

Review Article

Cancer, coping, and cognition: a model for the role of stress reactivity in cancer-related cognitive decline

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Abstract

Background: Cognitive decline and accompanying neurological changes associated with non-CNS cancer diagnosis and treatment have been increasingly identified in a subset of patients. Initially believed to be because of neurotoxic effects of chemotherapy exposure, observation of cognitive decline in patients not treated with chemotherapy, cancer-diagnosed individuals prior to treatment, and patients receiving alternative treatment modalities (surgery, endocrine therapy, and radiation) has led to the investigation of additional potential etiologies and moderating factors. Stressful experiences have long been posited as a contributor to these cognitive changes. Through reciprocal connectivity with peripheral systems, the brain maintains a dynamic circuitry to adapt to stress (allostasis). However, overuse of this system leads to dysregulation and contributes to pathophysiology (allostatic load). At this time, little research has been conducted to systematically examine the role of allostatic load in cancer-related cognitive dysfunction.

Methods and Results: Here, we integrate theories of stress biology, neuropsychology, and coping and propose a model through which individuals with a high level of allostatic load at diagnosis may be particularly vulnerable to the neurocognitive effects of cancer.

Conclusions: Opportunities for future research to test and extend proposed mechanisms are discussed in addition to points of prevention and intervention based on individual variation in stress reactivity and coping skills.

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Introduction

A large body of evidence using subjective reports and neuropsychological testing points to enduring subtle but significant neurocognitive changes in a subset of individuals diagnosed with and treated for cancer that can negatively impact an individual's functional ability and quality of life [1]. These cognitive changes are consistent with neurophysiologic changes, including cortical atrophy as well as decreased neuronal density and connectivity in critical brain regions [2,3]. Originally referred to as 'chemobrain', this constellation of biobehavioral alterations, including, but not limited to, problems in attention, concentration, learning, memory, and mental speed, was attributed to the potential neurotoxic effects of chemotherapy exposure during the course of cancer treatment. Evidence has been found for neurotoxic effects of chemotherapy, but these effects do not fully account for all neurocognitive changes in individuals with cancer [4]. Variability exists in neuropsychological profiles for individuals exposed to particular chemotherapeutic regimens, with only approximately one third of patients actually

exhibiting cognitive effects [5]. Further, findings for cognitive changes across non-CNS cancer types (e.g., breast, prostate, and leukemia) and multiple treatment modalities (e.g., chemotherapy, radiation, and hormonal therapy) have led to the suggestion that such cognitive changes would be better referred to as 'cancer-associated or cancer-therapy associated cognitive change' [6] to better address what is likely a multifactorial etiology beyond solely the neurotoxicity of chemotherapeutic agents. Notably, several recent studies observe below expected performance on cognitive tests [7] and related neurological changes [8] in patients before treatment commences, lending support to premorbid vulnerability to neurocognitive alterations in this population.

To date, research on cancer-related cognitive decline has focused primarily on treatment effects to the exclusion of the vast literature recognizing the neurocognitive effects of stress and dysregulation of stress reactivity systems. While the brain maintains a dynamic circuitry through reciprocal connectivity with the body to adapt to stress, overuse of this system has been shown to result in dysregulation known as

'allostatic load' and contributes to pathophysiology. Here, we propose a model through which individuals with a history of chronically stressful experiences may possess heightened allostatic load at the time of their cancer diagnosis (Figure 1). We propose that psychophysiological changes to prefrontal regions as a result of allostatic load, which may be reflected in below expected pretreatment performance in a subset of patients, can serve as a 'double-hit', promoting a recursive cycle of stress axis disruption and hindering cognitive resources underlying adaptive coping with cancer stress. This process can be exacerbated by disease and treatment effects and ultimately increases a patient's risk for deleterious long-term physical, cognitive, and psychosocial outcomes.

Chronic stress and allostatic load

The brain is a dynamic system that coordinates behavioral and physiological responses to stress using reciprocal signaling with the rest of the body. Because of the fluctuating demands of the internal and external environment, this stress reactivity system functions through 'allostasis', an active process of maintaining homeostasis. The distributed network involved in stress adaptation encompasses a multitude of systems (i.e., hypothalamic–pituitary–adrenal (HPA) axis, autonomic nervous system, gut, kidneys, and the immune system) and biomediators (i.e., cortisol, sympathetic/parasympathetic mediators, cytokines, and

