Original Article

Negative Affect and Stress-Related Brain Metabolism in Patients With Metastatic Breast Cancer

Joaquim C. Reis, PhD [1]; Luzia Travado, PhD [2]; Michael H. Antoni, PhD [3]; Francisco P. M. Oliveira, PhD [4]; Silvia D. Almeida, MSc [1]; Pedro Almeida, PhD [1]; Aaron S. Heller, PhD [3]; Berta Sousa, MD [2]; and Durval C. Costa, PhD [4]

BACKGROUND: Cancer and its treatment represent major stressors requiring that patients make multiple adaptations. Despite evidence that poor adaptation to stressors is associated with more distress and negative affect (NA), neuroimmune dysregulation and poorer health outcomes, current understanding is very limited of how NA covaries with central nervous system changes to account for these associations. **METHODS:** NA was correlated with brain metabolic activity using ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) in several regions of interest in 61 women with metastatic breast cancer. Patients underwent ^{18}F-FDG PET/CT and completed an assessment of NA using the Brief Symptom Inventory. **RESULTS:** Regression analyses revealed that NA was significantly negatively correlated with the standardized uptake value ratio of the insula, thalamus, hypothalamus, ventromedial prefrontal cortex, and lateral prefrontal cortex. Voxel-wise correlation analyses within these 5 regions of interest demonstrated high left-right symmetry and the highest NA correlations with the anterior insula, thalamus (medial and ventral portion), lateral prefrontal cortex (right Brodmann area 9 [BA9], left BA45, and right and left BA10 and BA8), and ventromedial prefrontal cortex (bilateral BA11). **CONCLUSIONS:** The regions of interest most strongly negatively associated with NA represent key areas for successful adaptation to stressors and may be particularly relevant in patients with metastatic breast cancer who are dealing with multiple challenges of cancer and its treatment. ***Cancer* 2020;0:1-10**. © *2020 American Cancer Society*.

KEYWORDS: distress, metastatic breast cancer; negative affect, stress-related brain metabolism.

INTRODUCTION

Up to 40% of patients who have cancer experience cancer-related distress or psychological morbidity.[1,2] Cancer-related distress includes various negative emotions and psychological symptoms, such as feelings of increased vulnerability, worry, sadness, fear about the future, concern about illness, depression, anxiety, anger, and hostility, and may be accompanied by poor sleep, decreased appetite, difficulty concentrating, and thoughts of illness and death.[3] The assessment of psychological distress in patients with cancer typically relies on self-reports, which focus on negative affect (NA) and include symptoms of depression, anxiety, and hostility along with other symptoms of adversity.

There is substantial evidence that NA is associated with stress-related biologic alterations that could promote cancer progression once a tumor has been established.[4,5] In the stress response, 2 brain-body pathways have a crucial role linking NA with physical health in general and with cancer progression in particular: the sympathetic–adrenal–medullary (SAM) axis and the hypothalamic–pituitary–adrenal (HPA) axis.[6] The SAM and HPA axes secrete catecholamines and glucocorticoids, respectively, which bind with tumor and immune cells, modulating their functioning and interactions within the tumor microenvironment, stimulating angiogenesis, and promoting tumor cell growth, migration, and invasive capacity of the cancer cells.[7,8] Moreover, through its effects on biobehavioral factors, NA and these stress-related processes may negatively influence comorbidities associated with neuroendocrine-immune mechanisms (eg, metabolic syndrome) that are risk factors for cardiovascular disease.[9,10] As such, reducing NA in patients with cancer may have positive effects on both mental and physical health outcomes. However, we still have very limited understanding of how NA covaries with central nervous system (CNS) changes to govern these neuroimmune processes in patients who have cancer.[11]

Corresponding Author: Joaquim C. Reis, PhD, Instituto de Biofísica e Engenharia Biomédica, Faculdade de Ciências, Universidade de Lisboa, Campo Grande, Lisbon, 1749-016, Portugal (jdcreis@fc.ul.pt).

