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REVIEW ARTICLE

Emotional distress, brain functioning, and biobehavioral processes in cancer patients: a neuroimaging review and future directions

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Despite emerging evidence that distress and adversity can contribute to negative health outcomes in cancer, little is known about the brain networks, regions, or circuits that can contribute to individual differences in affect/distress states and health outcomes in treated cancer patients. To understand the state-of-the-science in this regard, we reviewed neuroimaging studies with cancer patients that examined the associations between negative affect (distress) and changes in the metabolism or structure of brain regions. Cancer patients showed changes in function and/or structure of key brain regions such as the prefrontal cortex, thalamus, amygdala, hippocampus, cingulate cortex (mainly subgenual area), hypothalamus, basal ganglia (striatum and caudate), and insula, which are associated with greater anxiety, depression, posttraumatic stress disorder (PTSD) symptoms, and distress. These results provide insights for understanding the effects of these psychological and emotional factors on peripheral stress-related biobehavioral pathways known to contribute to cancer progression and long-term health outcomes. This line of work provides leads for understanding the brain-mediated mechanisms that may explain the health effects of psychosocial interventions in cancer patients and survivors. A multilevel and integrated model for distress management intervention effects on psychological adaptation, biobehavioral processes, cancer pathogenesis, and clinical outcomes is proposed for future research.

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Key words: Brain functioning, cancer biobehavioral model, emotional distress, neuroimaging, stress-related biobehavioral pathways and cancer progression.

Introduction

A cancer diagnosis with a life-threatening prognosis is an event that forces people to confront their own mortality and find ways to negotiate uncertainty about the disease and their future.[1,2] Facing this new reality and the treatments required for curing or controlling cancer involves a series of complex and dramatic challenges and changes in the lives of individuals and their families, as well as the social context in which they live. These changes can affect the physical, psychological, social, spiritual, and existential dimensions of a person's life.[3–7] They can also have a major impact on their well-being and quality of life.[8–13]

Cancer patients face and must strive to master many challenges across their disease trajectory. These include loss of health, uncertainty about the future, threat of possible death, physical symptoms and limitations, emotional instability (eg, fear, anxiety, worry, sadness, despair), loss of control and autonomy, the need to rely on others, and the change of perspective toward the future. These stressors may be more or less intense and lead to increased suffering for patients and their families, further contributing to the emotional distress associated with cancer.[14] A substantial number of cancer patients and survivors experience high levels of cancer-related distress (30–45%),[15] mainly anxiety and depression.[16–18] For example, a study conducted in Italy, Portugal,

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and Spain, which sought to identify patients' psychosocial needs and psychological morbidity associated with cancer, indicated that about one-third of cancer patients had clinically significant levels of anxiety (33.08%), and about one-quarter had clinically significant levels of depression (24.81%). Over one-quarter of patients (28.2%) had general psychological morbidity.[16]

Despite the well documented psychosocial challenges of cancer and its treatment, and their potential impact on cancer progression and negative health outcomes,[19] relatively little is known about the brain networks, regions, or circuits that can contribute to the individual differences in affect/distress states and their health consequences in treated cancer patients. Identifying specific brain regions and networks that are sensitive to fluctuations in psychological states and interventions during cancer treatment can provide insights into the "hard-wiring" of a biobehavioral model of cancer, and may guide the development of more targeted psychosocial, behavioral, and pharmacological interventions to optimize psychological functioning/adaptation, quality of life, and health outcomes in cancer patients and survivors.

We provide a review of neuroimaging studies relating changes in the metabolism or structure of specific brain regions or networks with negative affect or distress states in cancer patients and integrate this with growing evidence that distress may hasten disease progression via biobehavioral pathways governed by several of these brain regions or networks. First, we consider the brain regions and pathways implicated in stressor appraisals in the context of the illness uncertainty construct. Second, we review neuroimaging studies that correlate negative affect with alterations in the function and structure of the brain in cancer patients and summarize the key brain regions and networks that might be involved in emotional distress in cancer patients and which should be included in studies that investigate brain-mediated biobehavioral processes, cancer progression, and clinical outcomes. Third, we summarize evidence for a multilevel integrative analysis of biobehavioral processes in cancer research, linking affective, behavioral, and biological factors with cancer progression once a tumor has been established, in the context of contemporary biobehavioral models in the field. Fourth, we present results from studies about the effects of psychological interventions on biobehavioral processes and clinical outcomes in cancer patients. Finally, we discuss some of the issues involved in this line of research and propose a multilevel and integrated model for distress management intervention effects on psychological adaptation, biobehavioral processes, cancer pathogenesis, and clinical outcomes. This model can guide future directions by illuminating the mechanisms underlying the effects of distress management interventions to improve outcomes in cancer patients observed to date, and targeting psychosocial, behavioral, and pharmacological interventions to modulate specific brain-mediated biobehavioral processes and health outcomes going forward.

Distress and the Brain

The search for the neural basis of affect has fueled numerous studies in the neuroimaging literature.[20,21] One area of research is related to how perceived stress (ie, subjective or personal meanings) impacts the brain in ways that influence multiple systems of the body.[22,23] Studies in the psychophysiology of psychological stress usually follow Lazarus's model based on the cognitive appraisal theory.[24] He proposed that stress responses result from 2 types of meanings: (a) meanings about environmental, social, or bodily changes (threats), and (b) meanings about the personal or social resources to cope with the threat. A stress response results when the threat-related meanings tax or exceed the individual's perceived coping resources. From the point of view of psychophysiology, the question is, how does psychological stress translate into physiological effects or disease? Or, in other words, what are the brain–body pathways linking subjective interpretation of stressors to health effects?

Brain regions and pathways implicated in stressor appraisals

In the context of medical conditions, one particularly salient cognitive appraisal construct—illness uncertainty—has been proposed as a common phenomenon characterizing the experience of a life-threatening or chronic diseases, like cancer.[25–28] Illness uncertainty includes appraisals such as the ambiguity and unpredictability of the disease course and prognosis, issues related to treatment complexity, and lack of information regarding the illness and treatment. The brain–body pathways related to meanings of uncertainty were recently described by Peters et al.[23] Accordingly, a stress response results when the person perceives environmental changes and she/he is uncertain of a strategy that can be used to protect physical, mental, or social well-being. This appraisal process (ie, what is threatening to the individual) is originated in the brain after receiving both sensory and viscerosensory inputs. The lateral prefrontal cortex (lPFC), pre-supplementary motor area (pre-SMA), ventromedial prefrontal cortex (vmPFC), and orbitofrontal cortex (OFC), respectively, are where the subjective meanings about the current state of the world and the body seem to be represented.[23]

How are physiological, behavioral, cognitive, and emotional responses initiated following the appraisal of the perceived stressor? In accordance with this model, the anterior cingulate cortex (ACC) "makes" the risk assessment of a certain state and selects a strategy. If this strategy "resolves" the current state of uncertainty, the pre-SMA and primary motor cortex initiate the respective

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behavioral response. If the individual has a state of uncertainty about what has to be done and the situation (ie, changes in the internal body or the external environment) remains threatening, the ACC stimulates the amygdala (Amg), which increases Locus coeruleus (LC), sympathetic nervous system (SNS), and hypothalamic–pituitary–adrenal axis (HPA axis) activity; this initiates the biological stress response. The ACC-Amg complex is crucial since it stimulates 2 important descending projections: (1) the pathway to the LC, which releases norepinephrine, which then causes a hypervigilant state, increasing "attention"; and (2) the pathway to the ventromedial hypothalamus (Hy) and the paraventricular nucleus, stimulating SNS and HPA axis, secreting glucocorticoids (cortisol in humans) from the adrenal cortex and epinephrine from the adrenal medulla in response to stress.

Physiological sequelae of stress responses

Both acute and chronic stress alter brain structure and function and can produce peripheral changes in the cardiovascular, immune, and endocrine systems.[29-32] The brain is considered the key organ of the response to stress, because it determines both the meaning of the threat and the physiological and behavioral responses.[33] Two key stress-response subsystems mediating these effects are the autonomous nervous system (ANS) and the HPA axis.[34] Moreover, as was referred to above, the brain complex formed by the ACC and the Amg has a main role in the initial activation of these subsystems.[23] A study with rhesus monkeys supports the crucial role of ACC, particularly the subgenual area, in HPA output.[35] Jahn et al.[35] suggested that individuals with elevated activity in the subgenual anterior cingulate cortex (sgACC) may show heightened cortisol levels and may be at risk for stress-related HPA dysregulation.

