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Pre-Treatment effects of peripheral tumors on brain and behavior: Neuroinflammatory mechanisms in humans and rodents

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Abstract

Cancer patients suffer high levels of affective and cognitive disturbances, which have been attributed to diagnosis-related distress, impairment of quality of life, and side effects of primary treatment. An inflammatory microenvironment is also a feature of the vast majority of solid tumors. However, the ability of tumor-associated biological processes to affect the central nervous system (CNS) has only recently been explored in the context of symptoms of depression and cognitive disturbances. In this review, we summarize the burgeoning evidence from rodent cancer models that solid tumors alter neurobiological pathways and subsequent behavioral processes with relevance to affective and cognitive disturbances reported in human cancer populations. We consider, in parallel, the evidence from human clinical cancer research demonstrating that affective and cognitive disturbances are common in some malignancies prior to diagnosis and treatment. We further consider the underlying neurobiological pathways, including altered neuroinflammation, tryptophan metabolism, prostaglandin synthesis and associated neuroanatomical changes, that are most strongly implicated in the rodent literature and supported by analogous evidence from human cancer populations. We focus on the implications of these findings for behavioral researchers and clinicians, with particular emphasis on methodological issues and areas of future research.

Keywords

cancer; depression; cognition; cytokines

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1. Introduction

Cancer patients suffer from a high prevalence of depression, anxiety, and cognitive disturbances (Evans et al., 2005). In fact, these disturbances are common among numerous other populations with chronic, inflammatory disease (e.g, cardiovascular disease, metabolic disease, HIV/AIDS), a fact that has stimulated discussion of potential shared biological mechanisms (Irwin & Miller, 2007; Lee et al., 2004). In the field of cancer research, it is widely acknowledged that various interrelated factors may underlie these behavioral comorbidities: tumor biology, distress associated with the cancer diagnosis, and/or cancer treatments (e.g., "chemobrain"). However, in spite of a recent burst of research activity in this area, these factors are rarely differentiated and their likely mechanistic interactions remain either entangled or ignored (Dantzer et al., 2012). For example, many clinical cancer studies do not encompass pre-diagnosis or pre-treatment psychological or physiological measures and most rodent studies of the impact of cancer treatment on the central nervous system (CNS) use tumor-free models. This results in a knowledge gap concerning the independent impact of tumor-associated biological processes on affective and cognitive symptoms despite the acknowledgment that tumors are capable of exerting an influence on the CNS (Cleeland et al., 2003; Lee et al., 2004), and that inflammation is inherent to all phases of tumor growth and metastases (Colotta et al., 2009). Addressing this deficit will help to identify specific underlying biological causes and underlying mechanisms of cancer-associated affective and cognitive disturbances, with the potential to improve treatment.

This review addresses this knowledge gap by presenting the current literature on the potential for tumor-associated biological processes to affect brain function (e.g., affect and cognition) independent of cancer-associated stress and treatments. We focus on behavioral changes that are most strongly associated with the presence of a tumor outside of the CNS and on identifying underlying mechanisms using data from human and rodent research. Direct effects of tumor associated biological processes on the brain would indicate that patients suffer affective and cognitive disturbances prior to the receipt of treatment. The clinical impact of psychological comorbidities should not be underestimated in the context of cancer. Both quality of life and adherence to treatment plans significantly deteriorate when depression and other mood disturbances are present (DiMatteo, 2003). Poor treatment adherence is a significant risk factor for decreased quality of life and increased mortality (Gripp et al., 2007). Isolating the specific influence of tumor biology on CNS processes and empirically testing how tumor biology interacts with the biology of stress and cancer treatments may allow for tailored treatment of cancer-associated affective and cognitive comorbidities. This review first provides a brief summary of inflammation-induced changes in behavior, and then summarizes the quickly growing body of behavioral research in rodent cancer models and clinical investigations of cancer patients prior to treatment. Evidence for affective and somatic symptoms of depression, cognitive impairment, and their mechanistic correlates are reviewed.