[1]Institute of Biophysics and Biomedical Engineering, Faculty of Science, University of Lisbon, Lisbon, Portugal; [2]Breast Unit, Champalimaud Clinical Center, Champalimaud Foundation, Lisbon, Portugal; [3]Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, Department of Psychology and Cancer Control Program, Miami, Florida; [4]Nuclear Medicine-Radiopharmacology, Champalimaud Clinical Center, Champalimaud Foundation, Lisbon, Portugal

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The CNS has a central role in the stress response, including appraising the meaning of stressors (ie, threat) and determining appropriate physiological and behavioral responses.[12] Levels of stress and distress alter the activity of brain neural circuits underlying social and emotional behavior, which could affect coping responses.[13] In rodent models, chronic stress causes neuronal proliferation in the amygdala, with opposite effects in both the hippocampus (impaired neurogenesis and atrophy of dendritic trees) and prefrontal cortex (neurons in the medial prefrontal cortex shrink, and those in the orbitofrontal cortex grow).[14,15]

Neurobiological models suggest that stress is primarily caused by environmental and contextual uncertainty[16] and that these and other brain regions are central to appraising environmental stimuli and engaging the stress response. Uncertainty is a common experience in those experiencing life-threatening or chronic diseases, including cancer.[17,18] Such experiences may be accompanied by changes in these same key brain circuits, including areas such as the lateral prefrontal cortex (lPFC), ventromedial prefrontal cortex (vmPFC), anterior cingulate cortex (ACC), and amygdala (Amy). These brain regions, and others, such as the thalamus (Th), hippocampus (Hi), hypothalamus (Hy), basal ganglia (BG) (striatum and caudate), and insula (Ins), have been identified in functional and structural neuroimaging studies as being involved in NA (ie, anxiety, depression, and posttraumatic stress) in patients with cancer.[19] However, research examining neural-affect associations in cancer has primarily focused on patients with cancer at the initial stages of the disease and has not included patients with metastatic cancer. Including those who have metastatic disease is particularly critical because these patients deal with a far more life-threatening condition than those with early stage disease.[20] Yet we know very little about the association between NA and brain activity in this group.

To our knowledge, the current study is the first to examine the association of NA with brain metabolism in a priori determined brain regions of interest (ROIs) in a homogeneous sample of patients with metastatic breast cancer (mBCa) in terms of disease stage and type of treatments received while controlling for confounding variables. In contrast, most of the samples previously studied[19] in the field have included different sexes, various cancer types and stages, and different types of treatment, all of which can produce different effects on the brain.[21-23] The current study focuses on ROIs known to be associated with: 1) major depression in patients without cancer,[24-29] 2) NA in patients with nonmetastatic cancer,[19] and 3) stress responses to environmental and contextual uncertainty.[16] We hypothesized that patients reporting greater NA would evidence less metabolism in the Amy, ACC, Hi, Hy, Ins, lPFC, vmPFC, Th, and BG.

TABLE 1. Clinical and Demographic Characteristics, N = 61 Women

Characteristic	Mean ± SD	Mode	Median	Range
Age, y	59.9 ± 10.6	49	60	45
BMI, kg/m^2	26.3 ± 5.1	29.6	25.8	24.22
Plasma glucose level, mmol/L	5.8 ± 1.1	4.4	5.1	4.4
^{18}F-FDG-activity, MBq	230.5 ± 49.14	—	222.7	216.8
Education, y[a]	14.8 ± 3.3	17	17	16
Disease duration, mo	101.7	30	61	427
Metastasis duration until ^{18}F-FDG PET/CT scan, mo	20.1	6	14	98
Prevalence of NA: Percentage of patients above the cutoff score[b]	37.7[b]			

Abbreviations: ^{18}F-FDG, ^{18}F-fluorodeoxyglucose; BMI, body mass index; MBq, megabecquerels; NA, negative affect; PET/CT, positron emission tomography/computed tomography.
[a]Values indicate the years of full-time education completed.
[b]The clinical cutoff score indicates the score at which an individual has a greater probability of belonging to a clinical sample rather than a nonclinical sample using the Brief Symptom Inventory cutoff score for the Portuguese population.

MATERIALS AND METHODS

The study sample consisted of 61 women with mBCa who were receiving treatment at the Breast Unit of the Champalimaud Clinical Center in Lisbon, Portugal. Table 1 presents the clinical and demographic characteristics of the patients. Recruitment was conducted between June 2017 and May 2019.