Processing of stressful events is, thus, mediated by the nervous system, which regulates physiology through the "participation" of the immune, neuroendocrine, and autonomic systems. These brain–body pathways linking cognitive (stressor) appraisal processes to changes in brain structure and function, and reactions in the cardiovascular, immune and endocrine systems, may increase risk for physical disease or may aggravate existing disease. According to the *uncertainty stress model*, some brain regions are proposed as having a key role in the stress response, such as the LC, insula (Ins), prefrontal cortex (PFC), cingulate cortex (CC) (mainly the ACC and the subgenual area), and Amg. Neuroimaging studies in a variety of medical populations have now accrued to the point that one can observe reliable patterns of association between distress states and changes in the structure and functional activity of specific brain regions and networks. One subset of these studies in cancer patients that has examined the association of distress states with brain activity has identified specific brain regions that overlap with those proposed in the *uncertainty stress model*. This research is reviewed below.

Distress and the Brain in Cancer Patients

Neuroimaging studies that correlated negative affect with alterations in brain activity in cancer patients started in 1999[36] and were inspired by the studies that investigated the association between major depression and the structure and functioning of brain regions in healthy persons.[37-41] These seminal neuroimaging studies used mainly resting state (ie, when patients are not focusing on any particular thought or task/stimulus) or task-based positron emission tomography (PET), magnetic resonance imaging (MRI), or functional resonance imaging (fMRI) to distinguish between patients with major depression and healthy controls in terms of the structure and function of hypothesized brain regions.[42-46] More recent studies use other types of neuroimaging, such as diffusion tensor imaging (DTI), to assess the integrity of the white matter tracts that connect regions of the brain. We based our synthesis of brain regions involved in depression in cancer patients using existent reviews of the larger body of research on depression.[37-39,47-49] These key regions include the PFC, thalamus (Th), Amg, hippocampus (Hi), CC (mainly subgenual ACC), basal ganglia (striatum and caudate), and Ins, which are coincident with most of the key brain regions proposed by the uncertainty stress model as being involved in the stress response. As will shown below, these brain regions overlap with key brain regions related to emotional distress in cancer patients.

To identify studies that used neuroimaging techniques for studying the effects of depression and other distress states in cancer patients, we conducted a search with PubMed, Google Scholar, and *Psycho-Oncology Journal*, up until April 2018, using key terms including "distress," "negative affect," "neuroimaging," "PET," "MRI," "cancer," "anxiety," "depression," and "trauma." The term "cancer" was always present in the search specifications (eg, "depression" and "PET" and "cancer"). Bibliographies were also reviewed for further citations. We limited our search to studies in humans and published in English. We found a total of 13 papers. Eleven were published between 1999 and 2008, one in 2015, and another in 2016.

Table 1 presents a list of these studies with reference to aim, distress/negative affect measures, brain regions that showed metabolic or structural alterations related to distress, and sample size of cancer patients and controls. The studies in this review utilized one of 2 neuroimaging techniques: (1) functional neuroimaging with fludeoxyglucose (^{18}F) positron emission tomography (^{18}F-FDG-PET) to examine the association between

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TABLE 1. Neuroimaging studies examining the association of emotional distress with brain metabolic activity and volume changes in cancer patients

Ref. number	Aim	Distress/negative affect measures	Main findings	Sample size of cancer patients and controls
36	To assess influences of psychological factors on the rCMRglc of patients with cancer.	Self-rating Depression Scale (SDS).[57]	Hypometabolism: anterior and posterior cg, basal ganglia, insular cortex, dlFC, and OFC.	19 patients with several types of cancer vs 17 control inpatients with ophthalmopathy who were free from other physical or mental problem. Cancer patients with depression (n = 4).
54 (A replication of the previous study)	To assess influences of psychological factors on the rCMRglc of patients with cancer.	Self-rating Depression Scale (SDS)[57] and Taylor's Manifest Anxiety Scale (MAS)[58].	Hypometabolism: anterior and posterior cg, basal ganglia, insular cortex, dlFC, and OFC.	20 patients with several types of cancer vs 10 control patients with chronic hepatitis. Cancer patients mildly depressed (n = 15).
53	To investigate the relationship between rCMRglc and different clinical phases of malignant diseases (pre-treatment, post-treatment, recurrence and terminal) and possible associations with distress.	Measures were not available due to retrospective nature of the PET study.	Hypometabolic levels constantly low in all phases: orbitofrontal, basolateral prefrontal, and ventral anterior cingulated cortices and Ins; metabolic levels that fluctuate: prefrontal, anterior cingulated, and posterior cingulated cortices, subcortical nuclei.	77 patients with several types of malignant diseases vs 17 control inpatients with benign diseases.
52	To investigate influences of depressive states on the rCMRglc of cancer patients.	Self-rating Depression Scale (SDS).[57]	Hypometabolism: bilateral frontal cortex, bilateral anterior and posterior cingulate gyri, bilateral temporo-parietal cortex, left Ins, anterior temporal cortex, and basal ganglia.	21 patients with several types of cancer vs 10 control patients with a benign peripheral disease. Cancer patients with depression (n = 7).
55	To explore neurobiological risk factors for major depressive disorder and adjustment disorder in cancer patients by examining rCMRglc before psychiatric manifestation.	Hospital Anxiety and Depression Scale (HADS).[63] All the patients were assessed by a psychiatrist for psychiatric symptoms.	Hypometabolism: right medial frontal gyrus. Hypermetabolism: right posterior cingulate, right anterior cingulate, left sgACC, and left caudate gyri.	44 patients with various types and severity of cancer. Patients that developed MDD or AD (n = 10).
51	Investigate the relationship between trait anxiety, relative rCMRglc, and natural killer cell activity.	Taylor's manifest anxiety scale (MAS)[58] and Self-rating Depression Scale (SDS).[57] Natural killer cell activity (NKA) was measured using a blood sample taken from each patient just prior to injection of FDG.	Positive correlation between NKA and rCMRglc: left visual association cortex, right anterior cg, left posterior parietal cortex and primary sensorimotor area; negative correlation between NKA and rCMRglc: the inferolateral PFC, bi-lateral PFC, left OFC, Ins, and anterior temporal cortex. Positive correlation of anxiety with rCMRglc: left visual association cortex, left primary sensorimotor cortex, right anterior cg and left posterior parietal cortex; and negatively correlated with rCMRglc in the right inferolateral PFC, left PFC, left OFC, and anterior temporal cortex.	8 cancer patients with various types of malignant diseases (lung, breast, esophageal, prostate, colon, and thyroid).
56	To examine the rCMRglc in pancreatic cancer patients with a depressive episode after their cancer diagnosis and before their cancer treatment.	Structured Clinical Interview for DSM-IV-Axis I Disorder to determine whether the subjects had a depressive episode; The Hamilton Depression Rating Scale;[59] Impact of Event Scale-Revised[185] and the State and Trait Anxiety Inventory.[60]	Hypermetabolism: sgACC.	21 cancer patients. 6 had depressive episode after pancreatic cancer diagnosis. 2 had major depressive episodes, and 4 had minor depressive episodes.

(*Continued*)

TABLE 1. (*Continued*)

