HHS Public Access

Author manuscript

Med Hypotheses. Author manuscript; available in PMC 2016 March 01.

Published in final edited form as:

Med Hypotheses. 2015 March ; 84(3): 231–237. doi:10.1016/j.mehy.2015.01.002.

Measuring sickness behavior in the context of pancreatic cancer

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Abstract

Sickness behavior has been widely recognized as a symptom cluster that is associated with pro-inflammatory cytokine activation resulting from diverse conditions. The symptoms that comprise sickness behavior overlap substantially with major depressive disorder (MDD), which raises questions about the relationship between these two constructs, both of which occur frequently in patients with cancer. The construct of sickness behavior, while well-established in animal research, has rarely been applied to studies examining cytokines and depression in humans, perhaps because no reliable or validated measure of sickness behavior has been developed. We developed a version of a sickness behavior measure (the Sickness Behavior Inventory or SBI) and conducted a preliminary examination of its scale properties. Specifically, we hypothesized that a measure of sickness behavior would be significantly associated with five biomarkers of immune functioning (serum IL-6, TNF-α, IL-1b, IL-4, IL-10) in a human sample. The sample was comprised of four groups: individuals with pancreatic cancer and MDD (n=16), individuals with pancreatic cancer and who did not have a diagnosis of MDD (n=26), individuals without cancer who had MDD (n=7), and individuals who did not have cancer or MDD (n=25). The SBI demonstrated moderate reliability (Cronbach's alpha=.66), and total scores were significantly correlated with IL-6 (r_s=.26, p=.03), but not with other immune functioning markers. Factor analysis supported a 3-factor model of sickness behavior with different associations between the three SBI factors and cytokines. These results highlight the need to further refine symptom measurement to better understand the relationships among immune functioning, cancer, depression, and sickness behavior.

Introduction

"Sickness behavior" is widely recognized as an expression of immune system activation (1-3). The symptoms typically ascribed to this syndrome include fatigue, sleep disturbance,

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Conflict of Interest: The authors have nothing to disclose in regards to this study and manuscript.

hyperalgesia, and decreased appetite, among others. This constellation of symptoms frequently occurs in the context of cancer and its treatment, likely because of the immune system activation that accompanies the disease. Major depressive disorder (MDD) is another condition that has a high prevalence in patients with cancer. The constructs of sickness behavior and MDD share a number of symptoms, which raises questions about whether a common pathophysiology (i.e., immune system activation) underlies both disorders. Increasing evidence suggests that pro-inflammatory cytokines are potent mediators of sickness behavior, linking the body's stress response with the observed behaviors. Although numerous theories exist regarding the mechanisms by which the immune system engenders a behavioral response, several cytokines (e.g., interlukin-6 [IL-6], tumor necrosis factor-a [TNF-a], interlukin-1b [IL-1b]) have emerged as most closely linked to both sickness behavior and depression (4-6).

The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM-5) criteria for the diagnosis of MDD requires that either depressed mood or anhedonia be present for at least two weeks, in addition to the presence of three (if both depressed mood and anhedonia are present) or four (if only one is present) of the following symptoms: appetite/weight disturbance, sleep disturbance, psychomotor retardation/agitation, loss of energy, feelings of worthlessness or guilt, concentration difficulties/indecisiveness, and thoughts of death/ suicidal ideation/suicide (7). Contributing to diagnostic heterogeneity, depressed patients also exhibit a number of symptoms that are not part of the criteria of a DSM-5 diagnosis of MDD such as pain, decreased libido, pessimism, hypochondriasis, and anxiety (7-11). The pathophysiology of a specific depressive episode may be affected by diagnostically superfluous factors such as age, severity, duration, number of previous episodes, or presence of a precipitating stressor or medical illness.

Depression has been shown to co-occur in a number of chronic medical illnesses, including cancer, in rates that exceed that of healthy populations (12, 13). Depression is particularly common in patients with pancreatic cancer, where the prevalence rates for depression have typically ranged from 25% to 75% (14, 15). The link between pancreatic cancer and depression has been enduring; anecdotal reports of patients being treated for psychiatric symptoms that directly precede a diagnosis of pancreatic cancer date back to 1923 (16). Yaskin (1931) published a case study series describing the onset of depressive symptoms such as “vague pain,” “anorexia,” “general weakness and fatigability,” “insomnia,” “depression,” “lack of appetite,” and “mental fatigability,” which developed three to five months prior to detection of a pancreatic tumor (17). This relationship has continued to be reported in the literature in the form of case reports, population studies, retrospective reviews and prospective studies (14, 15, 18-23).