1.1 Inflammation-Induced Behavioral Changes

There is now considerable evidence that inflammatory pathways modulate affective and cognitive processes (Dantzer et al., 2008; Maes et al., 2012; Miller et al., 2009). Various

aspects of this concept have been termed the “cytokine” or “macrophage theory of depression” and “sickness behavior.” These concepts are primarily supported by literatures demonstrating that: 1) pathways exist between the periphery and CNS that allow for modulation of neural structure and function (e.g., enhanced permeability of the blood-brain-barrier and signaling via the vagus nerve; Dantzer et al., 1999), 2) acute cytokine or bacterial mimetic injection in rodents (i.p. lipopolysaccharide [LPS]; Dantzer et al., 2008) induces behavioral changes that are reversible by anti-inflammatory pharmacologic treatment, 3) inflammatory/immune responses and markers are elevated in patients with psychological disorders such as major depressive disorder (Maes et al., 2012; Miller et al., 2009) and, 4) anti-inflammatory drugs can be efficacious in the treatment of some psychiatric disorders (Köhler et al., 2014). For example, patients with clinical depression display elevations in proinflammatory cytokine concentrations in the blood and cerebral spinal fluid, increases in other circulating inflammatory effector and target molecules (e.g., prostaglandins, acute phase proteins, chemokines, cell adhesion molecules; Maes et al., 2012) and altered adaptive immune cell function (Howren, Lamkin, & Suls, 2009; Miller, 2010). Cytokine-based treatment of cancers (i.e., interferon-alpha) also result in considerable increases in depression (Capuron et al., 2002; Udina et al., 2012), which resolve when the treatment is terminated.

Studies using animal models have delineated inflammatory mechanisms underlying changes in behavior, including sickness behavior, affective symptoms, and cognitive function. However, the majority of the research in this area has focused on models of acute illness. The canonical acute bacterial infection model, a single, sub-toxic i.p. injection of LPS (a component of the cell wall of E. coli bacteria), causes proinflammatory cytokine production primarily by first-responder monocytes in the peritoneal cavity. Then, through both neural and humoral signaling pathways (Dantzer et al., 2008; Quan & Banks, 2007; Quan, 2014), cytokine production rapidly ensues in the brain (hippocampus, hypothalamus, forebrain) and stimulates the production or activation of other inflammatory effectors (IDO, iNOS, Nf-kB, COX; Quan et al., 1998). The roles of these inflammatory markers in cytokine-induced behavioral changes, and consistent with clinical research in depressed patients, are summarized in Box 1. Acute sickness behaviors (e.g., lethargy, social withdrawal, fever, anorexia) akin to “somatic” or “vegetative” symptoms of depression, subsequent affective-like behaviors, and impaired learning and memory (Pugh et al., 1998) follow for several days after LPS treatment. The experimental manipulation of cytokines in these models (e.g., pharmacologic blockade, cytokine gene knockout) has established that brain-production of cytokines are necessary and sufficient for the subsequent behavioral changes (Dantzer et al., 1998, 1999; Kent et al., 1992). As with all preclinical studies, there is the assumption that affective-like behaviors assessed by rigorously validated rodent behavioral tests (Dantzer et al., 2012) are analogous to some affective symptoms of depression in human beings.

A longer-enduring infectious disease model (i.p., injection of Bacillus Calmette-Guerin [BCG]) has been used to probe for differences in chronic versus acute bacterial illness. Like the LPS model, BCG induces depressive-like behaviors after overt sickness behaviors have subsided. Coincident with the behavioral changes, the BCG model triggers brain cytokine and IDO production (Lestage et al., 2002; Moreau et al., 2005). While longer-lasting than

the LPS model, the behavioral and inflammatory consequences of BCG infection still last only 3–4 weeks (Moreau et al., 2008).

In summary, the majority of the mechanistic postulating about mental comorbidities within the cancer context (and other chronic inflammatory diseases) logically focuses on neuroinflammatory pathways (Cleeland et al., 2003; Dantzer et al., 2012; Illman et al.; Lee et al., 2004). Peripheral tumors and their microenvironment are sources of various cytokines and potentially use neural and/or humoral signaling pathways similar to peripheral infection to gain access to the brain. A review of the current literature that best encapsulates the purely biological influence of peripheral tumors on brain physiology and depression and cognition follows. Here we organized the corresponding behavioral data from rodent and human research and discuss the putative inflammatory mechanisms associated with these behaviors. Finally, we discuss how this compilation of data may be used to modify current treatment strategies and future research design in an effort to move towards more individualized, mechanism-based treatment approaches.