Inclusion Criteria

Patients who were eligible for the study had to comply with all of the following: 1) women age >18 years, 2) an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 (the ECOG scale is used to assess performance status and for prognosis assessment and ability to tolerate chemotherapy; an ECOG score of 0 indicates fully active, no performance restrictions; ECOG 1, strenuous physical activity restricted, fully ambulatory and able to perform light work; ECOG 2, capable of all self-care but unable to perform any work activities up to approximately >50% of waking hours[30]); 3) the presence of metastatic or locally advanced breast cancer (BCa) not amenable to curative treatment by surgery or radiotherapy; 4) patients with positive hormone receptors and HER2-negative BCa; 5) under treatment with endocrine therapy (ie, tamoxifen or aromatase inhibitors) or oral chemotherapy

(vinorelbine, capecitabine, or metronomic cyclophosphamide/methotrexate) or targeted therapy; 6) receipt of first-line or second-line of treatment (these criteria were included because patients who are receiving the first or second line of treatment have good performance status, absence of visceral crisis, and reduced burden of disease; these criteria allowed us to have a homogeneous sample regarding disease condition and severity, functionality, and treatment exposure); 7) adequate bone marrow, coagulation, liver, and renal function (assessed by physicians at the clinical visits); and 8) have been prescribed an ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography (^{18}F-FDG PET/CT) scan by the oncologist to assess remission or disease progression.

Exclusion Criteria

Patients were not eligible to participate in the study if they had at least 1 of the following: 1) the presence of brain or other CNS metastases, 2) receipt of radiation therapy to the brain or skull lesions, 3) the presence of neurodegenerative and neurologic disease, 4) current treatment with corticosteroids or intravenous chemotherapy, 5) current or previous irradiation to the brain, and 6) HER2-positive BCa, the presence of visceral crisis, and/or significant burden of disease.

After being selected by her oncologist for participating in the study, based on the above criteria, the patient was informed about the study and invited to participate. Those who accepted signed an informed consent form. After that, and before the ^{18}F-FDG PET/CT scan, a psychologist interviewed the patient to assess mental health problems, current or past. The Distress Thermometer and its Problem Checklist subscales[31] and the Brief Symptom Inventory (BSI)[32] were used to assess mental and emotional problems. None of the eligible patients who participated in this study showed any serious mental health problems or significant psychiatric symptoms, such as paranoid ideation or psychoticism, as assessed by the BSI. However, there were many patients taking psychotropic drugs for anxiety and/or depressive symptoms (ie, a serotonin-norepinephrine reuptake inhibitor [SNRI]). Therefore, we examined the potential effect of SNRI intake in our analyses of brain metabolism.

Procedure

The study was approved by the local ethical committee. All eligible patients underwent a PET scan with ^{18}F-FDG under baseline conditions and completed an assessment of NA. A signed informed consent form was obtained.

^{18}F-FDG PET/CT Scanning

Data acquisition was performed on the Gemini TF16 (Philips) after intravenous administration of ^{18}F-FDG (227.4 $\pm$ 55.9 megabecquerels), always in the same room and under similar conditions for all patients (ie, eyes open, lying flat on a couch after a rest period of 10-15 minutes). Data were acquired for 15 minutes at 180 minutes postinjection. The results here report on the 180-minute postinjection scan only. We specifically examined the delayed ^{18}F-FDG PET/CT acquisition because the time postinjection influences brain ^{18}F-FDG uptake, increasing to a plateau and slowly decreasing, while ^{18}F-FDG is exiting the cell's compartment. The delay of acquisition time postinjection reflects much more of the brain's metabolic component versus the earlier radioligand vascular distribution, resulting in improved contrast between gray matter and white matter.[33] Previous studies examining FDG uptake rates for different scans demonstrated that ^{18}F-FDG PET/CT imaging at delayed times can increase diagnostic accuracy in differentiating malignancies from benign lesions.[34] For example, compared with standard brain acquisition (60 minutes postinjection), a 180-minute delayed ^{18}F-FDG PET/CT acquisition provided a more accurate diagnosis of large blood vessel inflammation.[35,36] However, it should be noted that all results were similar at both the immediate and 180-minute postinjection scans.

The LOR-RAMLA (line-of-response row-action maximum likelihood algorithm) reconstruction algorithm (Gemini TF) was used for data reconstruction, with attenuation and scatter correction, using a sharp reconstruction filter, according to the routine protocol. An isotropic voxel size of 2 mm was defined. The acquisition was done at the Nuclear Medicine-Radiopharmacology Unit at the Champalimaud Foundation in Lisbon.