A review conducted by Green and Austin (1993) found that 50% of pancreatic cancer patients experience mood and anxiety symptoms prior to the cancer diagnosis (23). In a large, retrospective, population-based study, Carney and colleagues (2003) found that men who sought psychiatric treatment developed pancreatic cancer more often than men who did not seek treatment (Odds Ratio [OR] = 2.4; 95% Confidence Interval [CI] = 1.15 to 4.78), and that depression preceded pancreatic cancer more often than other types of cancer (OR = 4.1; 95% CI = 1.05 to 16.0) (18). Fras, Litin, and Pearson (1967) conducted a prospective

study with 139 patients known or suspected to have pancreatic cancer (*n*=46), colon cancer (*n*=64) or other medical disorders (included other types of cancer, pancreatitis, peptic ulcers, and undetermined illnesses; *n*= 29) (19). Twenty-two of 46 patients (48%) that were diagnosed with pancreatic cancer reported experiencing psychiatric symptoms prior to the onset of physical symptoms, and the incidence of psychiatric symptoms at the time of study participation was 76% in the pancreatic cancer group, versus 17% in the colon cancer group and 20% in the mixed illness group. More recently, a significantly higher rate of depression was observed in patients with pancreatic cancer (78%, 39/50), compared to liver (60%, 36/60), gastric (36%, 18/50), esophageal (24%, 12/50), and colorectal (19%, 10/52) cancers (22). In this study, there were no significant differences between groups in terms of age, gender, Tumor Nodes Metastasis (TNM) staging, and type of cancer treatment. This seemingly strong association between depression and pancreatic cancer has raised questions about whether a specific pathophysiological link exists between these two illnesses. For example, the emergence of psychiatric symptoms prior to the cancer diagnosis suggests that the high rate of depression observed is not simply a psychological reaction to a distressing diagnosis. One approach to exploring the link between these illnesses is to focus on identifying biomarkers that explain the phenomenology of depression in patients with pancreatic cancer.

Cytokines and Sickness Behavior

Pro-inflammatory cytokines, such as interlukin-6 (IL-6), interlukin-1 and (IL-1 and IL-1β) and tumor necrosis factor-α (TNF-α), act as messengers that trigger a metabolic, physiological, and behavioral response to infection. Anti-inflammatory cytokines, such as IL-4 and IL-10, are thought to attenuate the pro-inflammatory immune response (24). This literature proposes that in response to bodily insult or infection, cytokines communicate with the brain to produce sickness behavior (1). Sickness behavior has been described as a combination of symptoms that includes anhedonia, decreased appetite, decreased libido, psychomotor retardation, hyperalgesia, diminished energy, impaired cognition, hypersomnia, and social isolation (2, 3, 25). These symptoms serve the adaptive purpose of conserving energy to fight infection (1, 3, 26). Because many of these symptoms also overlap with MDD, it has been suggested that depression is a form of cytokine-induced sickness behavior (1), but the causal links between these three phenomena (depression, sickness behavior and immune system activation) are not yet clear. This ambiguity is compounded by the polythetic conceptualization of depression in current and previous editions of the DSM (27).

Inflammation and Sickness Behavior in Animals

There is a wealth of animal research examining the relationship between cytokine levels and sickness behavior. A seminal paper by Hart (1988) described a number of behaviors that accompany sickness in animals that constitute an integral component of the immune system response (28). Hart cited behavioral alterations such as “sleepiness, depression, loss of appetite, reduction of water intake, and cessation of grooming” (p. 124) that occur with fever in most animals, as well as evidence to suggest that IL-1, IL-6, and TNF-α mediate this behavioral response. Elevated pro-inflammatory cytokines have been shown to interfere with the acquisition of new information and cause reductions in spontaneous movement,

consumption of saccharin fluid (considered analogous to anhedonia), sexual behavior, social interaction, and food intake in rats (29,30). Frenois and colleagues (2007) examined the behavioral effects of cytokine activation after resolution of an induced sickness in rodents (31). They found that symptoms such as anhedonia persisted even after the acute sickness had subsided. This literature highlights the potentially important role of pro-inflammatory cytokines in causing symptoms typically associated with depression.