2. Rodent Models of Cancer

Recent basic research in rodents provides compelling evidence that primary tumors and tumor-associated inflammation alter brain physiology and behavior. Essentially, these models are comparable to patients with cancer prior to treatment, though both human and rodent research reflects considerable heterogeneity in the type and timing of neoplasms investigated. Rodent modeling allows for both the differentiation of potentially additive/synergistic biopsychological factors and for the empirical study of underlying mechanisms. For the purpose of this review, we focused on PubMed primary reports in the English language of rodent models with malignant primary tumors outside of the CNS, using the search terms [“rodent;” “cancer” or “tumor;” “inflammation” or “cytokine” or “neuroinflammation” or “serotonin;” “behavior” or “cognition” or “learning” or “affect” or “depression” or “anxiety, indexed from “no determined start date” to January, 2015]. Additional criteria were that the reports included tumor-free control groups and groups in which both cancer therapies and psychosocial stressors were absent.

2.1 Evidence for Inflammation in Tumor-Bearing Rodent Models

In rodent models of solid neoplasms, tumor cells, surrounding stromal cells, and leukocytes recruited to the tumor site produce many inflammatory mediators (cytokines, chemokines) in the tumor microenvironment (reviewed in Allavena et al., 2008; Candido & Hagemann, 2013; Coussens & Werb, 2002). Commonly identified inflammatory mediators include various cytokines, chemokines, and their receptors (e.g., IL-1, TNFα, IL-6, IL-10, IL-12, TGFβ, MIP1α, CXCR4; Candido & Hagemann, 2013; Turrin et al., 2004), prostaglandin E2, NF-κB and STAT3 signaling cascades, and enzymes such as IDO, COX, and iNOS (reviewed in Cesario et al., 2011; Karin et al., 2002; Landskron et al., 2014; Munn & Mellor, 2013; Uyttenhove et al., 2003). Cytokine production in the tumor microenvironment is sometimes significant enough to be detectable in the general circulation of experimental models (Fang et al., 2012; Lamkin et al., 2011; Norden et al., 2014; Uomoto et al., 1998; Yang et al., 2014). However, this detection appears to be dependent upon the type of tumor and the timing of the blood sampling relative to tumor growth, as elevations in circulating

cytokines do not necessarily accompany elevations in tumor cytokines, brain cytokines, or behavioral changes in these models (Catalano et al., 2003; Pyter et al., 2009). Given the known interactions between the HPA axis and inflammatory responses, it is important to note that solid tumors either increase or have no effect on basal circulating corticosterone concentrations (Azpiroz et al., 2008; Bojková et al., 2011; Chuluyan et al., 2000; Pyter et al., 2009; Yang et al., 2014), decrease stressor-triggered corticosterone responses (Pyter et al., 2009), and increase glucocorticoid receptor expression in brain regions involved in the HPA axis negative feedback loop (Pyter et al., 2009) in some rodent models.

2.2 Sickness, Affective-Like and Cognitive Impairment Behaviors in Tumor-Bearing Rodent Models

In rodents, many somatic-like symptoms of depression have considerable overlap with "sickness behaviors" (e.g., food intake, physical activity, motivation for social interaction). Several tumor models have been developed specifically for their extreme negative effects on food intake, weight loss, and muscle wasting (Emery, 1999; Tisdale, 2002). More broadly, however, in studies of tumor models that focus on other behaviors (e.g., affective-like), weight loss ranges widely from significant (Lamkin et al., 2011; Norden et al., 2014; Wang et al., 2001; Yang et al., 2014) to absent (Coma et al., 2003; Pyter et al., 2009), depending on the tumor type, the rate of tumor growth and the time of assessment. In one study, total weight loss includes a specific reduction in brain mass (Coma et al., 2003).