Negative Affect

Two days after ^{18}F-FDG PET/CT investigation, participants completed the Portuguese version[37] of the BSI,[32] which consists of 53 items and covers a broad range of symptoms of NA, characterizing the intensity of distress during the past 7 days. Each item is rated on a Likert scale from 0 (not at all) to 4 (extremely), and responses are summed to generate the Global Severity Index (GSI), which reflects both the number and severity of all items endorsed. The GSI is considered the most sensitive single quantitative indicator concerning the patient's overall psychological distress status.[38] The BSI has been used in many studies of patients with cancer and has shown good levels of sensitivity and specificity compared with other psychometric tests.[38,39]

TABLE 2. Linear Regression Analyses for Negative Affect (Brief Symptom Inventory Global Severity Index Score), Age, and Standardized Uptake Value Ratio in Patients With Metastatic Breast Cancer

	Multiple Linear Regression Analyses					
			Independent Variable			
			BSI-GSI		Age	
Region	Overall R^2	F Statistic (*P*)	Std β	*P*	Std β	*P*
Ins	0.448	$F_{[2,58]} = 23.577$ (.0001[a])	−0.281	.006[a]	−0.576	<.0001[a]
Amy	0.113	$F_{[2,58]} = 3.702$ (.031)	−0.145	.249	−0.287	.025
BG	0.317	$F_{[2,58]} = 13.458$ (.0001[a])	−0.240	.032	−0.482	<.0001[a]
Th	0.366	$F_{[2,58]} = 16.770$ (.0001[a])	−0.284	.009[a]	−0.502	<.0001[a]
ACC	0.394	$F_{[2,58]} = 18.827$ (.0001[a])	−0.205	.051	−0.570	<.0001[a]
Hi	0.278	$F_{[2,58]} = 11.144$ (.0001[a])	−0.120	.290	−0.499	<.0001[a]
Hy	0.438	$F_{[2,58]} = 22.574$ (.0001[a])	−0.279	.007[a]	−0.568	<.0001[a]
vmPFC	0.422	$F_{[2,58]} = 21.140$ (.0001[a])	−0.295	.005[a]	−0.545	<.0001[a]
lPFC	0.399	$F_{[2,58]} = 19.219$ (.0001[a])	−0.343	.001[a]	−0.492	<.0001[a]

Abbreviations: lPFC, lateral prefrontal cortex; ACC, anterior cingulate cortex; Amy, amygdala; BG, basal ganglia; BSI-GSI, Brief Symptom Inventory Global Severity Index; Hi, hippocampus; Hy, hypothalamus; Ins, insula; R^2, coefficient of determination; Std β, standardized β value; Th, thalamus; vmPFC, ventromedial prefrontal cortex.
[a]This *P* value was significant after Holm-Bonferroni correction for multiple comparisons.

Imaging Processing

The 180-minute ^{18}F-FDG brain images were registered to Montreal Neurological Institute space (template ICBM 2009a Nonlinear Symmetric T1; resampled to an isotropic voxel size of 2 mm), using a suitable deformation model based on rigid, affine, and cubic B-spline transformations. Next, the registered images were smoothed with a Gaussian kernel with an 8-mm full width at one-half maximum and then intensity normalized to obtain the standardized uptake value (SUV) ratio (SUVr). This normalization was done independently for each patient, using the pons as the reference region: ie, the SUV of each voxel was divided by the mean SUV of the pons, identified in this work as the SUVr. This ratio is an indirect measure of the regional cerebral metabolic rate measured by the glucose uptake.

After spatial normalization to Montreal Neurological Institute space, intensity normalization, and smoothing, each brain image was segmented into the 9 ROIs according to the Automated Anatomical Labeling (AAL) brain atlas.[40] Before applying the ROIs mask from the AAL brain atlas to the normalized ^{18}F-FDG images, those ROIs were eroded by 2 mm in each direction to minimize the errors that might be introduced by partial volume effects and cortical thickness. Mean SUVr values were extracted from each region, for each patient, for the 180-minute postinjection image. Registration techniques were implemented in Python language, using PyCharm (JetBrains) as the interpreter and SimpleElastix[41] for image registration.

Statistical Analysis

Statistical analyses were conducted using IBM SPSS version 25 (IBM Corporation), and a significance level of 5% was set. To examine the correlation between levels of NA (BSI-GSI score) and the mean SUVr in the several ROIs, a linear regression model was applied to the 180-minute postinjection acquisition brain images. In individual regression models, NA was the independent variable. The correlations of age, disease duration, metastasis duration, education, plasma glucose level, SNRI intake, and body mass index (BMI) with the SUVr were also assessed.

The SUVr in each of the predefined ROIs was included as the dependent variable in separate regression tests. Correction for multiple comparisons across the ROIs were addressed using the Holm-Bonferroni method.[42] Finally, for solely descriptive purposes, we computed a voxel-wise Pearson correlation (corrected for significant covariates) between NA and the whole-brain SUVr.