Ref. number	Aim	Distress/negative affect measures	Main findings	Sample size of cancer patients and controls
61	To investigate the associations between the Distress Thermometer scores and rCMRglc of structures involved in stress response.	Distress Thermometer and HADS	The DT scores were positively correlated with rCMRglc in the hypothalamic and midbrain areas immediately below the Th, especially the periventricular areas. Physical Problems score were positively correlated with activity in the same areas as the DT, but the clusters extended to additional areas, including caudate, Th, globus pallidus, putamen, bilateral Amg, Hi, para-Hi, high pons, and medulla. Emotional Problems subscores were positively associated with the activity in four clusters: the Hy, the midbrain in front of the right Amg, the upper pons, and the medulla. DT scores were the best predictor, among all the other clinical and demographical variables, of the hypothalamic metabolism.	21 cancer patients: lymphoma (n = 15; 71%; 12 non-Hodgkin and 3 Hodgkin subtype); other diagnoses (n = 6; 29%; one ovarian, one bladder, 3 lung and 1 rectal).
50	To investigate abnormalities in resting-state metabolic brain networks using graph analysis in pre-chemotherapy cancer patients characterized by depression relative to matched normal controls.	Beck Depression Inventory (BDI)-II.[71]	Depression severity was negatively correlated with PFC (left inferior frontal gyrus), Th and cuneus metabolic levels and positively correlated with regional metabolic activity in the parietal, limbic, and temporal lobes, such as the rolandic operculum, Hi, and para-Hi, Ins, and Amg. Topological organization of whole-brain metabolic networks may be disrupted in cancer and that this disruption may be more disrupted in cancer patients with comorbid states of emotional distress such as depression.	78 pre-chemotherapy cancer patients with depression vs 80 matched healthy non-depressed subjects. Cancer patients: 44 reported minimal depression (score 1-13, X = 6; SD = 3); 16 mild depression (score 14-19, X = 15; SD = 1) and 18 moderate/severe depression (score 20-63, X = 26; SD = 6).
72	To determine the association between distressing cancer-related recollections, regarded as a component of PTSD and hippocampal volume.	Distressing cancer-related recollections based on a modification of criterion B1 of the PTSD module in DSM-IV: "recurrent and intrusive distressing recollections of the cancer-related event, including images, thoughts, or perceptions with a duration of 1 month or more" and assessed by psychiatrists.	Smaller left Hi volume.	67 women who had had breast cancer surgery 3 or more years earlier. 28 (42%) met the criteria for a history of distressing cancer-related recollections. 39 participants without any such a history.
73	To assess the possibility of structural alteration of the Amg in cancer survivors with intrusive recollections.	Same as previous study.[72]	Smaller Amg volume.	35 breast cancer survivors with a history of cancer-related intrusive recollections vs 41 breast cancer survivors who had no such history.

(*Continued*)

TABLE 1. (*Continued*)

Ref. number	Aim	Distress/negative affect measures	Main findings	Sample size of cancer patients and controls
74	To investigate the association between hippocampal volume and a first major depressive episode after cancer diagnosis in cancer survivors.	Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), by a trained psychiatrist.	No differences in Hi volume.	68 female breast cancer survivors who had undergone breast cancer surgery 3 or more years earlier. 17 (25%) met the criteria for major depressive episode after cancer diagnosis.
75	To investigate the association between PFC and Amg volumes and a first minor or major depressive episode after cancer diagnosis in cancer survivors.	Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I), by a trained psychiatrist.	Smaller left Amg volume in patients with a first minor and/or major depressive episode. No brain region volume in the PFC was significantly different among the three groups.	51 female breast cancer survivors. 11 had a first minor depressive episode and 11 had a history of a first major depressive episode after cancer diagnosis.

Notes: **rCMRglc**: regional cerebral metabolic rate of glucose; **Th**: thalamus; **Ins**: insula; **Hy**: hypothalamus; **cg**: cingulate gyrus; **Hi**: hippocampus; **OFC**: orbitofrontal cortex; **Amg**: amygdala; **PFC**: prefrontal cortex; **sgACC**: subgenual anterior cingulate cortex.

distress and alterations in regional cerebral metabolic rate of glucose (rCMRglc)[1]; and (2) structural neuroimaging with MRI to determine changes in the volume (enlargement or atrophy) of certain brain regions suggesting a chronic functional abnormality.

Distress and brain function (^{18}F-FDG-PET studies)

The studies presented in Table 1 aimed to assess associations between distress (depression and/or anxiety) and rCMRglc in specific brain regions of patients with various types of cancer. Only 1 study[50] examined the association of distress with the metabolism of brain networks.

Most of studies were conducted by the same team of researchers.[36,51–56] The participants were cancer patients with various types of cancer, and the control group was composed of patients with benign diseases. To assess levels of distress (anxiety and/or depression), investigators used questionnaires or interviews such as the Self-Rating Depression Scale,[57] Taylor's Manifest Anxiety Scale,[58] Structured Clinical Interview for DSM-IV-Axis I Disorder, Hamilton Depression Rating Scale,[59] and the State and Trait Anxiety Inventory.[60] Across all these studies the brain regions that revealed abnormal metabolism in cancer patients in association with higher distress scores were the OFC, Ins, posterior and ACC, Th, and basal ganglia.

A study by another team[61] used the National Comprehensive Cancer Network's Distress Thermometer (DT)[62] and the Hospital Anxiety and Depression Scale (HADS)[63] to assess levels of distress in 21 patients with various types of cancer. The DT has been adopted internationally as a screening measure to identify and address psychological distress in individuals with cancer. The study provided provocative evidence that distress levels assessed by the DT were the best predictor, among all the other clinical and demographic variables, of hypothalamic metabolism, a key indicator of the HPA axis. Specifically, DT scores were positively correlated with rCMRglc in the hypothalamic and midbrain areas immediately below the Th, especially the periventricular areas. In fact, the hypothalamic metabolism was the best indicator to classify patients as distressed according to the DT cut-off score of 4.

Another line of neuroimaging research examines the association of distress with the metabolism of brain networks as opposed to specific brain regions. This follows emerging views in neuroscience that emotional processes

[1]Fluodeoxyglucose is an active tracer molecule, an analogue of glucose, that is injected into the blood, and the concentrations of this tracer will indicate tissue metabolic activity. Thus, ^{18}F-FDG-PET images will reflect measures of the regional cerebral metabolic rate of glucose uptake (rCMRglc), which reflects cerebral activity, when the uptake decreases reflects less cerebral activity, and when uptake increases reflects more cerebral activity.

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are a function of the whole brain and that research should consider the biological organization in the brain, operationalized as large-scale distributed networks.[64–67] From this perspective, brain structures such as the Amg or the Ins function within a complex network of other brain structures with which they are connected. Accordingly, many neuroimaging studies now aim to examine the properties of whole-brain networks using a graph perspective.[68] For example, "nodes" are distinct brain regions and "edges" represent functional connectivity among them. Many conditions, such as depression,[69,70] can be described not only as influencing the function and structure of specific brain regions but also as "dysconnectivity" syndromes: disrupting the connectivity patterns among spatially distributed regions of the brain that support normal functioning.

In one recently published connectivity study,[50] researchers examined abnormalities in resting-state metabolic brain networks using graph analysis in pre-chemotherapy cancer patients with depression (n = 78; 44 had minimal depressions, 16 mild depressions, and 18 moderate/severe depressions) relative to matched healthy non-depressed normal controls (n = 80). The hypothesis was that cancer patients would show altered "small-world properties" and "topological architecture" in the metabolic brain network. Specifically, investigators examined differences in regional metabolism in cancer patients vs controls, and the potential association between regional hypo-metabolism and severity of depression symptoms, assessed by the Beck Depression Inventory (BDI-II).[71] The whole brain was segmented into 90 regions (45 regions in each hemisphere) to construct a metabolic brain network. Metabolic connections were defined as statistical associations in normalized glucose metabolism between each possible pair of brain regions (metabolic connectivity aims to detect functionally interacting brain regions based on rCMRglc). Four global network properties (clustering coefficient, characteristic path length, small-world attribute, and connectivity patterns) and one regional nodal property (betweenness centrality) were combined to investigate the topological architecture of the metabolic brain network in control and cancer groups. Possible whole-brain metabolism differences between cancer patients and healthy subjects were evaluated on a voxel-by-voxel basis.

The main results were separated into 4 areas:

1. *Regions of abnormal glucose metabolism in cancer patients vs controls*: a significant decrease in metabolism in cancer patients in the right inferior temporal gyrus, left middle frontal gyrus, left fusiform gyrus, right Th, caudate nucleus, left superior temporal gyrus, Ins, right postcentral gyrus and left superior frontal gyrus, which suggests that the brain networks of cancer patients had declining global efficiency, or the brain regions had less neuronal activity.
2. *Correlation between depressive symptoms and metabolism in specific brain regions*: Depression severity was negatively correlated with PFC (left inferior frontal gyrus), Th, and cuneus metabolic levels and positively correlated with regional metabolic activity in the parietal, limbic, and temporal lobes, such as the rolandic operculum, Hi, para-Hi, Ins, and Amg. It was suggested that these metabolic abnormalities associated with depression might affect processing in the whole-brain network and thereby influence the social and emotional impairments in the daily life of cancer patients.
3. *Global network measures in cancer patients vs controls*: The strength of connectivity[2] was lower in many brain regions in the parietal and frontal lobes in cancer patients, which predominantly belonged to long-range connectivity. These changes in connectivity might lead to an increase in regional efficiency and long path length disruption in cancer.
4. *Regional network measures in cancer patients vs controls*: Cancer patients displayed decreased connectivity (nodal betweenness centralities[3]) in several regions of frontal, temporal, and limbic lobes, including the triangular part of the inferior frontal gyrus, the orbital part of the middle frontal gyrus, the olfactory cortex, the Heschl gyrus, the caudate nucleus, the bilateral Hi, the right para-Hi, the Amg, and the ACC. According to the researchers, this pattern might lead to lessened outflow to the thalamus and fusiform gyrus and subsequent hypometabolism in cancer patients. Increased nodal betweenness centralities in cancer patients were mainly located in the middle frontal gyrus, Ins, superior occipital gyrus, and pallidum, and were positively correlated with activity in others (Amg and Hi).