The weight loss observed in some models is coincident with electrophysiological muscle fatigue (Aulino et al., 2010; Baltgalvis et al., 2010; Murphy et al., 2012; Norden et al., 2014), reduced locomotor activity (Lamkin et al., 2011; Murphy et al., 2012; Xiu et al., 2010), and reduced voluntary wheel running (Baltgalvis et al., 2010; Wood et al., 2006). Reduced locomotor activity may reflect fatigue or physical limitations due to the tumor location and/or changes in areas of the CNS that regulate movement (Dantzer et al., 2012). While the tumor may infringe on physical movement or muscle endurance in some models, thereby confounding results of affective-like or cognitive behavioral testing, depressive-like behaviors persist in other tests that are virtually independent of locomotion (e.g., sucrose anhedonia, see below). In contrast, the effects of peripheral tumors on sleep, a component of fatigue, remain understudied. Finally, limited investigation of social withdrawal, a common component of sickness behavior, indicates that tumor-bearing rodents are no less interested in social interactions (Pyter et al., 2009) or E2-primed lordosis with a mate (Walf & Frye, 2010) than their tumor-free counterparts. In contrast to tumor-associated sickness behaviors, the vast majority of studies to examine affective-like or cognitive behaviors in cancer models were published within the last five years, excepting some research in the 1970s–80s on learned taste aversion as it relates to cancer anorexia. Based on the previously described criteria, all but one of the 13 reports that assessed affective-like behavior found significant increases in depressive-like behavior in a broad range of solid tumor models and one leukemia model relative to tumor-free controls (Table 1). Therefore, it appears that varying tumor types and induction methods produce similar affective-like consequences s, though more studies would be necessary to determine if model type influences behavioral outcomes. One of the standardized tests validated to assess depressive-like behavior (Krishnan & Nestler, 2008) is a tail suspension test in which mice are suspended by their tail and the

latency and duration of immobility (versus active struggling) is quantified over a 5-min period. Immobility behavior in this context is hypothesized to be analogous to clinical symptoms of despair. As evidence of this test's predictive validity, pharmacological treatment with antidepressants for several weeks prior to testing ameliorates the immobility behaviors. For example, mice that are subcutaneously inoculated with murine hepatoma cells display significant increases in immobility duration using the tail suspension test 12 days after inoculation, a behavioral change that is not observed earlier (6 or 8 days after inoculation), when tumor size is relatively small (Qi et al., 2009). Other reported increases in depressive-like behaviors in tumor-bearing rodents include what is termed "behavioral despair" using the Porsolt forced swim test and reduced preference for sucrose-infused drinking water (i.e., sucrose anhedonia). In rodents, the absence of preferential consumption of sucrose solutions over tap water is hypothesized to be homologous to symptoms of anhedonia in depressed patients. Tumor-bearing animals consistently display reductions in sucrose preference (DeWys, 1974; Godbout et al., 2005; Lamkin et al., 2011; Pyter et al., 2009; Smith et al., 1994; Xiu et al., 2010), which do not appear to be driven by changes in nutritional motivation nor changes in taste thresholds, as preference for a saccharine solution (non-nutritive) is also reduced and aversion to noxious solutions (e.g., quinine, hydrochloric acid) remains unchanged (Smith et al., 1994).

In addition to being a measure of fatigue, total locomotor activity in an open field also assesses whether hyperactivity, a hypothesized indicator of anxiety-like behavior, is manifest in tumor-bearing models. In contrast, hypoactivity (i.e., lethargy) is noted in several tumor models (Table 1). An arguably more anxiety-specific measure gleaned from the same open field paradigm is central tendency, the conflict between rodents' exploration of the bright, exposed center of the open field versus remaining in close proximity to the relatively protected, dark edges of the field (Crawley, 2006). Central tendency is not affected by the presence of mammary tumors in rats (Pyter et al., 2009). A similar light-dark conflict is presented using the elevated plus maze test for anxiety-like behavior, and the results in tumor-bearing rodents indicate that there is no apparent deficit in this behavior either (Pyter et al., 2009; Walf & Frye, 2010). In contrast, obsessive-compulsive anxiety-like behavior is significantly elevated in tumor-bearing rats (Pyter et al., 2009). Finally, one study indicates that behavioral responses of tumor-bearing mice to a social defeat paradigm, in which a highly aggressive conspecific interacts with the tumor-bearing subject, are characterized by increased avoidance of social interactions and decreased non-social exploration (Vegas et al., 2004). The authors argue that these behaviors may be consistent with avoidance behaviors, which are typical symptoms of depressed individuals.