RESULTS

Correlation Between NA and Brain Metabolic Alterations in Patients With mBCa

Univariate analysis showed that disease duration, metastasis duration, education, plasma glucose level, and SNRI drugs intake did not correlate with the SUVr in the predefined ROIs. Age was correlated with the SUVr in all ROIs. Although BMI had correlated significantly with the SUVr in a few regions on univariate analysis, on multivariate

TABLE 3. Intercorrelation Matrix Among the 5 Regions of Interest That Were Significantly Correlated with Negative Affect

	ROI: Pearson Correlation Coefficient (r)[a]			
ROI	Th	Hy	vmPFC	lPFC
Ins	0.685	0.550	0.869	0.827
Th		0.599	0.680	0.705
Hy			0.512	0.458
vmPFC				0.959

Abbreviations: lPFC, lateral prefrontal cortex; Hy, hypothalamus; Ins, insula; ROI, region of interest; Th, thalamus; vmPFC, ventromedial prefrontal cortex.
[a]$P < .001$ for all correlations.

analysis, the effect of BMI on the SUVr of the ROIs was not significant. This may be explained by its correlation (r) with NA ($r = 0.307$). Thus, in the multivariate model, we included only age as a covariate.

As indicated in Table 2, all models are significant (NA and age were identified as predictors of the SUVr in each ROI), except for the Amy model. The overall coefficient of determination (R^2) indicates how much each model explains the variance of brain metabolism in each ROI. The contribution of each predictor (BSI-GSI score and age) for the dependent variable (NA) is indicated by the respective standardized β values and P values. Considering the contribution of each predictor, NA (BSI-GSI score) is negatively and statistically correlated with the SUVr of the Ins, Th, Hy, vmPFC, and lPFC after Holm-Bonferroni correction. Age is significantly negatively correlated with the SUVr in all ROIs after Holm-Bonferroni correction, except for the Amy. As can be seen in the intercorrelation matrix (see Table 3), the 5 ROIs that were significantly negatively correlated with NA in individual age-adjusted linear regressions are highly intercorrelated.

Voxel-Wise Correlation Analysis Between SUVr and NA Scores

Figure 1 presents the voxel-wise correlation distribution between NA and the SUVr in the whole brain. Table 4 presents the coordinates (x, y, z) of the most relevant peaks and respective Pearson correlation coefficients within the predefined ROIs of our a-priori hypothesis that had a significant correlation between NA and the SUVr.

As can be seen in Table 4, in general, subregions show high left-right symmetry in their NA correlations. The Ins shows a higher correlation with NA in the anterior portion versus the posterior portion. Correlation distribution in the Th is highly symmetrical (left-right), and the medial and ventral portions have a higher NA correlation. In the lPFC, the subregions that are most correlated with NA are the right Brodmann area 9 (BA9), a subregion that contributes to the dorsolateral and medial prefrontal cortex; the left BA45, a subregion situated in the ventrolateral PFC; the right and left anterior prefrontal cortex, BA10, and the left part of an area situated just anterior to the premotor cortex, BA8. In the vmPFC, activity in a subregion that covers the medial portion of the ventral surface of the frontal lobe (BA11) bilaterally is moderately correlated with NA and has a higher correlation than the surrounding portions.

DISCUSSION

In the current study, we examined brain metabolic activity in patients who had mBCa using ^{18}F-FDG PET/CT imaging in several ROIs that had previously been associated with NA in healthy populations and in patients with nonmetastatic cancer. Patients with mBCa endure multiple stressors during treatment,[44] and individual differences in adaptation to these challenges are associated with distress and NA states,[45,46] adrenal stress hormone dysregulation,[47] inflammatory processes,[48,49] and poorer long-term health outcomes[50,51] (for a review, see Antoni and Dhabhar[52]). It is important to note that previous work relating brain activity to distress in patients who have cancer has been conducted in patients with early stage BCa. In contrast, all patients with mBCa carry a more negative prognosis and have more challenges requiring greater adaptation, which, if inadequate, may relate to poorer health outcomes, mediated through alterations in neuroimmune stress physiology that can affect circulating tumor cells or immune and cancer cells in the tumor microenvironment.[5,7] In our study, we observed that regions linked to stress appraisal and regulation were particularly linked to individual differences in NA.