It was concluded that the topological organization of whole-brain metabolic networks may be disrupted in cancer and that this disruption may be more severe in cancer patients with comorbid states of emotional distress such as depression.

Distress and brain structure (MRI studies)

Another set of studies[72–74] investigated the correlations between distress states and anatomical changes of neural structures based on the assumption that chronic functional abnormality might be associated with morphological

[2]Connectivity strength is a global measure of functional connectivity and is represented as the strength of the association between each pair of nodes in a graph.

[3]Betweenness centrality is the fraction of all shortest paths in the network that pass through a given node.[185]

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abnormalities. Two studies[72,73] examined the association between distressing cancer-related recollections (DCRR), regarded as a component of posttraumatic stress disorder (PTSD), and hippocampal and Amg volume, respectively, in breast cancer (BCa) patients. In the first study, 67 patients revealed DCRR versus 39 without, and, in the second, 35 BCa patients had DCRR versus 41 without. In the first study, the volume of the left Hi was significantly smaller in the subjects with a history of DCRR. In the second study, the same authors found that the total (left and right) volume of the Amg was significantly smaller in patients with DCRR vs those without, even after controlling for age, height, and major depressive disorder.

Two other MRI-based studies[74,75] examined associations between hippocampal, PFC, and Amg volumes and a first major depressive episode (MDE) after cancer diagnosis in female cancer survivors who had undergone BCa surgery 3 or more years earlier. One of these studies (n = 68; 17 with MDE) showed no significant differences in the left or right hippocampal volumes of cancer survivors who did and did not experience a first MDE after cancer diagnosis. The other study (n = 51; 11 with MDE) showed that left Amg volumes in patients with a first minor and/or MDE were significantly smaller than in those with no incident of depressive episode, though there were no significant differences in the volume of the Hi among groups, which is consistent with the results of previous work.[74] Thus, the authors suggested that Amg volume was associated with a first minor and/or MDE after cancer diagnosis, which is similar to the findings noted above for DCRR.

Thus, this set of studies utilizing MRI to determine changes in the volume (enlargement or atrophy) of certain brain regions associated with distress (depression or intrusive thoughts) suggested that among diagnosed cancer patients, distress may be associated with reduced left Hi and Amg volumes. Interestingly, these 2 regions were referred to, in functional neuroimaging studies, as being involved in metabolic abnormalities in cancer patients with distress.

Conclusions from the review

Strengths

The findings of these structural and functional neuroimaging studies with cancer patients suggest that "distress" factors may relate to changes in function and structure of specific brain regions and networks. While chemotherapy and paraneoplastic factors also affect the brain, the effect of psychological factors may be independent of these.[76] There are multiple points of convergence in the findings reported in the studies reviewed. First, the key brain regions identified by these neuroimaging studies were similar to those demonstrated in previous imaging studies of non-cancer patients with major depression[76] and with those proposed in the *uncertainty stress model*. Second, distress states appear to be associated with the metabolism of brain networks in cancer patients, in studies suggesting that depression might affect processing in the whole-brain network. Third, the severity of depressive symptoms was associated with metabolic activity in brain regions overlapping with those referred to in the other studies with cancer patients, such as the Amg, ACC, Hi, Ins, PFC, and Th. Interestingly, these key brain regions are all included in the brain regions of an important brain network: the *interoceptive network* (that is made up of 2 overlapping networks: the *salience network* and the *default mode network*).[65,66,77] As will be shown below, this network has crucial functions, such as the control of body metabolism (eg, cardiac output, breathing rhythm, cortisol release) and interoception, which refers to the sensing of the internal state of one's body.[78] Moreover, this network regulates the autonomic, neuroendocrine, and immune systems, and, as such, its dysregulation may be involved in some physical illnesses such as cancer, on the one hand, and mood disorders on the other.[66]

Based on the areas of convergence in these studies, we can enumerate key brain regions that potentially might be involved in emotional distress processes in cancer patients. We think that it is reasonable to propose the interoceptive network as a key brain network that should be included in studies investigating brain-mediated biobehavioral processes (Figure 1).

Curiously, neuroimaging studies about the effects of psychotherapy in the brains of depressed persons have observed changes in many brain regions that overlap with most of those proposed in Figure 1, such as the ACC, prefrontal cortices, Hi, and Amg.[79] As we will note below, cognitive-behavior therapy (CBT), a specific model of psychotherapy commonly used with cancer patients, is associated with changes in the activity of the interoceptive system, which may be a critical consideration in studying the brain mechanisms underlying the effects of such interventions on emotional distress and related biobehavioral processes of cancer patients going forward.

Limitations

Despite the provocative findings across this body of work with cancer patients, there are some limitations that should be considered when interpreting these results and should be considered in future studies. One recurring issue is sample size and statistical power. An important task in planning a neuroimaging study is to calculate the statistical power and determine an adequate sample size.[80] No study presented that calculation. In general, the sample size in these neuroimaging studies is small, as was recognized by some of the authors, which can

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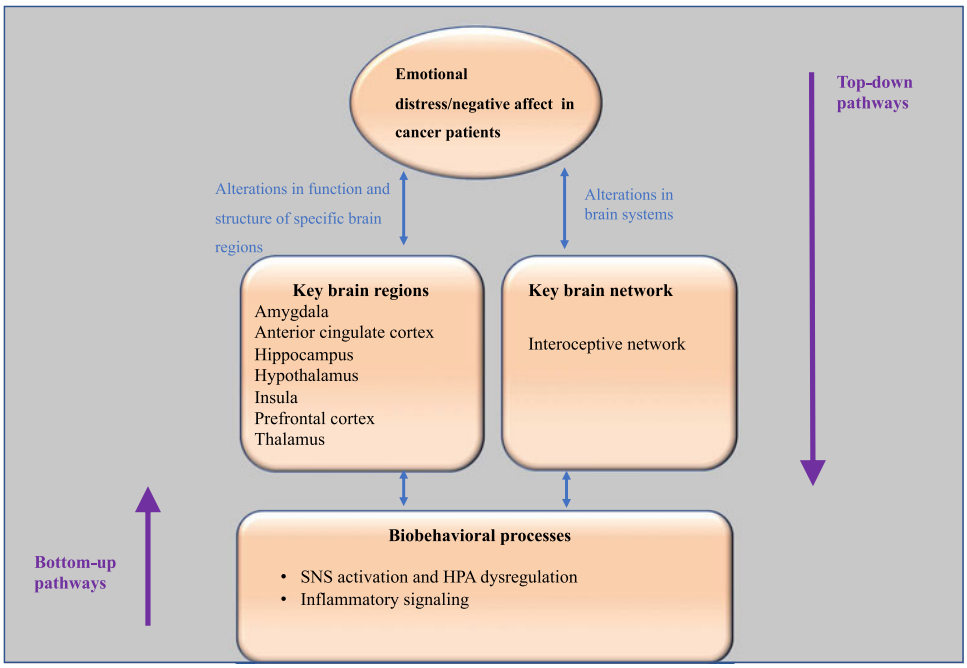

FIGURE 1. Key brain regions and brain systems that potentially might be involved in emotional distress processes in cancer patients. These brain regions and the interoceptive network, are involved in the regulation of autonomic, neuroendocrine and immune systems and, as such, its dysregulation may be involved in some physical illnesses such as cancer, on the one hand, and mood disorders on the other.

undermine the results and increase the likelihood of Type II errors.[81]

Another issue is clinical heterogeneity of cancer patients. Many of the samples investigated across the neuroimaging studies reviewed were composed of multiple groups, each having different types and stages of cancer and, consequently, distinct types of treatment. This is a major limitation because these different treatments (eg, chemotherapy, radiation therapy, surgery, hormone therapy, immunotherapy) can produce different effects in the brain and in other body systems.[82–84] These are confounding variables. Comparing subgroups of patients (eg, depressed versus nondepressed) for differences in brain function and structure when using heterogeneous types and stages of cancer receiving different treatments may complicate the interpretation of results and limit their applicability to specific populations of cancer patients going forward. Future neuroimaging work should focus on patients within specific types and stages of cancer in order to confirm preliminary findings.