metabolic hormones). For example, when the biological stress-response cascade of the HPA axis is activated by perception of a stressor, cortisol as well as adrenalin circulate systemically and prepare the individual to address the stressor in a 'fight or flight' response. Through a negative feedback loop, glucocorticoids bind to receptors in pituitary, hypothalamus, cortical, and limbic regions, promoting changes in neural activity, cognition, and mood-related behaviors and signaling the shutoff of the cascade once the threat has been addressed. While such allostatic mechanisms are finely tuned to help the individual meet the demands of acute threats, they lack the capacity to respond effectively to prolonged and repetitive psychological stressors, which may, in turn, lead to overactivity and dysregulation of the nonlinear network of allostasis. When mediators of adaptation and survival are overused with respect to their normal balance, 'allostatic load' can result and contribute to pathophysiology [9]. In the case of the HPA axis, for example, a 'healthy' diurnal cycle involves a steep, early morning rise in cortisol, followed by a consistent decline over the course of the day, allowing for brief periods of reactivity and adaptation to acute stress. However, the presence of allostatic load can be marked by a flattened, elevated level of cortisol that does not allow for environmental or situational flexibility [9] and is linked to neurocognitive dysfunction and deleterious effects on physical health.

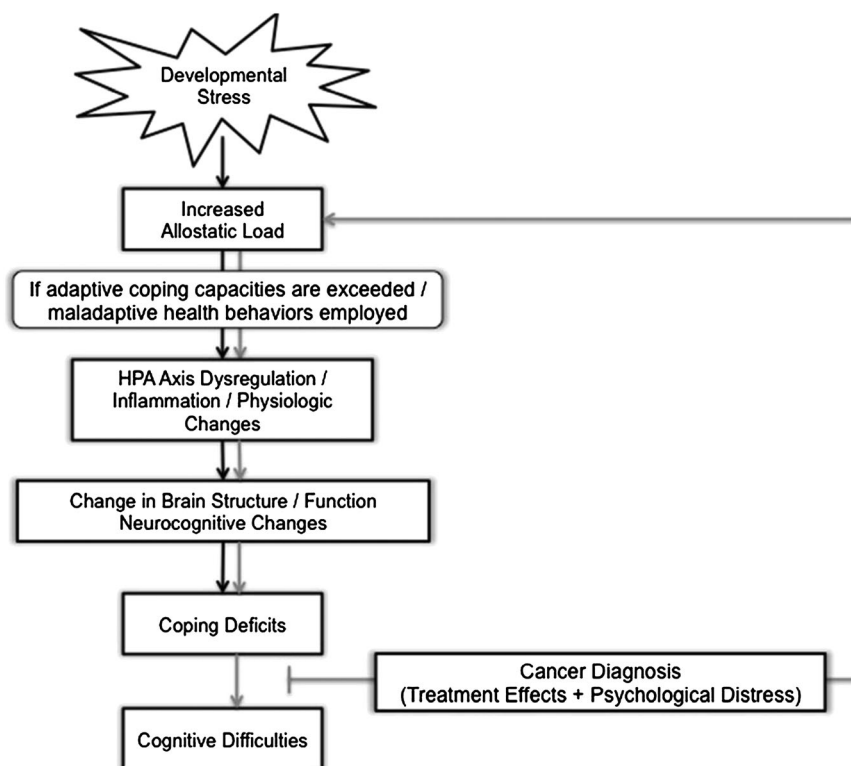


Figure 1. Development stress promoting heightened allostatic load may result in diminished cognitive resources underlying adaptive coping with cancer stress and increased risk for cancer-related neurocognitive sequelae

The HPA axis and brain plasticity

Research using animal models has provided significant insight into the effects of chronic stress on the functioning of the specific biological cascade of the HPA axis and resulting downstream neurocognitive effects. These studies suggest that prolonged or repeated activation of the HPA axis, along with release of excitatory amino acid transmitters, leads to neuronal atrophy in the prefrontal cortex and hippocampus and hypertrophy of neurons in the amygdala and orbitofrontal cortex, a pattern linked to increased anxiety [10].

Significantly, medial regions of the prefrontal cortex are acutely affected by allostatic load [11]. These regions are responsible for critical aspects of higher order attention, such as gating and overcoming distraction, which require reciprocal interactions between prefrontal inhibitory control processes and sensory encoding by both cortical and subcortical structures [12]. For example, prefrontal regions may upregulate focus on a specific representation or stimulus quality and retain goal-relevant information while avoiding environmental noise [13]. These cognitive control abilities may thus be particularly sensitive to the effects of chronic stress exposure.