Cognition is primarily assessed through tests of learning and memory in non-human animals. Four out of seven of the reports included in the present search focus on learned taste aversion in the context of cancer-associated anorexia and cachexia. By manipulating the type of chow that was administered throughout the tumor induction and growth paradigm, these studies inadvertently examined the effects of tumors on classical conditioning. Rats implanted with sarcoma, leydig cell, or mammary tumors successfully develop a learned taste aversion to novel diets (conditioned stimulus) eaten during tumor growth (unconditioned stimulus) (Bernstein & Sigmundi, 1980; Bernstein, 1985; Treneer & Bernstein, 1987); but see one experiment using mammary tumors (Bernstein & Fenner,

1983). Extinction of this taste aversion (i.e., the learned acquisition of a new relationship between the same two stimuli), at least 25 days after the tumor is removed, however, is impaired relative to both tumor-free controls on the same diet scheme and tumor-bearing controls that receive a novel (and therefore, preferred) diet post-tumor excision (Bernstein, 1985; Treneer & Bernstein, 1987). This suggests that: 1) although the pairing of the conditioned and unconditioned stimuli is longer in duration and less intense than other classical conditioning paradigms, the aversions developed are quite robust, and 2) the resistance to extinction in rats that previously had tumors may reflect an impairment in reversal learning. Finally, in advanced stages of both mammary and leydig cell tumor progression, the learned taste aversion spontaneously dissipates, indicating that the taste aversion memory may become impaired or disrupted over prolonged or advanced stages of tumor development (Bernstein, 1985).

The remaining studies on cognitive function in tumor-bearing models examined other modalities of learning and memory using a variety of standardized behavioral tests. For example, the ability to distinguish between novel and familiar objects is remarkably impaired in tumor-bearing rats and mice (Pyter et al., 2010; Yang et al., 2014). Using a fear-based classical conditioning paradigm, tumor-bearing rats and mice tend to display modest impairments in passive auditory conditioning (Pyter et al., 2010), but not in contextual conditioning (Pyter et al., 2010; Yang et al., 2012). In terms of hippocampal-based learning, rats with tumors make more long-term, reference memory errors in an appetitive radial arm maze task, while working memory remains similar to tumor-free controls. Long-term memory in an aversive water maze test is unchanged by the presence of a tumor (Pyter et al., 2010).

2.3 Neuroinflammatory Correlates of Sickness, Affective-Like, and Cognitive Impairment Behaviors in Tumor-Bearing Rodent Models

The evidence for the direct involvement of inflammatory cytokines (IL-1, IL-6, TNFα, INF-γ) in the induction of the somatic behaviors of anorexia/cachexia is quite prevalent (for reviews see Dianliang, 2009; Matthys & Billiau, 1997; Plata-Salamán, 2000; Tisdale, 2002). Given the high likelihood of mechanistic overlap, much may be gained by assimilating the previously discreet older literature on metabolism and the more recent affective/cognitive research in cancer models.

From the metabolic work, it is evident that many cancer cachexia models display elevated proinflammatory cytokine and cytokine receptor proteins and transcripts in the whole brain (Catalano et al., 2003), within brain regions known to regulate affective-like and cognitive behaviors (e.g., hippocampus, hypothalamus, cortex, brainstem, cerebellum; Chance et al., 2003; Plata-Salamán, 2000; Turrin et al., 2004; Wang et al., 2001), and even in CSF (Opara et al., 2005) relative to pair-fed tumor-free controls or simply tumor-free controls. The null-finding exceptions are rare (Carson et al., 1998; Wang et al., 2001). Mounting evidence indicates that this central cytokine production is tumor-initiated rather than host-derived (Baltgalvis et al., 2010; Cahlin et al., 2000; Kawamura et al., 1999; Rebeca et al., 2008). Notably, evidence of elevations in circulating cytokines need not be present for tumor-induced inflammation to be transduced into brain cytokine production (Quan, 2014). In

cancer models of depressive-like behavior and select cognitive impairments, elevations in brain proinflammatory cytokine production are observed primarily in the cortex and hippocampus (Norden et al., 2014; Pyter et al., 2010; Pyter et al., 2014; Pyter et al., 2009; Yang et al., 2014).