Despite evidence that distress states (depressive symptoms, NA, social isolation) are associated with alterations in stress physiology and poorer cancer outcomes,[7,53] there has been relatively little evidence for specificity indicating how the CNS could mediate these associations in patients with cancer.[19] What evidence does exist come from studies of small heterogeneous samples of patients with cancer that include men and women as well as various disease types, disease stages, and treatments received.[19] Therefore, we tested associations between individual differences in NA and brain

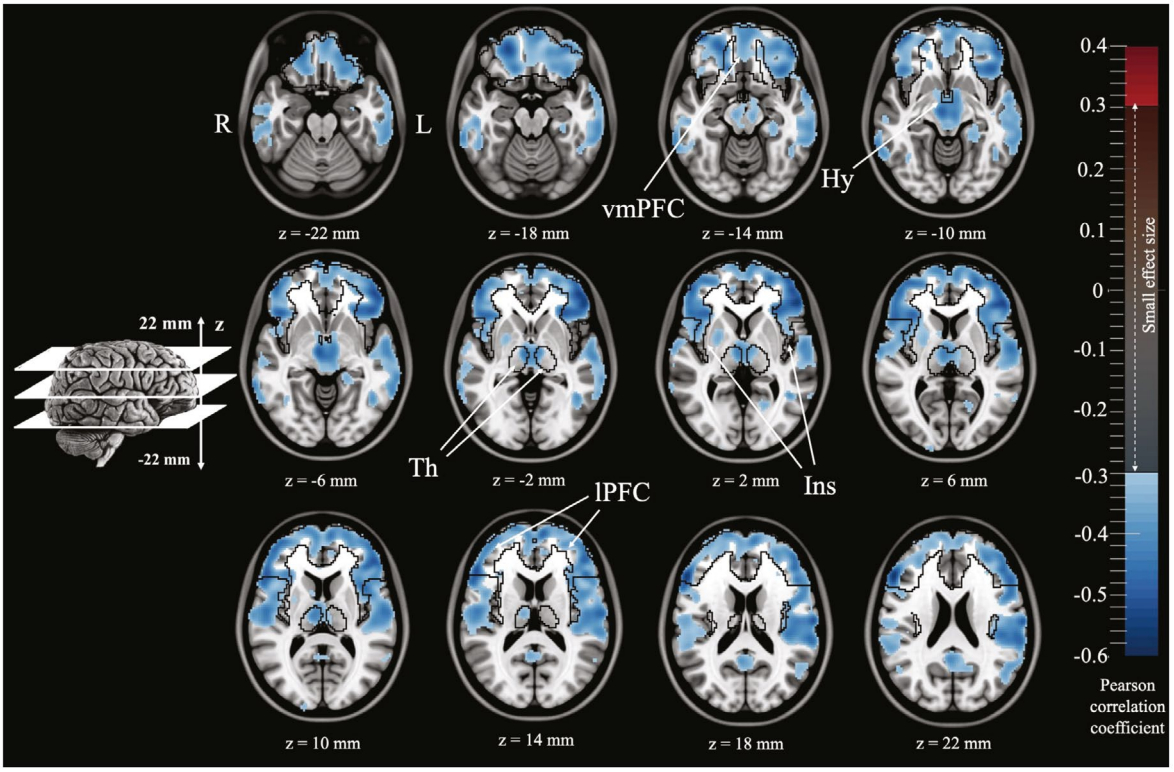

FIGURE 1. Whole-brain, voxel-wise correlation between negative affect (NA) and the standardized uptake value ratio (SUVr) is illustrated. Images represent 12 representative axial views of the Montreal Neurological Institute gray-scale T1 magnetic resonance images overlapped by the Pearson correlation coefficients (color bar). Only voxels with at least a moderate Cohen effect size ($r > 0.3$) are represented.[43] Arrows indicate the 5 regions of interest (ROIs) (ventromedial prefrontal cortex [vmPFC], hypothalamus [Hy], thalamus [Th], lateral prefrontal cortex [lPFC], and insula [Ins]) that had a significant correlation between NA and the SUVr, which are outlined in black. The figure shows that, although significant correlations between NA and the SUVr might exist in brain regions other than the 5 ROIs, the analyses suggest that correlation with NA is somewhat specific for the 5 ROIs and broadly supports the symmetrical correlation between the left (L) and right (R) hemispheres.

metabolic activity in a sample of patients with mBCa who were all women and who were homogenous not only in type and stage of disease but who also had received limited types of treatments. We also controlled for age. Therefore, we believe the current study represents one of the better controlled examinations of NA and brain metabolic activity in patients with cancer conducted to date.