Both animal and human studies link the experience of stress with neurocognitive changes. Using a rodent model, Liston *et al.* [10] found that chronic restraint stress was associated with changes in dendritic morphology in the orbitofrontal cortex, which was related to deficits in attentional set shifting. A subsequent study by Liston and colleagues [11] provided evidence of a similar process in humans. In this study, medical students studying for an important exam performed a task of selective attention while undergoing functional neuroimaging. High levels of reported stress were related to disruptions in prefrontal networks that underlie attentional processing as well as diminished behavioral performance on attentional tasks.

Further, associations between biomarkers of allostatic load and human brain morphology have been reported. For example, diurnal cortisol patterns have been associated with hippocampal volume [14, for review], with higher daily cortisol output characteristic of increased allostatic load linked to decreased hippocampal size [15]. In addition, increased diurnal cortisol levels have been found to be related to reduced prefrontal cortical thickness [16], suggesting associations between chronic stress-related patterns of HPA axis dysfunction and cortical structure in regions underlying higher level cognitive abilities.

Consistent with observed relations between HPA axis function and brain morphology, a significant association has been found between glucocorticoid levels and the cognitive functions subserved by these regions, for example, Abercrombie *et al.* [17]. For example, cortisol levels are related to memory ability, with effects in learning, recall, and retention over time. Contradictory evidence for

enhancement versus impairment of function currently exists in the literature, suggesting the presence of factors that modulate the link between the neuroendocrine stress-response system and cognition [18]. Research in animal and human models suggests an inverted U-shape curve representing the relation between dose of corticosteroids and several cognitive abilities [19]. Under conditions of acute stress and short-term affective arousal, the HPA axis becomes activated, and low to medium levels of glucocorticoids enhance cognition [20]. Nevertheless, high levels of circulating glucocorticoids acutely suppress excitability and impair memory and attention [21]. In sum, chronic activation of the HPA axis, along with elevated excitatory neuronal activity, causes atrophy of prefrontal and hippocampal neural architecture and decreased memory and attentional abilities [22].

HPA axis dysregulation resulting from repeated or prolonged activation is a major contributor to cognitive deficits associated with chronic stress exposure. However, additional physiological and behavioral processes can also enhance allostatic load. When attempting to cope with stress, an individual may actively engage in health-damaging behaviors, such as alcohol consumption, tobacco use, or a change in diet, or may modify health-promoting behaviors, such as sleep and social connectedness, and neglect regular exercise, in ways that are detrimental [23]. While these lifestyle factors involved with an individual's attempt to deal with stress are part of allostatic adaptation, they can have deleterious effects on the brain, often because of both immediate neurological effects as well as the downstream sequelae of chronic diseases that they promote. The current Western diet, for instance, especially when combined with a sedentary lifestyle, increases risk for type II diabetes. Smoking promotes cardiovascular disease. Both diseases have known neurocognitive effects impacting cognition [24,25]. Disrupted sleep [26] and psychosocial isolation [27] as a result of feeling 'stressed out' more directly impair neurocognitive function. A high level of allostatic load at the time of cancer diagnosis from cumulative HPA axis dysregulation, and environmental and lifestyle factors may thus confer an increased vulnerability to further cancer-related and cancer treatment-related stress and neurocognitive effects.

Cancer as a stressor

The experience of a cancer diagnosis and treatment exemplifies the type of stressor that would draw on the body's evolutionary based stress reactivity systems. The diagnosis and ensuing existential anxiety involving concerns about death represent acute stressors for many patients [28], and as treatment is initiated, several successive long-term psychological and physical stressors often arise. For example, patients with breast cancer,

especially those diagnosed at younger ages, report experiencing significantly higher levels of financial and job-related stress because of insufficient sick leave, lack of psychosocial support, and continuous pain or discomfort compared with their healthy counterparts [29]. Protracted, often multiphase treatments and ongoing uncertainty about prognosis can serve as additional physical and psychological stressors with chronic effects.

The psychological stress of cancer diagnosis and treatment has been reflected in biological measures of heightened allostatic load [30]. Several studies of women with breast and ovarian cancer suggest elevated basal cortisol levels and decreased acute cortisol reactivity in these patients, even those in current remission, compared with their healthy counterparts [31]. The biology of the cancer disease process itself [32], as well as several common cancer treatments, may also contribute to allostatic disruptions [33, for review]. Platinum-based chemotherapies, high-dose steroids, and as radiotherapy protocols [34] can impact HPA axis function, altering circulating levels of glucocorticoids [35]. While the mechanism through which the HPA axis can be dysregulated in individuals with cancer is likely multifold, patterns of elevated diurnal cortisol levels, including decreased acute reactivity, are related to poor sleep quality and disrupted circadian rhythms [36], fatigue [37], and depressive symptoms [38], all factors that can exacerbate cognitive difficulties.