Finally, the neuroimaging studies reviewed here examined the associations between distress-related phenomena (including PTSD symptoms, anxiety and depression disorders) and several brain regions in diagnosed cancer patients. Thus, these psychophysiological studies represent a "top-down" approach since they analyzed the effects of psychological phenomena on neural processes in the brain without consideration of peripheral changes that were occurring contemporaneously (eg, inflammation), and which could act as "bottom-up" influences on psychological state and brain activity. Only 1 study added another level of variables: the measurement of immune system functioning (ie, natural killer cells).[51] The limitations of this top-down approach are introduced next and at the same time we propose an integrative model of research of biobehavioral processes in cancer.

Toward a Multilevel Integrative Analysis of Biobehavioral Processes in Cancer Research

Top-down and bottom-up pathways

The top-down paradigm, although it can produce leads and hypotheses for further studies, is restrictive in relation to all the variables and body systems that are involved in adaptation to cancer. To date we have a very limited knowledge about the brain changes that account for the influence of distress in cancer processes. This information could ultimately inform the development of theoretically driven distress management behavioral interventions, which could contribute to enhanced clinical cancer care and improved health outcomes. Studies in this research area should progress to a paradigm that includes multilevel integrative analyses and in which the formulation of structure–function relationships should integrate "top-down" and "bottom-up" information,[85] that is, the study of bidirectional mind–body interactions, including behavioral and social factors, brain activity and structure, neural peripheral systems, and the endocrine and immune systems.

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Brain networks and body metabolism

The *executive homeostatic network* was proposed to explain the bidirectional bottom-up and top-down pathways between "mind" and body and is an example of an integrative model.[86] In this network, and in a simplified description, the bottom-up pathways have their influence via parallel ascending projections within the spinal cord and brain. Vagal sensory pathways and spinal visceral and somatic sensory pathways provide information regarding inflammation, pain, and other important conditions to regulatory brain regions including the Hy and Th, which ultimately reach components of the executive homeostatic network, comprised of the ACC, PFC, and insular cortex. Accordingly, information regarding bodily states gives rise to the experience of symptoms associated with illness and injury.

In turn, top-down pathways influence bodily functions via modulation of sympathetic, vagal, spinal, and adrenal output, which may interact with peripheral tissue, including immune and tumor cells in the circulation and the tumor microenvironment, via neuroendocrine (norepinephrine (NE), epinephrine (E), and cortisol) ligands. Changes in the state of these cells (eg, inflammation) can feed back to the brain (bottom-up), for instance, via cytokines. For example, interleukin-1 (IL-1) receptors were found in the Hi and Hy and brain stem.[87] This cytokine has an important role in memory loss and suppressed neural plasticity in cases of infection, injury, and severe emotional distress.[88] Empirical evidence indicates that that there is communication between peripheral cytokines and cytokines inside the central nervous system (CNS) that stimulate neuronal and supportive cells to release cytokines in the brain.[89-91] Cytokines produced in those brain areas activate the HPA axis and SNS, participating in a network of reverberating feedback loops within and between the multiple levels of brain–body system (eg, peripheral sensory-to-brain-to-peripheral-sensory).

More recently this network was called the *interoceptive network*.[65,77] As noted previously, distress-related brain regions (Amg, ACC, Hi, Hy, Ins, PFC, and Th) are included in this important network. In fact, it includes (1) cortical regions, such as the CC, medial PFC (including both the ventral and dorsal sectors), anterior Ins, mid- and posterior Ins (primary interoceptive cortex), inferior frontal gyrus, supplementary motor cortex, superior temporal sulcus and temporal pole, and the parahippocampal gyrus; and (2) subcortical regions, such as the Amg, ventral striatum, Th, Hy, periaqueductal gray (PAG), parabrachial nucleus (PBN), and nucleus tractus solitarius.[65] These brain regions are proposed to constitute the functional and anatomical substrates of an allostatic-interoceptive system, that is, a system that continually anticipates the body's energy levels and demands, and prepares to meet those needs before they arise.[77]

Considering the brain as a predictive internal model of the world, in which mental events are generated as predictions, not reactions,[92] the cortical regions that are the substrates of the allostatic-interoceptive system make visceromotor predictions through their connections to the Hy, the periaqueductal gray (PAG), and other brainstem nuclei (eg, PBN, Nucleus Tractus Solitarius (NTS)), which control the body's internal milieu to regulate the autonomic, neuroendocrine, and immune systems.[65]

Thus, this allostasis model assigns a central role to the brain, considered an organ for predictive regulation. Contrary to the classical model in which the regulation of the internal milieu is based on the preservation of its constancy (homeostasis), in allostasis the maintenance of an efficient regulation requires anticipating needs and preparing to satisfy them before they arise.[93] These brain predictions are top-down influences. Bottom-up influences are ascending sensory inputs from the body's organs and systems (eg, levels of insulin or cortisol, heart rate, inflammatory cytokine levels), which are interoceptive sensations about the state of the body.[77] When body metabolism is chronically unbalanced, like when individuals are chronically anticipating a threat (anxiety) or loss (depression), having chronic perceptions of social adversity, or other experiences that may accompany cancer diagnosis and treatment, the brain might regularly predict that individuals need more energy than their body requires. This can cause a problem: these predictions, based on a chronic "false" alarm, cause the body to release hormones, like cortisol, which over time promotes leukocyte glucocorticoid receptor resistance[94] and exacerbates inflammatory signaling, causing a vicious cycle in prediction.[66,93] Dysregulation within the interoceptive system may be involved in some physical illnesses and mood disorders as well, since they share a common neural substrate.[77]

Interestingly, as noted previously, CBT, a therapeutic intervention designed to modify cognitive appraisals in order to improve affect and behavior, is associated with changes in the activity of the interoceptive system, such as decreased activity in agranular cortex in depression[95] and enhanced ACC activity and decreased activity of the insular cortex, dorsolateral prefrontal cortex (dlPFC), and Amg in PTSD.[96] These changes in the activity of brain regions of the interoceptive network accompanying CBT may, in part, explain the effects of psychosocial interventions on psychological adaptation, stress-related biobehavioral processes, and disease progression in cancer patients.[6] This follows from the notion that the interoceptive system not only controls the body's internal milieu to regulate the autonomic, neuroendocrine, and immune systems but is also the main source of our phenomenology and feelings.[66,97]

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Interoception and sickness behaviors

Interoception refers to the perception of autonomic, hormonal, and immunological homeostatic signals that describe the physiologic state of the body.[77,98,99] Interoceptive information is conveyed to the CNS through spinal, cranial, and humoral homeostatic pathways[100,101] and is integrated with learned associations, memories, and emotions, creating a subjective experience (ie, feeling).[99] Thus, feelings are subjective experiences that accompany a change in body state[66,97] and have an intensity and a valence (positive or negative, pleasant or unpleasant, or neutral), influencing motivation.[66] The experience of unpleasant feelings resulting from a change in a body state can be illustrated by immune-to-brain communication, namely the neural and humoral pathways that transduce immune signals through mediators called pro-inflammatory cytokines, from the periphery (bottom-up influences) to brain regions such as the nucleus of the tractus solitarius, PBN, the hypothalamic paraventricular and supraoptic nuclei, central Amg, and the bed nucleus of the stria terminalis.[102]

These cytokines include IL-1α, IL-1β, TNF-α, and IL-6, and are responsible for a constellation of behaviors called *sickness behaviors*, which influence emotion[103] through motivational changes that include anhedonia, reductions in social affiliative behavior, and irritability.[102,104] Thus, when we get a viral or bacterial infection, and possibly cancer, we experience symptoms (eg, sad, nauseated, reduced appetite and motivation). These cytokines may induce depressive symptoms and are also associated with compromised cognitive performance (eg, impaired attention and short-term memory).[102,105] In fact, there is evidence for the crucial role of cytokines in mediating the effects of cancer itself and cancer-related therapy on cognitive dysfunction (ie, the subjective experience when one has deficits in his or her cognitive function) and cognitive impairment (ie, objectively measured cognitive deficits).[106] This post-treatment cancer-related cognitive dysfunction or impairment has been called "chemobrain" due to the attribution of these symptoms to chemotherapy. However, chemobrain may be caused by multiple factors such as cancer itself, chemotherapy, secondary medical conditions (ie, comorbidities), and emotional distress, which may affect patient cognition and brain function and structure.[107] In fact it has been proposed that chemobrain would be more accurately labeled "cancer- or cancer-therapy-associated cognitive change."[108] One can view chemobrain symptoms as a type of sickness behavior in cancer patients, and one that may be mediated by inflammatory signaling. The role of pro-inflammatory cytokines has been enlightened, indicating their crucial role in bottom-up and top-down influences occurring in chemobrain syndrome.[109] Actually, there is evidence that underlying chemobrain cognitive dysfunction are peripheral cytokines that stimulate neuronal and supportive cells that signal the release of central cytokines, which act to alter neuronal plasticity and brain functioning,[106,109] which, in turn, affects peripheral biobehavioral processes such as the activation of the HPA-axis, resulting in the production of high levels of cortisol to down-regulated immune activity.[88]