Results from this study indicated that greater reported NA was significantly associated with decreased activity in 5 ROIs: the Ins, lPFC, vmPFC, Th, and Hy. More fine-grained, voxel-wise analyses revealed that, within these 5 ROIs, most subregions associated with NA showed high right-left symmetry in NA correlations. A descriptive whole-brain analysis suggested that correlation between NA and brain activity might also exist in brain regions other than the 5 ROIs. However, the strongest correlations were somewhat specific for the 5 ROIs. Examining whether NA has significant correlations with other brain regions through exploratory, whole-brain, voxel-wise analyses is an important avenue for future studies.

The regions and subregions that have the strongest negative associations with NA represent the key areas involved in functions that are crucial for successful adaptation to stressors. To interpret the possible relevance of the ROIs that we correlated with NA, we consulted the literature in which specific functions were attributed to the regions that putatively are involved in responding to stressors (eg, making stressor appraisals and interpreting the meaning of interpersonal processes). Because we did not assess or manipulate these stress-related processes directly in the current study, the interpretive comments below, by necessity, are speculative and should be viewed with caution. Future studies should examine the ways in which the dysregulation of brain metabolism associated with NA can mediate alterations potentially involved in stress physiology and poor outcomes in patients with cancer.

TABLE 4. Subregions in Each Region of Interest That Had a Significant Correlation With Negative Affect

	Brain Regions		Peak Level		
Region	Brodmann Area	Hemisphere	R Score	kE Voxels[b]	Coordinates (x, y, z), mm[a]
Hy		Right	0.43	10	6, −6, −8
		Left	0.42	6	−4, −6, −8
Anterior Ins		Right	0.50	221	32, 24, 4
		Left	0.51	300	−32, 26, −2
lPFC	BA9	Right	0.58	2100	56, 26, 20
	BA10	Right	0.44	167	18, 66, 16
	BA45	Left	0.56	3443	−52, 36, 0
	BA10	Left	0.49	220	−8, 60, 14
	BA8	Left	0.42	32	−6, 46, 48
vmPFC	BA11	Right	0.50	172	18, 44, −18
		Left	0.44	206	−6, 58, −20
Th		Right	0.46	193	6, −12, 8
		Left	0.43	32	−6, −12, −2

Abbreviations: lPFC, lateral prefrontal cortex; Ins, insula; R Score, correlation coefficient; Th, thalamus; vmPFC, ventromedial prefrontal cortex.
[a]Coordinates refer to Montreal Neurological Institute space.
[b]Values indicate the number of contiguous connected voxels.

The Ins has connections with prefrontal regions, mainly the vmPFC, playing a role in autonomic control, in the interoceptive pathways and nuclei involved in the generation of feelings, and in environmental awareness (attention and salience processing).[54,55] These pathways are necessary for anticipating and responding to both perceived and objective challenges to homeostasis (allostatic responses[56]). The anterior Ins, which was negatively associated with NA in the current study, is known to integrate the primary perceptive signals processed by the posterior Ins into higher level, abstract, subjective information about the state of the body,[57] is involved in the production of subjective feelings and uncertainty in the context of decision making,[16] and has a role in the regulation of peripheral inflammation.[58] Thus metabolic dysregulation of this region could result in poorer management of stressors and physiologic regulation.[59] This could manifest as greater NA, including greater depressive symptoms, which are known to be associated with perceived inability to control external stressors,[60] disruption in the HPA axis,[61] and greater inflammation[48] in patients with BCa.

The lateral PFC, the activity of which also was associated negatively with NA in the current study, is known for its role in executive functions (eg, working memory), decision making, planning, and the rational execution of behavioral action strategies.[62] Hypometabolic activity in this region and in the BAs we identified could reflect poorer ability to enact coping responses to the daily challenges of cancer and its treatments. Maladaptive coping (denial, behavioral disengagement) has previously been associated with greater NA in patients with BCa who are undergoing treatment.[46]