Inflammation and Behavioral Symptoms in Humans

Several lines of evidence support a role of pro-inflammatory cytokines in the development of depressive symptoms in humans. First, elevated pro-inflammatory cytokines have been observed in physically healthy psychiatric patients with depression. Dowlati and colleagues (2010) conducted a meta-analysis examining 24 well-designed studies examining plasma cytokine levels in patients with MDD compared to the healthy comparison samples (32). Although they analyzed a number of cytokines, their data demonstrated higher levels of two pro-inflammatory cytokines among depressed patients: IL-6 ($Z=6.36$, $p < .00001$) and TNF-α ($Z=4.48$; $p < .00001$). Studies have also shown that effective treatment with anti-depressant medication and electroconvulsive therapy reduce elevated pro-inflammatory cytokine levels (33-36). A small clinical treatment study found that an anti-inflammatory immune targeted therapy, in combination with an anti-depressant medication, resulted in significantly greater improvement in depressive symptoms than antidepressant medication alone (37).

A second line of evidence supporting the link between immune functioning and symptoms associated with depression comes from patients receiving cytokine-based anti-cancer therapies (38, 39). Experimental clinical trials establishing the tolerability of adjuvant high-dose intravenous interferon-α-2b (INF-α-2b) for the treatment of melanoma cited the occurrence of psychiatric symptoms as a common side effect (40, 41). Significant psychiatric and cognitive side effects have also been observed in patients with metastatic cancer receiving interlukin-2 and lymphokine activated killer cells (42).

Capuron and colleagues (2000) examined the effects of cytokine monotherapy and combination cytokine therapies on alterations in mood (38). Patients without a prior psychiatric history who had a diagnosis of renal cell carcinoma or melanoma were treated clinically with subcutaneous injections of IL-2 ($n=20$), subcutaneous injections of IL-2 and INF-α-2b ($n=6$), subcutaneous injections of INF-α-2b ($n=8$), and intravenous high-dose INF-α-2b ($n=14$). Although there were no significant differences in depressive symptom severity at baseline, differences between groups began to appear as early as day three and significant differences were evident by day five, with patients receiving IL-2 becoming more depressed than patients who received only INF-α-2b. The emergence of depressive symptomatology after treatment with IL-2 was also associated with increased serum IL-10 (an anti-inflammatory cytokine) on day five of therapy (43). Because IL-10 is not theorized to contribute to the emergence of depressive symptoms, the authors explained this unexpected finding by suggesting that IL-10 may represent a vestige of inflammation (43). Evidence also suggests that pre-treatment variables, such as low mood and sleep disturbance (i.e., mild depressive symptoms without a diagnosis of MDD), have been identified as risk

factors for the development of moderate to severe depressive symptoms in patients receiving cytokine-based cancer treatments (39, 44, 45). In sum, there is an abundance of scientific evidence citing the role of immune activation in producing behavioral alterations, although existing evidence for the link with MDD is inconclusive. The heterogeneity in response to immune activation, both within and across studies, suggests that inflammation may be related to a subtype of depression, but is not implicated in all cases of MDD. An inflammatory depressive illness may be the result of a vulnerability to immune system dysregulation, which would explain the behavioral risk factors for developing depression observed in cytokine therapy studies (39, 44, 45).

Hypothesis

Research exploring the relationships between depression, cancer, and cytokines has suggested that cytokines may represent the mechanism by which some cancer patients are at greater risk than others for developing depressive symptoms. However, this line of research has been handicapped by the reliance on a traditional conceptualization of depression, as outlined in the current diagnostic manual (7). The construct of “sickness behavior,” while well-established in animal research, has rarely been applied to studies examining cytokines and depression in humans, likely because no reliable or validated measure of sickness behavior has been developed for use in humans. This study sought to begin to fill this void, by analyzing an index of sickness behavior grounded in the theoretical and animal literature. We examined the psychometric properties of this index of sickness behavior (the Sickness Behavior Inventory or SBI), and its associations with immune functioning (via serum levels of cytokines. Our sample was comprised of four subgroups: patients with pancreatic cancer with and without MDD, as well as healthy controls with and without MDD.