Few studies have been conducted to date on the potential effects of diurnal cortisol rhythm and reactivity on cognition specifically in patients with cancer [31,39,40]. Findings from these studies did not support consistent, significant differences in diurnal cortisol rhythms between cancer-diagnosed and healthy control groups or links between cortisol levels and cognitive performance in patients with cancer. However, several study characteristics (e.g., small sample size and substantial variability in other aspects of circadian patterns in patient groups) likely hindered detection of the associations in question. Further, the comparison of group means (i.e., patients versus healthy controls) may have obscured subgroup effects in cognitive function among patients that would be expected given current findings of vulnerable subsets of patients. When Andreano and colleagues [41] specifically examined patients at high risk for HPA axis dysregulation, hypothesized relations between inadequate cortisol reactivity and decreased performance on cognitive tasks were observed.

Coping and cognition

A patient's ability to cope with stress may serve to modulate the psychobiological impacts of stress and cancer treatment and thus shape long-term outcomes. Engagement coping [42], specifically cognitive reappraisal strategies [43], has been shown to contribute to better physical health and psychosocial adjustment, including lower levels of anxiety and depression in patients with cancer. Further, threat

appraisal and subsequent initiation of specific coping strategies have been clearly linked to neuroendocrine responses [44, for review]. While primary and secondary control strategies are associated with reductions in HPA axis disruption in response to stress, disengagement strategies may augment HPA axis disruption, leading to higher ambient cortisol levels [45].

The use of cognitive reappraisal coping strategies calls on several higher level cognitive functions modulated by the prefrontal cortex, including both selective attention and working memory [46–48]. Selective attention is necessary to maintain concentration on essential aspects of the stressor without interference from other information that may be emotionally salient but ultimately irrelevant. Working memory allows for the reframing of the current information in more neutral or positive terms, as the information being held in mind is manipulated [49]. Campbell *et al.* [50] assessed the role of these cognitive functions in coping and psychosocial outcomes in survivors of childhood acute lymphocytic leukemia. Measures of cognitive function were significantly positively correlated with the use of secondary control coping strategies (e.g., cognitive reappraisal) and negatively correlated with emotional and behavioral problems. Further, secondary control coping accounted for the relationship between coping and emotional/behavioral problems. Results from the study suggest that cognitive deficits in domains such as attention and working memory may underlie the use of maladaptive coping strategies leading to poorer psychosocial functioning in cancer survivors. As such, psychophysiological changes to prefrontal regions as a result of allostatic load may serve as a 'double-hit', impeding cognitive resources necessary for adaptive coping with cancer stress, leading to further disruption in stress reactivity systems and deleterious long-term physical, cognitive, and psychosocial outcomes.

A model proposed by Arndt *et al.* [51] explores the interaction of cognitive resources with cancer-related stress in coping and neuropsychological outcomes that is driven by a recursive, feed-forward cycle involving self-regulation and executive function. That is, escalations in cognitive demands during the period of diagnosis and treatment (e.g., remembering novel medication regimens and scheduling medical appointments) may reduce cognitive resources available for cognitive reappraisal during this stressful period. Diminished ability to cope and reduced engagement of adaptive strategies may promote continued psychobiological stress reactivity that fosters stress-related neurocognitive impairments in cortical areas subserving executive function and coping. An initial study by Reid-Arndt and Cox [52] found coping to be a significant mediator of the relationship between stress and neuropsychological outcomes in patients with cancer, confirming active coping to be one mechanism linking cancer stress and neuropsychological outcomes.

Points of prevention and intervention

The proposed role of allostatic load in cancer-related cognitive decline sheds light on multiple points of potential prevention and intervention in individuals diagnosed with and treated for cancer. Cognitive-behavioral interventions have historically been shown to be effective in this population, as a means of directly enhancing an individual's repertoire of adaptive coping skills and relieving distress. Further, these interventions have been linked to reductions in psychobiological markers of allostatic load [53], factors that may ultimately account for enhanced neurocognitive and health-related outcomes in patients [54].

More recently, mindfulness-based programs drawing on complementary techniques, including meditation, yoga, and tai chi, have been shown to be particularly effective in not only reducing distress and improving quality of life but also regulating HPA axis function, restoring normal diurnal cortisol rhythms, improving coping, and decreasing symptoms of anxiety and depression in patients with cancer [55, for review]. Of note, reductions in stress and improvements in cognitive reappraisal abilities related to mindfulness intervention programs were correlated with decreased amygdala volume [56] and mediated reductions in distress and mood improvements [57], respectively. In addition, behavioral interventions specifically targeting exercise are associated with hippocampal volume enlargement and accompanying memory enhancement [58]. Taken together, these results emphasize the importance of HPA axis regulation as well as the preservation and potential enhancement of cognitive control capacities in the prevention of the recursive feed-forward cycle of stress reactivity and neurocognitive decline in patients with cancer. To this end, cognitive remediation paradigms aimed directly at improving cognitive control abilities have been proven successful in ameliorating cancer-related cognitive sequelae, especially in pediatric populations [59, for review]. Such a bottom-up approach may enhance coping abilities through augmentation of underlying cognitive control skills, potentially leading to better HPA axis regulation and long-term psychosocial outcomes.

