0.25	−0.33
Slope (LogT1–T3)	−0.14	(0.05)	−0.16	(0.05)	−0.13	(0.03)	p=0.02	−0.68
AUC (LogT1,T2,T3)	−32.11	(6.78)	−32.38	(7.04)	−31.77	(6.62)	p=0.76	−0.09

Abbreviations: THQ = Trauma History Questionnaire; FACT-Cog = Functional Assessment of Cancer Therapy – Cognitive; ISI = Insomnia Severity Index; CESD-D = Center for Epidemiologic Studies – Depression; STAI = State-Trait Anxiety Inventory; T1 = waking cortisol before getting out of bed; T2 = 30 minutes after awakening; T3 = 9:00 pm; AUC = area under the curve.

Table 3

Simultaneous linear regression predicting variance in cognitive functioning (n=56).

Variable	B	SE B
Age	0.28	0.24
Education	5.61	5.41
Weeks since chemotherapy	>0.01	0.01
Depression	0.16	0.32
Anxiety	−0.87**	0.26
Insomnia	−2.08**	0.60
Childhood trauma exposure	−10.16*	4.28
	$R^2 = 0.47$**	

Abbreviations: SE = Standard error

Note:

* statistically significant at the 0.05 level;

** statistically significant at the 0.01 level.

Table 4

Simultaneous linear regression testing mediation of the relationship between childhood trauma exposure and cognitive functioning by cortisol slope (n=56).

Predictors of Cognition	Association (r)	p-value
Trauma	−0.210	0.17
Cortisol Slope (LogT1–T3)	0.352	0.02
Trauma × Slope (LogT1–T3)	−0.079	0.61

Abbreviations: T1= waking cortisol before getting out of bed, T3= cortisol collected at 9pm.