We hypothesized that the SBI would demonstrate adequate levels of reliability and concurrent validity. Specifically, we anticipated that the SBI would have internal consistency (Cronbach's Coefficient alpha) of .70 or greater, with item-total correlations ranging from .20 to .70, and that the 8 items would load onto a single factor. We also hypothesized that the SBI would be significantly correlated with pro-inflammatory cytokines (IL-1b, IL6, and TNF-a), and negatively correlated with anti-inflammatory cytokines (IL-4 and IL-10).

Method

Participants

The sample (*N*=74) included 40 men (54.1%) and 34 women (45.9%), all of whom were at least 40 years old (mean age=57.6, SD=11.4, range: 0 to 85), and had an average of 15.8 years of education (SD=2.7, range: 11 to 20 years). Approximately one-third (*n* = 23; 31.1%) of the sample met criteria for a current major depressive episode based on the Structured Clinical Interview for DSM-IV Axis I disorders (46). There were no significant differences between the four subgroups on any of the demographic or medical variables studied (with the exception of depressive symptom severity and cancer diagnosis, as described below).

All patients with pancreatic cancer had Stage III or IV disease and were receiving outpatient chemotherapy treatment consisting of Gemcitabine or Gemcitabine-based combination therapies. This common chemotherapy regimen was selected in order to minimize the potential confounding influence of treatment on immune functioning. Patients were excluded if they had a comorbid medical condition that is associated with elevated cytokines or were currently receiving treatment known to affect immune functioning (e.g., cytokine-based treatments or nonsteroidal anti-inflammatory drugs within two weeks). Patients were also excluded if they had a history of bipolar disorder with psychosis, schizophrenia, schizoaffective disorder, substance abuse, or serious cognitive impairment (based on Mini-Mental State Exam (MMSE) scores below 20 (46). Premenopausal women, and women on hormone replacement therapy, were also excluded. The physically healthy comparison samples (depressed and non-depressed) met the same inclusion and exclusion criteria listed above, but without a diagnosis of cancer.

Procedures

All eligible patients provided written informed consent following disclosure of the study procedures, risks, and benefits. Trained interviewers administered the MMSE and questionnaires to elicit sociodemographic information and medical history, as well as a battery of clinician-rated and self-report questionnaires assessing a range of psychological and physical concerns. Individual items from these measures were extracted to create the SBI (described in more detail below). Ten cubic centimeters of blood were collected from each participant and processed by the hospital's Ludwig Center for Cancer Immunotherapy. Sera were stored in a freezer and processed as a single batch. The assay was completed using Meso Scale Discovery multiplex cytokine measurement techniques. Multiple cytokines were assayed, five of which were analyzed in the present study: IL-1β, IL-4, IL-6, IL-10, and TNF-α. A more detailed description of this process was previously reported (47).

The SBI was developed using eight items taken from the study measures (see Table 1). Although a definitive set of symptoms that comprise sickness behavior have not been established, we selected items that have most consistently been reported in the literature (3, 25, 48). For example, Raison and Miller (2003) identified the following symptoms as comprising sickness behavior: anhedonia, psychomotor retardation, anorexia/weight loss, decreased libido, fatigue, hyperalgesia, sleep disturbance, cognitive disturbance, and social isolation (25).

For the present study, four of the symptoms identified as part of the sickness behavior construct were extracted from Hamilton Rating Scale for Depression-21 (HRSD, (9) items: anhedonia, psychomotor retardation, anorexia/weight loss, and decreased libido. Fatigue was assessed using the Brief Fatigue Inventory (BFI, (49). Usual Fatigue in the Past 24 Hours item, while hyperalgesia was assessed using the Brief Pain Inventory (BPI, (50) Average Pain item. Sleep disturbance was assessed using the Pittsburgh Sleep Quality Index (PSQI, (51) Overall Sleep Quality item, which has been shown to serve as an adequate measure of overall sleep disturbance. Finally, cognitive disturbance was assessed using the Trail Making Test Part B, which measures executive functioning and is sensitive in detecting a wide range of cognitive disturbances (52). Social isolation was not assessed by any study

measure and therefore could not be included in this index. Because the different scales from which SBI items were drawn often used different metrics, all items were converted to an ordinal rating from 0 to 3 and values were summed.