Each patient brings to the cancer experience his or her own unique developmental history, which may be accompanied by significant individual variability in allostatic load, HPA axis function, and coping ability at the time of cancer diagnosis. According to this proposed model of vulnerability for cancer-related cognitive decline, high levels of preexisting allostatic load from chronic developmental stress as a result of such factors as low socioeconomic status, family instability, and abuse as well as alterations in health behaviors may exacerbate the psychobiological effects of cancer diagnosis and treatment and place these vulnerable patients at particularly high risk for negative neurocognitive and psychosocial sequelae [60]. For these particular subgroups of patients, cognitive-behavioral

therapy with a focus on reappraisal elements might reduce the adverse effects of existing vulnerability and therefore reduce the risk for long-term neurocognitive sequelae.

It is possible based on the model posited here that such patients may be less likely to benefit from cognitive-behavioral therapy because of reduced cognitive control abilities from irreversible allostatic-load-related damage to critical brain regions. However, a large body of research has provided support for effective cognitive-behavioral interventions in populations exposed to significant early stress, suggesting that at-risk individuals are capable of engaging in cognitive reappraisal but may be less inclined to do so without more direct training in coping skills. Early screening for HPA axis dysregulation in individuals receiving a cancer diagnosis may therefore allow for effective prevention and outcome improvement in high-risk populations.

Directions for future research

Self-report measures related to perceived psychological stress have not been consistently associated with performance on neuropsychological measures in patients with cancer [61,62]. However, coping behaviors, especially those that are maladaptive (e.g., alcohol use), may ameliorate or mask self-perceived stress, while still increasing allostatic load. As such, self-reported perceived stress may not be a reliable predictor of biomarkers of stress and allostatic load [63]. Given the potential deleterious effects of heightened allostatic load on individuals with cancer and the multifactorial mechanism of disruption in this population, the links between allostatic load and cancer-related cognitive decline warrant further study. As such, the first step will be in confirming a relation between markers of allostatic load (i.e., HPA axis function) and risk for cancer-related cognitive decline, even in the absence of patient-reported stress. Future research may rely on a multimethod approach, directly measuring biomarkers of diurnal and reactivity processes in newly diagnosed patients as well as long-term survivors. Such an approach may begin to parse how specific elements of HPA axis function (e.g., high baseline, low reactivity, and blunted diurnal cycle) in individuals with cancer are linked to neurocognitive sequelae and CNS pathology. If alterations in stress reactivity profiles are associated with risk for cancer-related cognitive decline as hypothesized by this model, it will be necessary to examine the biological bases of individual variability in stress axis function.

Recent work examining variation in glucocorticoid receptor gene polymorphisms [64] and epigenetic patterns for methylation of glucocorticoid receptor genes may aid in the identification of those individuals who may be at highest risk for cancer-related cognitive decline. That is, individuals with greater methylation of glucocorticoid receptor genes [65], which effectively downregulates coding for glucocorticoid receptors in the brain and further

exacerbates HPA axis dysregulation, may be more likely to exhibit cognitive decline. Conversely, those with specific 'protective' glucocorticoid gene polymorphisms may be less sensitive to the effects of allostatic load and thus less likely to show signs of cancer-related cognitive decline, even if a history of chronic stress prior to cancer diagnosis is present [66]. These studies will potentially provide additional targets for molecular pharmacological interventions in the future.

Finally, coping strategies likely act as a protective factor for individuals at high risk for cancer-related cognitive decline and may be the most easily addressed point of preventative intervention. As such, therapies aimed at augmenting patients' repertoires of adaptive coping skills and reducing deleterious

health-related behaviors (i.e., smoking, alcohol use, sleep cycle disruption, and social isolation) may not only help directly with psychosocial adjustment but also have been demonstrated to directly affect brain structure and function [67] and can thus assist in regulating the HPA axis, improving long-term neurocognitive and health outcomes. Such interventions would be a highly effective and feasible next step in reducing cancer-related cognitive decline morbidity and improving survivors' quality of life.

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