Local brain cytokine production, in turn, can influence a number of neural pathways by which tumors may induce behavioral changes (Plata-Salamán, 2000; Tisdale, 2002). Those known to overlap with the hypothesized mechanisms underlying cytokine-induced affective, somatic and cognitive behavior involve: iNOS and COX enzymatic activities, neuronal death, and tryptophan metabolism. Briefly, the negative behavioral consequences of tumors are associated with elevations in iNOS expression among various hypothalamic regions (Wang et al., 2001; Yang et al., 2012) and elevations in cerebral blood vessel expression of COX-1 (Ruud et al., 2013; not COX-2 (Wang et al., 2001). The results from measuring constitutive hippocampal COX-2 expression in tumor-bearing models with affective-like behavior or cognitive impairment are mixed (Yang et al., 2012, 2014).. Evidence of microglial activation has also been detected in the hippocampus and cortex of tumor-bearing rodents (Norden et al., 2014; Pyter et al., 2014; but see Yang et al., 2012). Many of these elevations in neuroinflammatory markers are attenuated by the systemic administration of the anti-inflammatory agent, minocycline (Norden et al., 2014). Furthermore, adding a peripheral inflammatory challenge (i.p. LPS injection) to a rat model of mammary cancer exacerbates the neuroinflammatory signaling responses of IL-1β, IDO, and markers of NF-κB and microglial cell activation among various brain regions that regulate affective-like and cognitive behavior (Pyter et al., 2014). These results suggest that both baseline neuroinflammation and neuroinflammatory responses are altered by the presence of a peripheral tumor.

Peripheral tumors associated with poor novel object recognition also reduce cell proliferation, neurogenesis, and dendritic length (qualitatively) in the dentate gyrus of the hippocampus (Yang et al., 2014, but see Yang et al., 2012). Growth factors associated with neurogenesis, GMFβ and BDNF, are reduced or remain unaltered in the hippocampus in tumor-bearing rodents that display cognitive impairments or depressive-like behavior (Qi et al., 2009; Pyter et al 2010; Yang et al 2014) Neural redox homeostasis may underlie these changes in brain plasticity as reduced oxidase potential is detected in brains of tumor-bearing mice with depressive-like behavior (Chen et al., 2006; Papiez et al., 2009; Qi et al., 2009), which is reversible with antidepressant treatment (Qi et al., 2009).

Weight loss in a tumor-bearing model is also associated with cerebellar atrophy and reduced numbers and size of Purkinje neurons (Michalak et al., 2006), suggesting that neuronal apoptosis in the cerebellum may be a consequence of peripheral tumor growth. Other pathways downstream of brain cytokine production that are observed to be modulated in these models of cancer cachexia, but may be less relevant to affect/cognition, include changes in neuronal K+ channel expression (Coma et al., 2003; Vicente et al., 2004) and in metabolic neurohormone synthesis (Chance et al., 2003).

Lastly, altered amino acid production and turnover in the brain, the particularly relevant tryptophan catabolism (reviewed in Laviano et al., 1996), is reported in rodent cancer

models. Brain tryptophan concentrations are consistently higher in cachexic tumor-bearing rodents relative to pair-fed, tumor-free controls (Chance et al., 1988; Chance et al., 1983; Krause et al., 1979), even days prior to gross tumor palpability (Muscaritoli et al., 1996). The tryptophan metabolite and target of many antidepressant treatments, serotonin (5-HT), is also increased in brain tissue of tumor-bearing rodents (Chance et al., 1988, 1983; Muscaritoli et al., 1996), but see (Krause et al., 1979). Slightly different from the cachexia literature, however, whole brain 5-HT concentrations and SERT binding are decreased, whereas indicators of 5-HT turnover (5-HIAA, 5-HT/5-HIAA ratio;(Vegas et al., 2004) remain unchanged in tumor-bearing mice with depressive-like behavior. This may be counterintuitive given that depressive-like behavior is associated with reduced brain 5-HT concentrations (Muller & Schwarz 2007). However, 1) 5-HT concentrations do not reflect 5-HT release and, 2) turnover (or catabolism) of 5-HT may be simultaneously elevated as demonstrated by the concurrent elevations in brain 5-HT metabolites (e.g., 5-HIAA) and 5-HIAA:5-HT ratios (Chance et al., 1988, 1983; Chuluyan et al., 2000; Krause et al., 1979; Muscaritoli et al., 1996; Uomoto et al., 1998). Tumor resection resolves many of these alterations in brain amine concentrations (Chance et al., 1988). Future determination of the activity of the kynurenine pathway downstream from tryptophan in tumor-bearing models is necessary to elucidate the details of these potential neurotransmitter mechanisms.