Reliability of the SBI was assessed using Cronbach's coefficient alpha, an index of internal consistency, and an examination of corrected item-total correlations. Exploratory factor analysis, using principal components extraction, was also used to assess relationships among SBI items. Mean SBI total score differences between the four subgroups were analyzed using of analysis of variance. Given the highly skewed distribution of cytokines, non-parametric bivariate correlations (i.e., Spearman's Rho) were used to examine the relationship between sickness behavior and cytokines. Because this study was intended to be exploratory and the sample size was modest, no correction for type I error was employed. Similarly, these analyses were conducted using the entire sample, rather than within subgroups, in order to maximize variability in item scores and to provide a more heterogeneous sample in which to explore scale properties.

Results

The sample mean for the 8-item Sickness Behavior Inventory (SBI) total score was 5.99 (SD = 3.9, Range: 0 to 18). Depressed patients with pancreatic cancer had the highest SBI total score (Mean = 10.13, SD = 3.52), followed by depressed physically healthy patients (Mean = 9.14, SD = 2.67). Cancer patients without depression had significantly lower SBI total scores (Mean = 5.15, SD = 3.13), as did healthy non-depressed controls (Mean = 3.32, SD = 2.29).

The SBI demonstrated modest internal consistency, with Cronbach's coefficient alpha of .66. Corrected item-total correlations ranged from .12 for weight loss/appetite disturbance to .54 for anhedonia and fatigue. Weight loss/appetite disturbance was the only variable with an item-total correlation outside of (below) the *a priori* hypothesized range (.20 to .70). However, Cronbach's coefficient alpha was only increased by .01 with removal of this item.

Factor analysis was also used to identify the strongest elements of the hypothesized construct of sickness behavior. This analysis examined factor loadings onto a single factor extracted using the principle components method. Of the eight SBI items, only five had factor loadings that exceeded .40 (typically used as a threshold for identifying meaningful factor loadings): anhedonia (.77), psychomotor retardation (.70), fatigue (.72), sex drive/libido (.58), and sleep quality (.50). Lower factor loadings were observed for weight loss/appetite (.30), pain (.39), and cognitive disturbance (.36). An exploratory factor analysis, also using principle components factoring, indicated three factors with eigenvalues greater than 1.0, the first of which accounted for 31.8% of the variance. Analysis of this 3-factor model, based on a rotated factor solution (using Varimax rotation to maximize separation of the factors), indicated three variables that loaded onto the first factor: anhedonia, psychomotor retardation and sex drive/libido. The second factor, accounting for an additional 17.4% of the variance, also included three variables: pain, fatigue and sleep quality. The third factor, which accounted for 17.1% of the variance, included two variables: cognition disturbance and diminished appetite.

Concurrent validity of the SBI was evaluated by examining the associations between cytokine levels and the SBI items and total score. As expected, SBI total scores were significantly correlated with IL-6 (r_S = .26, p = .03; see Table 2). In addition, three of the individual SBI items were significantly correlated with IL-6: anhedonia (r_S = .26, p = .03), sex drive/libido (r_S = .37, p = .002), and psychomotor retardation (r_S = .32, p = .008). The remaining five SBI items (weight loss/appetite, pain, fatigue, cognitive disturbance and sleep quality) were not significantly associated with IL-6 in these analyses. Contrary to study hypotheses, the other cytokines studied were not significantly associated with SBI total scores (TNF-α, IL-1β, IL-4 and IL-10). Two of the individual SBI items were significantly associated IL-4: fatigue and sleep quality (r_S = .28, p = .02 and r_S = .31, p = .007, respectively). However, both of these associations were in the opposite direction to what was expected given that IL-4 is typically characterized as an anti-inflammatory cytokine.

Because our expectation of a single factor model was not supported, we used Spearman correlation coefficients to examine the associations between cytokine levels and the three factors identified in the exploratory factor analysis. This analysis indicated a significant correlation between the first factor (anhedonia, psychomotor retardation and sex drive/libido) and IL-6 (r_S = .32, p = .02), and between the second factor (pain, fatigue and sleep quality) and IL-4 (r_S = .36, p = .01). No other significant associations were observed between any the cytokines measured and the three factor scores. Of note, IL-4 and IL-6 were negatively correlated with one another (r_S = −.25, p = .05).

