



Research article

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.

1. 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

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(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; Meinschmidt & 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; Septho, Sapolsky, Kraemer, Spiegel, 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.

2. Methods

2.1. 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

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