The association of greater NA with lower metabolic activity in the vmPFC (BA11) is relevant, considering the role of this region in the representation of reward-based and value-based decision making, in the regulation of negative emotion, and in multiple aspects of social cognition, such as theory-of-mind skills and empathy.[63] Poor interpersonal skills (lack of social awareness and assertive communication skills) could prevent the acquisition and maintenance of social supports, a well established stress buffer in patients who have cancer.[64] Social support has also been associated with lower NA in patients with BCa who are undergoing treatment.[65] Diminished emotion regulation skills could contribute directly to greater NA, as demonstrated in multiple studies in patients with BCa.[66] Together, these findings suggest that, in women with mBCa, greater NA appears to be associated with less metabolic activity in at least 5 brain regions, which we hypothesize are central in successful adaptation to stressors and likely are relevant to navigating the challenges of cancer and its treatments. It follows that psychological interventions known to decrease NA in patients who have cancer (eg, cognitive behavioral therapy [CBT]-based approaches that target increased awareness, changing cognitive appraisals, reducing threat-associated arousal, teaching interpersonal skills, building social support, and improving emotion regulation)[67,68] might modulate the activity in these 5 brain regions to improve adaptation.[69] Future work should examine how activity in these brain regions and subregions is associated with patient reports of perceived cognitive, behavioral, and interpersonal coping and stress-management

skills. Identifying the neural correlates of both NA and stress-management skills is particularly relevant in patients with BCa given previous work showing that improved adaptation (decreased NA) after a CBT-based stress-management intervention is associated with greater increases in perceived stress-management skills,[70,71] which, in turn, are associated with improved markers of neuroendocrine activity in patients with BCa during primary treatment.[72,73] Developing these cognitive, behavioral, and interpersonal skills may relate to CNS-mediated changes in neuroimmune regulation in ways that could explain previously documented effects of CBT-based interventions on down-regulating proinflammatory and prometastatic processes[72,74] and improving long-term cancer outcomes in patients with BCa (eg, greater survival and disease-free survival).[51,75]

It is possible that patients with greater levels of NA and disease-related challenges (eg, patients with mBCa) may benefit the most from such interventions.[76] The current findings suggest that patients with mBCa who report the greatest levels of NA display reduced brain activity in regions that could be modulated by training in stress management that addresses the functions associated with these regions. Identifying high-NA patients could be relevant in distress screening and triaging to such interventions for optimizing limited resources for psychological support services in clinical oncology settings.

Strengths of this study include the recruitment of an adequately sized, homogenous sample of women with a specific type and stage of cancer (mBCa) who had a predefined exposure to different forms of cancer treatments; statistical controls for potential confounding variables and multiple comparisons; the application of standard brain-imaging and data-processing methods focused on a literature-based, predefined set of brain ROIs; and the assessment of NA or cancer-related distress that includes various negative emotions and a broad range of psychological symptoms.[24]

Limitations were the use of a cross-sectional design and a convenience sample of patients who were lacking diversity in race/ethnicity and sociodemographic status. The lack of a sample of healthy controls did not allow us to test whether the association of NA with brain metabolism was specific to patients who have mBCa. These factors act to limit any causal conclusions and generalizability to other populations beyond well educated Caucasian patients with mBCa. Another limitation is the lack of brain magnetic resonance imaging for these patients, which precludes us from accurately separating gray matter and white matter and thus correcting for possible gray volume reduction that may have occurred.

Conclusion

This work is an initial step in identifying brain regions that may underlie successful adaptation to the personal challenges of cancer and its treatment. Understanding how CNS-mediated adaptation processes relate to both NA and neuroimmune regulation could illuminate mechanisms to explain the documented effects of stress and stress-management interventions on health outcomes in patients with cancer.[4,52] Future work should relate activity in these brain regions with markers of neuroimmune regulation and, ultimately, longer term health outcomes, such as disease recurrence and survival, as well as long-term quality of life in patients who have BCa and those who have other types of cancer, whose course is known to be associated with NA and other psychological factors.[52] It is also important to explore associations between metabolic activity in these same *adaptation-mediating* brain regions and individual differences in other psychological constructs, such as positive affect, social support, social well-being, as well as meaning-making and benefit-finding—all of which are salutary factors associated with better psychological adaptation on the one hand and neuroimmune regulation on the other, in patients with cancer.[52]

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Joaquim C. Reis: Conceptualization, methodology, data collection, data analysis, writing–original draft, and writing–review and editing. **Luzia Travado:** Conceptualization, methodology, patient recruitment, data collection, writing–original draft, and editing. **Michael H. Antoni:** Conceptualization, methodology, formal analysis, writing–original draft, and writing–review and editing. **Francisco P. M. Oliveira:** Methodology (image processing and statistical analysis) and editing. **Silvia D. Almeida:** Methodology (image processing and statistical analysis) and editing. **Pedro Almeida:** Review and editing. **Aaron S. Heller:** Review and editing. **Berta Sousa:** Methodology (definition of patient inclusion/exclusion criteria, patient recruitment) and editing. **Durval C. Costa:** Conceptualization, methodology (image processing and statistical analysis), and editing.

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