Discussion

Evidence from human and animal research supports the link between inflammation and a range of symptoms that fall under the rubric of depression, although a clear relationship with Major Depressive Disorder (MDD) has not yet been established. Depressive symptoms are also a salient feature in the clinical presentation of pancreatic cancer, yet the precise nature of this relationship remains unclear. One possible explanation for this association is through the increased production of pro-inflammatory cytokines; molecules that have been implicated in tumor growth (53). The phenomenon of “sickness behavior,” as an adaptive response engendered by pro-inflammatory cytokines, is well-established (48). Sickness behavior and MDD have many overlapping symptoms, but the relationship between these two constructs is not well understood, hindered in part by the lack of a systematic method for assessing sickness behavior in humans. A radical, unprecedented proposal states that that sickness behavior is depression and organizes this syndrome around malaise (i.e., mood symptoms are secondary) (54). In contrast, sickness behavior and depression have also been conceptualized as phenomena that exist on a continuum such that sickness behavior is a precursor to depression in vulnerable individuals (55). It is also plausible that sickness behavior is a subtype of depression (akin to melancholia) with an inflammatory etiology, or that the two conditions are distinct such that both can occur at the same time (i.e., a patient with cancer may have sickness behavior superimposed on depression and vice versa). This study represents an initial step in the process of developing a measure to disentangle the indistinctiveness of these phenomena, by examining the psychometric properties of an index of sickness behavior, the Sickness Behavior Inventory (SBI). Most importantly, the

significant correlation between scores on the SBI and the pro-inflammatory cytokine IL-6 provides preliminary support for the validity of this scale. Although no other pro-or anti-inflammatory cytokines were significantly associated with SBI total score, IL-6 has been the cytokine most often identified in both animal and humans research on inflammation and sickness behavior.

Our analysis generated moderate reliability for the SBI, as evidenced by Cronbach's coefficient alpha, with some items highly correlated with one another but others less so. All items had at least a .30 loading on a 1-factor model, but exploratory factor analysis suggested that a 3-factor model provided a better fit for the data. Examination of the 3 SBI factors identified a significant association between IL-4 and a subset of sickness behavior symptoms (fatigue and sleep disturbance) that was obscured when analyzing only SBI total scores. This association contradicted our hypothesis, as IL-4 is typically considered an anti-inflammatory cytokine and hence should be negatively associated with SBI symptoms. These findings raise several questions, such as whether the construct of sickness behavior is less uniform than researchers have typically presumed. A multi-faceted construct would explain these findings, as well as the often-contradictory pattern of associations observed between inflammation and behavior.

Although the relationship between pro- and anti-inflammatory cytokines is far from straightforward, the pattern of correlations observed may also reflect temporal influences on immune functioning and sickness behavior symptoms. For example, if IL-4 elevations represent a response to inflammation, this association may indicate that some SBI symptoms emerge later in the progression of sickness behavior. On the other hand, the discrepancy in correlations between the three factors might indicate the inclusion of some symptoms that are not actually part of a cytokine-related symptom cluster, sickness behavior characteristics that were not adequately measured by the SBI, or that different symptoms arise in response to different types of inflammation. Clearly these findings require further study using more comprehensive measures of sickness behavior.

There are, of course, a number of limitations in the present exploratory study. Most importantly, because the SBI was created retrospectively, using items drawn from a series of different measures, many items had to be “adjusted” in order to create a uniform metric for SBI items. The resulting items varied in both their psychometric adequacy (e.g., number of response options, range of observed scores) and face validity (relationship to the sickness behavior symptoms described in the literature). For example, only three individuals obtained high scores on the psychomotor retardation item, suggesting either that this item may not adequately measure the symptom or that the sample lacked sufficient heterogeneity in this domain (e.g., highly lethargic patients may be less inclined to participate in research). Other SBI items represented an imperfect proxy for the variable of interest. For example, average pain severity was used as an index of pain sensitivity. Similarly, because no measure of memory or concentration was available, an index of executive functioning was used to measure cognitive disturbance. However, inflammation research has more often focused on the negative impact of inflammation on verbal memory (56, 57). One symptom commonly included in the construct of sickness behavior, social isolation, was not be measured by any of the scales administered and thus, had to be omitted from the scale. In short, stronger

results might have been obtained using a scale specifically designed to measure sickness behavior.