Some brain areas and networks were proposed as being associated with chemobrain and some (CC, PFC, and Hi) overlap with distress-related brain regions. A review of breast cancer chemotherapy-related cognitive dysfunction studies found evidence for reduced connectivity in the default mode network (DMN), suggesting that the cognitive dysfunction may represent a brain network disorder and that altered DMN activity may serve as a potential biomarker of chemotherapy-related brain injury.[110] This network includes brain regions such as the precuneus, posterior cingulate, medial frontal, middle temporal, and lateral parietal regions, as well as Hi,[111] and is part of the interoceptive network, which can indicate that this network can be also potentially disrupted.

A review[112] of structural and functional neuroimaging chemobrain studies concluded that although there were many contradictory results across studies, there was a convergence in some findings in cancer patients: (1) a diffuse decrease of gray matter (GM) and white matter (WM) volume together with a decrease of the overactivation in frontal regions in chemotherapy-treated patients compared to controls and (2) a long-term persisting decrease in GM and WM volumes together with a predominantly frontal cortex hypoactivation in only a subgroup of chemotherapy-treated patients. However, due to the complexity of chemobrain syndrome and the multiple factors involved, more studies are needed to better understand the mechanisms underlying the cognitive changes reported by cancer survivors.[108]

In conclusion, there are bidirectional bottom-up and top-down pathways between brain and the periphery that allow the communication among bodily systems in an integrated way. The research about the effects of psychological and emotional factors on peripheral stress-related biobehavioral pathways known to contribute to cancer progression and long-term health outcomes should progress to a more integrative analysis. Developing novel ways to integrate data from psychosocial assessments, neuroimaging studies of brain functioning, and peripheral indicators of neuroendocrine and immune/inflammatory processes will be key to the development of this line of work. The next logical step is to examine the association of distress and affect-related brain region activity with these peripheral immunologic processes relevant for the pathophysiology of cancer, in order to determine the relevance of specific brain regions and networks in

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the progression and/or metastasis of cancer. Establishing an evidence base for brain regions that are predictive of biobehavioral processes and disease outcomes may be relevant for future cancer research. As will be presented next, there is a growing body of evidence, in the field of psychoneuroimmunology (PNI), showing that distress and other indicators of adversity are associated with SNS- and HPA-mediated biobehavioral processes that contribute to biological activities that can promote cancer growth and metastasis.

Contemporary Biobehavioral Models in Cancer Research

Concepts and applications

The last decade has produced substantial evidence that psychosocial variables like distress, depression, lack of social support, and trauma history are associated with biological alterations that could promote cancer progression.[6,113,114] While there is some evidence for the contribution of these distress-related biobehavioral factors to cancer initiation,[114] there is a stronger evidence base for links between such biobehavioral factors and cancer progression once a tumor has been established.[113,114] Biobehavioral factors affect cellular immunity and modulate fundamental processes in cancer growth, such as inflammation, angiogenesis, invasion, and metastasis.[114]

Studies documenting bidirectional communication among the different body systems (psychosocial, neural, neuroendocrine, and immune) have been reported over the last 4 decades in the field of PNI,[115] a research domain that has more recently been applied to cancer research.[116,117] A growing body of PNI work has demonstrated that the interaction between psychosocial processes (eg, interpretation of events, social support, negative affect), sociodemographic factors (eg, sex, age, race, ethnicity, socioeconomic status), and health behaviors (eg, sleep, diet, exposure to viruses, screening behaviors) may influence cancer progression, treatment-associated symptoms, recovery, and survival after treatment, as well as long-term quality of life.

PNI research has identified some of the processes underlying these connections involving neuroendocrine (eg, cortisol and norepinephrine changes) and immune/inflammatory mechanisms (eg, using measures of leukocyte cytokine and chemokine gene expression and circulating pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α). This body of work has been used to generate multiple biobehavioral models of cancer that can be used to guide integrative analyses of distress, biobehavioral processes, and health outcomes in cancer patients and survivors.[113,114,117,118]

Biobehavioral models of cancer control emphasize that perceptions of events that are evaluated as threatening or stressful are associated with activation of limbic-cortical structures of the CNS, dysregulation of the HPA axis, and increased signaling of the SNS.[119] For example, studies report HPA axis abnormalities such as flattening of the circadian rhythm of cortisol secretion and elevated plasma cortisol levels in women with metastatic BCa (mBCa),[120] and other reports indicate that mBCa patients with flattened or abnormal diurnal cortisol rhythms had earlier mortality.[121] Other work indicates an association between flattened or abnormal diurnal cortisol patterns and increased risk of mortality in patients with Stage IV renal cell carcinoma[122] and lung cancer.[123] Thus, among patients with advanced cancers, abnormalities in HPA axis functioning may promote hastened mortality. Importantly, increased SNS signaling and HPA axis dysregulation may produce alterations not only in cortisol but also in catecholamines such as norepinephrine, which can act as ligands for immune cells, to down-regulate cellular immune function and up-regulate pro-inflammatory signaling.[6,119]

Some of this work has focused on the context of primary BCa treatment, given that BCa is one of the most prevalent cancers worldwide[124] and since women diagnosed at this point in the disease can showed marked variability in clinical outcomes over time. Among early stage BCa patients in the weeks after surgery, negative affect and depressive symptoms have been associated with greater levels of serum IL-1β, IL-6, and TNF-α,[125] and with up-regulated leukocyte gene expression for these cytokines.[126] Greater depressive symptoms in the weeks after surgery in this cohort were shown to predict shorter survival over an 11-year median follow-up.[127] Conversely, greater decreases in leukocyte pro-inflammatory and increases in anti-viral gene expression over the first year of treatment predicted a longer disease-free interval over this 11-year follow-up.[128] Thus, one way that stress factors (negative affect and depressive symptoms) can influence cancer progression is through their influence on the expression of adversity-associated genes in circulating immune cells and associated cytokines.[129]

Distress, regulation of leukocyte and tumor cell gene expression, and cancer progression

Studies from the recently developed field of *human social genomics*[130] show that changes in the expression of hundreds of genes can occur as a function of the physical and social environments that we live in.[131,132] These effects can result from physical threats but can also be a response to symbolic or imagined adversities. That is, our subjective meanings about our socio-environmental conditions can regulate the expression of broad sets of genes. We now know, for example, that extended periods of distress emanating from subjective evaluation of social-environmental threats or adversity are linked to co-occurring changes

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in patterns of SNS and HPA axis activity and alterations in the transcriptional programs expressed in immune and tumor cells, among others. This control of human gene expression by psychological and social stress is characterized by a pattern of upregulated proinflammatory activity and down-regulated antiviral immune response activity in leukocytes referred to as the *conserved transcriptional response to adversity* (CTRA).[119,130] These changes, when chronically expressed, can result in a variety of inflammation-related diseases such as cardiovascular disease and depression, caused by excessive proinflammatory immune response gene expression, and/or vulnerability to viral infections such as upper respiratory disease, caused by insufficient antiviral immune response gene expression.[133]

Emerging work suggests that psychological adversity may be related to an increased CTRA pattern of leukocyte gene expression in cancer patients. One study of women with non-metastatic BCa showed that greater negative affect (relative to positive affect) was associated with greater leukocyte pro-inflammatory (IL1, IL6, TNF) and pro-metastatic (eg, MMP9) gene expression in the weeks after surgery.[126] These alterations can be the result of both the disease and its treatment-related effects on endocrine regulation, as well as the elevated stress of diagnosis and treatment of BCa.[118,134,135]

Conversely, facilitating adaptation with group-based cognitive behavioral stress management (CBSM) intervention has been shown to decrease leukocyte pro-inflammatory and pro-metastatic gene expression and increase anti-viral gene expression (interferon response genes) in women undergoing primary treatment for BCa.[126] Importantly, this intervention was also shown to reduce negative affect and depressive mood; increase positive affect, social support, and relaxation skills; decrease afternoon serum cortisol levels; and increase cellular immune functional responses to in-vitro challenge.[126,134,136,137] Subsequently, bioinformatics analyses of these leukocyte gene expression changes implicated decreases in the NFκB transcriptional activity and increases in glucocorticoid receptor (GR) sensitivity as potentially mediating the pro-inflammatory and pro-metastatic gene expression changes over the 12-month period after CBSM.[126] Increases in GR sensitivity were hypothesized to follow from the decreased circulating cortisol levels documented in women who received CBSM[138] and may herald a reversal in the negative-affect–associated HPA dysregulation.