These results were also limited by the inability to control for some potentially confounding variables (e.g., psychotropic medication) and significant missing data on other variables (e.g., cigarette smoking status). Although many variables have been identified as potentially impacting cytokine levels, including age, gender, diet, cigarette smoking, sleep patterns and weight/body mass (58), we were only able to analyze a subset of these variables (gender, race, BMI, education). Finally, the modest sample size, and in particular, the small number of medically healthy subjects with depression (while larger than many studies of cytokines in humans), further limited the ability to disentangle the impact of pancreatic cancer on the cytokine-depression relationship.

The goal of this study, however, was not to propose the SBI as a measure of sickness behavior, but rather to spur the development of a more comprehensive scale. Such a scale would help better explore the complex relationship between immune functioning and "psychiatric" symptoms such as fatigue, poor sleep, and cognitive disturbance. Only with continued research exploring these relationships will we develop a better understanding of the causal pathways to depression and the possible role that biological factors play in the development and maintenance of depressive symptoms. This level of differentiation is an especially salient issue in cancer and other medically ill populations where the prevalence of affective, cognitive, and somatic symptoms is high. Clinicians routinely face the challenge of determining whether a patient's symptoms are indicative of a depressive disorder and if so, whether and what type of mental health treatment is indicated. A validated measure of sickness behavior could help clinicians distinguish a cytokine-induced illness from MDD, and may help monitor changes in symptom severity. Isolating this level of neurobiological dysfunction has the potential for improved treatment outcomes, such as interventions that attenuate inflammation and/or the stress response (e.g., non-steroidal anti-inflammatory drugs, mindfulness-based practices).

Acknowledgments

This research was supported by the National Cancer Institute, grant R21 101767 (PI W. Breitbart).

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Table 1

Sickness Behavior Inventory (SBI) items

Item (Scale)	Content of query for symptom
Anhedonia (HRSD)	"How have you been spending your time this past week? Have you felt interested in doing (those things) or do you feel you have to push yourself to do them? Have you stopped doing anything you used to do? If YES: Why? Is there anything that you look forward to?"
Appetite/weight loss (HRSD)	"How has your appetite been this past week? What about compared to your usual appetite? Have you had to force yourself to eat? Have other people had to urge you to eat? Have you lost any weight?"
Libido (HRSD)	"How has your interest in sex been this past week? Has there been any change in your interest in sex?"
Psychomotor retardation (HRSD)	Rating based on observation during interview: slowness of thought and speech, impaired ability to concentrate, decreased motor activity
Pain (BPI)	Rate your pain by circling the one number that best describes your pain on the average.
Fatigue (BFI)	Rate your fatigue (weariness, tiredness) by circling the one number that best describes your usual level of fatigue over the past 24 hours.
Cognitive disturbance (TMT-B)	Ratings based on performance using norm-referenced t-scores
Sleep (PSQI)	During the past month, how would you rate your sleep quality overall?

Table 2

SBI Correlations with Cytokine Levels

	IL-1β	IL-6	TNF-α	IL-4	IL-10
Total Score	−.14	.26*	−.06	.17	.16
Anhedonia	−.22	.26*	.08	.06	.16
Appetite/weight loss	−.03	.12	.01	.06	.09
Sex drive/libido	−.11	.37**	−.01	−.09	.20
Psychomotor retardation	−.22	.32**	.14	−.13	.13
Pain	.04	.12	−.07	.16	.01
Fatigue	.11	.15	−.06	.28*	.07
Cognition	−.10	.10	.03	−.11	.13
Sleep	−.05	−.07	−.11	.31**	−.11
Factor 1	−.10	.32*	.13	.20	.17
Factor 2	−.02	.04	−.17	.36*	−.02
Factor 3	−.08	.11	−.04	−.14	.11

Factor 1: anhedonia, psychomotor retardation, * sex drive/libido

Factor 2: pain, fatigue, and sleep

Factor 3: appetite and cognition

* < .05

** < .01