As noted above, there was also evidence that women assigned to CBSM showed a leukocyte gene expression profile consistent with an increased expression of key anti-viral immune genes such as Type I and II interferons, which is in line with prior reports that CBSM increases lymphocyte production of IFN-γ from stimulated lymphocytes in these women.[134] This suggests that the intervention may have hastened a recovery of cellular immune signaling relevant to defending against opportunistic infections and micrometastatic tumor cells during the first year of primary treatment.

Together this series of analyses converges on the notion that greater negative affect and lower positive affect states are related to a CTRA pattern identified in other populations, and that stress management interventions can reverse the CTRA pattern during a crucial point in cancer treatment.[131] But do these forms of intervention produce measurable improvements in clinical outcomes over the long term, and can these effects be attributable to intervention-associated biobehavioral changes?

Effects of Psychological Interventions on Biobehavioral Processes and Clinical Outcomes in Cancer Patients

Distress management interventions

Studies developed by a small number of teams, supporting biobehavioral models of cancer, demonstrated that psychosocial interventions shown to help cancer patients learn stress management may not only reduce depression and anxiety and modulate biobehavioral processes but are associated with greater survival and a longer time until recurrence.[126,128,136,139-141] These data have utility because they can culminate ultimately in the development of distress management interventions with the potential to improve both quality of life and clinical disease outcomes through changes in brain structure and function that have implications in peripheral biobehavioral processes that, in turn, will feed back into the brain. For instance, one team showed that a CBSM intervention targeting anxiety-related affective and behavioral processes reduced negative affect and increased positive affect while also reducing CTRA-related leukocyte gene expression over the initial 12 months of BCa treatment.[126] In a long-term follow-up of this cohort, investigators found that patients assigned to CBSM had longer 11-year overall survival and disease-free survival (longer period until recurrence),[141] and greater reductions in the CTRA leukocyte expression profile during the 12 months of primary treatment predicted a longer disease-free survival over the 11-year follow-up.[128]

Another team conducted a clinical trial (a 12-month CBT-based intervention with a total of 26 sessions of 1.5 hours in small cohort groups of 8–12 patients) in early-stage BCa patients, before adjuvant therapy, and analyzed the biobehavioral, immune, and health benefits of psychological intervention over a period of 11 years.[139,140,142-144] They reported that the intervention improved affect and immune function over the initial year of treatment[139] and was associated with a reduced risk of BCa recurrence and death from BCa and from

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all causes over an 11-year median follow-up.[140] Lower levels of inflammation during the follow-up period predicted lower odds of recurrence.[143] Moreover, a subgroup of patients that, on accrual, reported clinically elevated depressive symptoms and were assigned to the intervention showed a significant reduction in depressive symptoms, pain, fatigue, and inflammation biomarkers.[144] Finally, among the patients in both arms who did have a recurrence, intervention-arm patients had a reduced risk of BCa death vs controls.[142] Therefore, across 2 independent RCTs of CBT-based distress reduction in non-metastatic BCa patients, changes in biobehavioral processes preceded and were related to long-term clinical outcomes. What sorts of psychological processes or skill changes in these cohorts could have accounted for these biobehavioral alterations?

What psychological changes occurring during stress management interventions can account for changes in body physiology?

Hypothesized positive psychological changes occurring during CBSM that may explain its effects on physiological status include changes in the personal meanings that cancer patients have, reductions in perceived threats, and feeling less vulnerable via increased confidence (self-efficacy) in using personal (eg, relaxation and CBT skills) and interpersonal resources (social support) to cope with the distress.[145] For example we know that BCa patients assigned to CBSM show increases in finding benefit in the cancer experience (ie, benefit finding),[146] and greater increases in benefit finding after CBSM are associated with greater reductions in afternoon serum cortisol[147] and greater increases in cellular immune functioning.[148] In addition, BCa patients reporting greater increases in confidence in using relaxation and CBT skills showed greater reductions in afternoon cortisol levels.[137]

Actually, a basic assumption of CBT and psychotherapy, more broadly construed, is that the meaning a person attaches to a situation plays a key role not only in how that person will feel and behave but also has consequences on their physiology.[149-153] Thus, according to CBT intervention assumptions, to become more functional and adaptive, a person can reflect or become more aware of her/his mental processes in order to modify her/his interpretations of social and environmental conditions. There is a primacy of cognition in behavior and emotional change: whatever psychosocial method is used to promote patient adaptation (eg, relaxation, exposure, cognitive restructuring, teaching social skills, mindfulness meditation), there is a change in cognition.[151] Also the administration of antidepressant medication may have an effect on cognition, namely reducing the negative biases in information processing.[154]

The empirical literature has provided support for the efficacy of CBT in the treatment of several psychological disorders (eg, panic disorder, unipolar depression, generalized anxiety disorder, social phobia), as well a physiological benefit in medical patients (eg, changes in inflammatory parameters like reductions in C-reactive protein levels in rheumatoid arthritis patients).[155,156] Research on patients' illness perceptions have also shown their relevance in the self-regulation processes of health and illness[157] and as a main mediator of more positive adaptation to illness in cancer patients.[5,158-161] For example, a CBSM intervention tested among 199 women newly treated for stage 0-III BCa reduced reports of cancer-specific thought intrusions, clinician-rated anxiety, and negative affect compared with the control condition.[162] Thus, subjective meanings (eg, threat, loss) of social and environmental conditions may also play a central role in leukocyte transcriptional alterations through the CNS-mediated changes in the regulation of neural signaling and neuroendocrine production previously observed in this cohort.[131] With this in mind, it is paramount to understand how stress perceptions and concomitant negative affect alter activities within specific brain regions and/or *patterns* of activity across brain regions,[80] which in turn contribute to the regulation of SNS and HPA axis hormones in cancer patients.

Distress management effects on comorbidity

Another potential beneficial effect of distress management in cancer patients is on mitigating the risk of and effects of comorbidity or multimorbidity.[163,164] Depression, fatigue, sleep disturbances, and cognitive dysfunction are common in cancer patients and have an adverse impact on quality of life and cancer survival.[165,166] For example, insomnia associated with cancer has been linked to decreased quality of life,[165] impaired immune function,[167,168] cancer-related fatigue,[169] and may have implications for tumor progression[170-172] and greater mortality risk.[173]

These secondary medical conditions (eg, sleep disruption) can aggravate inflammatory processes and stimulate the release of central cytokines, which act to alter neuronal plasticity and brain functioning, affecting peripheral biobehavioral processes such as the activation of the HPA axis and the SNS, resulting in the production of high levels of cortisol. Thus, stress management interventions might help to reduce, mitigate, or prevent chemobrain syndrome indirectly by mitigating the risk of and effects of comorbidity or multimorbidity.

Other important comorbidities are those associated with metabolic syndrome (MetS) (ie, dyslipidemia, hypertension, central obesity, and insulin resistance),[174,175] which are risk factors of cardiovascular disease (CVD)[176] and should be considered in cancer survivors. In fact, a newly published statement from the American Heart

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Association notes that CVD and associated risk factors (obesity and dyslipidemia) are increasing in BCa survivors, and the development of these risk factors is higher in older BCa survivors than the risk of tumor recurrence.[177] Distress management interventions might have a role in preventing, reducing, or mitigating the effects of these comorbidities, since chronic psychosocial stress, which causes dysregulation of HPA axis, is a risk factor for the development of the MetS.[178-180] For example, a 1-year, CBT-based stress management of 20 2-hour sessions over 1 year with cardiac patients showed less fatal and nonfatal first recurrent CVD events and fewer recurrent acute myocardial infarctions than the control group.[181] Given the increase in CVD risk factors after BCa treatment, it is reasonable that distress management interventions might offer the dual benefit of decreased BCa recurrence[128,141] and less risk for developing comorbid CVD-related clinical outcomes, thereby contributing to longer survival and better quality of life.[6] Since CVD[182] and BCa recurrence[119] may both be hastened by shared inflammatory processes (eg, via myeloid cells in the arterial lumen and tumor microenvironment, respectively), it is important to understand the CNS and peripheral stress physiology pathways (neuroendocrine and immune) underlying these pathological processes in order to develop tailored psychosocial and pharmacologic interventions targeting those at greatest risk.

Pharmacologic interventions to block SNS signaling and inflammation in cancer patients

Because distress-associated alterations in SNS and inflammatory processes have been implicated in cancer progression,[19,118] and since related hormones and cytokines are elevated during surgery[183]—a common curative intervention used in cancer patients—a novel line of work uses pharmacologic interventions to block SNS signaling (eg, non-selective beta adrenergic blockade) and inflammation (eg, COX2 inhibitors) in patients undergoing cancer surgery. A recently published double-blind, placebo-controlled trial showed that perisurgical administration of a combined propranolol (beta adrenergic blocker) and etodolac (COX2 inhibitor) regimen downregulated leukocyte pro-inflammatory/pro-metastatic GATA and EGR family transcriptional factors and buffered increases in serum IL-6 and CRP, and prevented a decline in anti-viral immune responses to challenge (IL-12 and IFN-γ production) in BCa patients.[184] The pattern of down-regulated pro-inflammatory and pro-metastatic, and up-regulated anti-viral signaling is very similar to what has been observed in BCa patients receiving CBSM after surgery, which reflects a reversal of the CTRA.[126,128,134]

This work suggests that psychosocial and pharmacologic distress management interventions are capable of reducing distress-related biobehavioral processes (eg, neuroendocrine and inflammatory signaling), which may have significant beneficial effects on long-term clinical outcomes that are proportional to the biobehavioral changes induced during primary treatment and the skills that persist throughout cancer survivorship. Is there a potential for pharmacological agents to help regulate brain functioning by modulating SNS and inflammatory signaling, reversing the effects of stress? The future challenge in cancer research and neuroscience is to examine how these pharmacologic treatments, combined with behavioral (distress management) interventions, help to change brain structure and function in cancer patients promoting their well-being, quality of life, and better health outcomes.

Summary, Conclusions, and Implications

Emerging evidence shows that distress and adversity can contribute to negative health outcomes in cancer. However, little is known about the brain networks, regions, or circuits that can contribute to individual differences in affect/distress states and health outcomes in treated cancer patients. Based on the scientific literature, we highlighted some key brain regions that potentially might be involved in emotional distress in cancer patients and proposed the interoceptive network as a key brain network that should be included in studies that investigate brain-mediated biobehavioral processes.

We reasoned that studies examining the effects of distress in cancer patients should adopt a paradigm that includes multilevel integrative analyses and in which the formulation of structure-function relationships should integrate "top-down" and "bottom-up" communication, including behavioral and social factors, brain activity and structure, neural peripheral systems, and the endocrine and immune systems.

Moreover, we presented evidence from a small number of studies about the beneficial psychological, physiological, and clinical health effects of psychological interventions in cancer patients undergoing treatment. Despite the provocative results of these interventions, it remains unknown how changes in affect are precisely transduced through neural signaling pathways that can modulate peripheral immune cells and cancer cells in ways that could influence cancer disease course. One strategy to increase this knowledge base is to use developments in neuroimaging to examine associations among brain activity, psychological states, effects of psychological interventions, and peripheral neuroendocrine and immune processes in cancer patients and tie these to longer-term clinical outcomes in an integrated and multilevel way. Thus, we propose a multilevel and integrated

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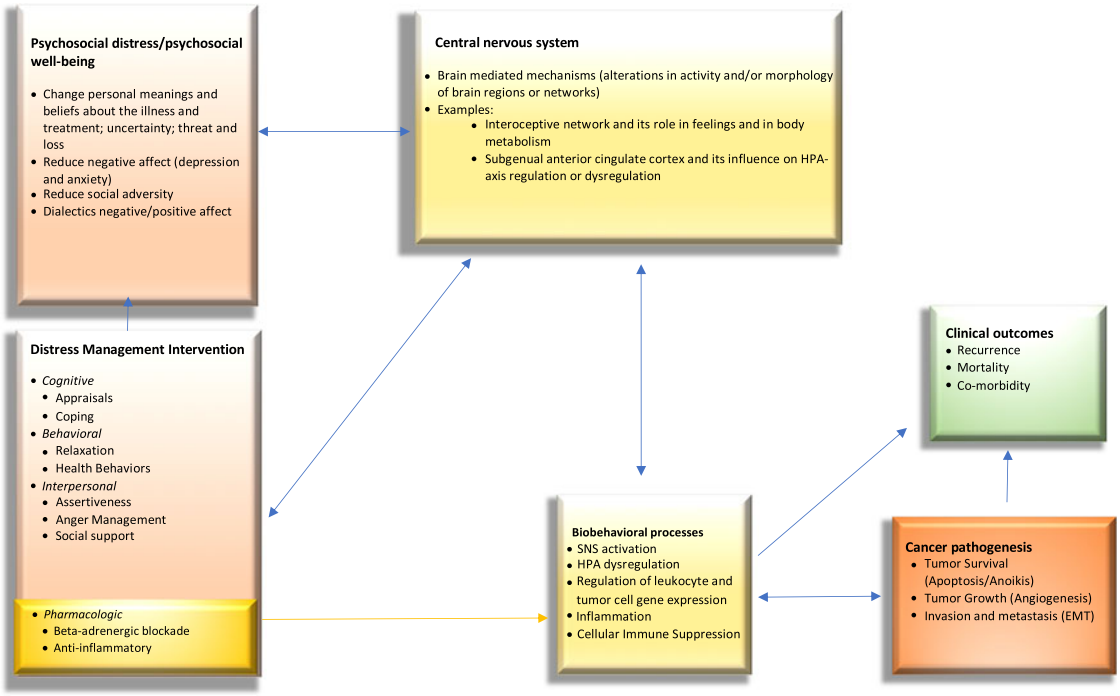

FIGURE 2. A multilevel and integrated model for distress management intervention effects on psychological adaptation, biobehavioral processes and cancer pathogenesis and clinical outcomes.

model for distress management intervention effects on psychological adaptation, biobehavioral processes, and cancer pathogenesis and clinical outcomes (see Figure 2), which may guide the development of more targeted psychosocial, behavioral, and pharmacological interventions to optimize the health of cancer patients.

This model integrates a previously presented heuristic for understanding psychosocial intervention effects on psychological adaptation, biobehavioral processes, cancer pathogenesis, and clinical outcomes[6] with emerging evidence for neural processes that accompany many of its elements. This update adds CNS activity because it is crucial to understand how stress perceptions and the concomitant changes in affect alter activities within specific brain regions or networks, which, in turn, contribute to the regulation of SNS and HPA axis hormones in cancer patients. This is a multilevel and integrated model with top-down and bottom-up pathways between mind and body. Psychosocial interventions are hypothesized to decrease chronic stress, negative affect, and social adversity and promote more positive affect and psychological growth and influence the activity of brain regions related with emotional experiences. Improvements in psychological adaptation are hypothesized to facilitate decreases in SNS activation, HPA axis dysregulation, inflammation, and cellular immune deficits. SNS activity and inflammation may also be modulated directly through pharmacologic interventions that block distress-associated pathways. These alterations in stress-related biobehavioral processes may decrease the likelihood of cancer pathogenic processes associated with tumor cell survival (resistance to apoptosis), growth (angiogenesis), invasion, and metastasis (endothelial-to-mesenchymal transition [EMT]), which could precede clinical outcomes such as disease recurrence and mortality. Alterations in stress-related biobehavioral processes may also influence clinical outcomes (eg, comorbidities) independent of the cancer pathogenic processes listed.

We conclude that future studies based on a multilevel integrative analysis that includes recent advances in psychoneuroimmunology, biobehavioral oncology, intervention science, cognitive neuroscience/neuropsychiatry, and molecular biology of cancer signaling processes will allow greater knowledge about the influence of distress on cancer processes and health outcomes. Understanding the specific multimodal mechanisms underlying the effects of distress will inform the refinement of theoretically driven distress management interventions for cancer patients, which could contribute to enhanced clinical care and improved health outcomes.

Disclosures

The authors do not have anything to disclose.

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