Arguably most consistent with data attainable in humans, a couple of studies have linked elevated circulating cytokines and sickness behavior in these rodent models. For example, significant negative correlations were found between blood IL-6 concentrations and voluntary wheel running, cachexia (Wood et al., 2006), and locomotion (Lamkin et al., 2011). Circulating tryptophan or relevant tryptophan ratios (to 5-HT metabolites) are also altered in cancer anorexia models (Chance et al., 1988, 1983; Krause et al., 1979; Meguid et al. 1998; Muscaritoli et al., 1996) and are significantly correlated with the onset of a palpable tumor (Källberg et al., 2010) and the reduction in food intake (Muscaritoli et al., 1996).

3. Cancer Patients Prior To Treatment

A separate line of inquiry concerns cancer patients prior to treatment (i.e., prior to surgical resection of tumor, chemotherapy, radiation). Pre-treatment data provides important insights into both biological consequences of tumor development and attendant psychological and behavioral symptoms. For this review, we focus primarily on English language original reports indexed in Pubmed that considered inflammatory factors and/or psychological and behavioral symptoms in cancer patients prior to treatment. Search terms included: “depression,” or “anxiety,” or “cognition,” or “neuropsychological test,” or “cancer,” or “tumor,” indexed from “no determined start date” to January, 2015. Studies that only examined these factors in patients during or following treatment were not included. For psychological and behavioral factors, we focused primarily on research that consider symptoms prior to diagnosis, as the diagnosis itself represents a major psychosocial stressor capable of inducing both depressive and immune consequences. For studies of cognitive impairment in cancer patients prior to treatment we focused on studies that assessed multiple cognitive domains and, due to the small number of available studies, included studies in

which patients were post-surgery but pre-chemotherapy/radiation in addition to studies of patients prior to all treatment.

3.1 Inflammation in Cancer Patients Prior to Treatment

Similar to in rodent cancer models, tumor-derived inflammation in humans originates from tumor cells, the surrounding stromal cells (Gogusev et al., 1993; Kinoshita et al., 1999; Offner et al., 1995; Pusztai et al., 1994; Watson et al., 1990) or tumor-associated macrophages (TAMS), and infiltrating T-cells (Allavena et al., 2008). Circulating pro-inflammatory cytokines are elevated in various cancer populations prior to any treatment including ovarian cancer (Lutgendorf et al., 2008), colorectal cancer (Belluco et al., 2000), lung cancer (Wojciechowska-Lacka, et al., 1996), breast cancer (Benoy et al., 2002), pancreatic cancer (Okada et al., 1998), gastric cancer (Kim et al., 2003), prostate cancer (Michalaki et al., 2004), head and neck cancer (Riedel et al., 2005), renal cell carcinoma (Yoshida et al., 2002), and bladder cancer (Mahmoud El-Salahy, 2002). High concentrations of circulating inflammatory cytokines such as IL-6 and TNF-α are associated with later stage disease (Belluco et al., 2000; Kim et al., 2003; Kozlowski et al., 2003; Michalaki et al., 2004; Okada et al., 1998; Yoshida et al., 2002), poorly differentiated tumors (Goswami et al., 2013; Kaminska et al., 2005; Ljungberg et al., 1997; Mahmoud El-Salahy, 2002; Yoshida et al., 2002) and tumor size/volume (Chung & Chang, 2003; Kaminska et al., 2005; Plante et al., 1994) in a variety of malignancies. Elevations of circulating pro-inflammatory cytokines have also been associated with less common indices of disease severity including extent of tumor necrosis in colorectal cancer (Guthrie et al., 2013; Richards et al., 2012). Spontaneous release of pro-inflammatory cytokines in cultures of primary tumor further suggests that circulating levels of inflammatory molecules are at least partially tumor-derived in some malignancies (Burger et al., 1995; Toutirais et al., 2003; Wigmore et al., 2002). Inflammatory cytokines are also elevated in ascites fluid proximal to the tumor in ovarian cancer patients (Moradi et al., 1993) and malignant pleural effusions in lung cancer (Yamaguchi, 2000). In ovarian cancer, levels of IL-6 from ascites are strongly associated with IL-6 in plasma;(Costanzo et al., 2005), similar to that of malignant pleural effusions from lung cancer patients (Yamaguchi, 2000). Other systemic effects of tumor-associated inflammation have been noted, especially alteration of the hypothalamic-pituitary-adrenal (HPA) axis. Altered cortisol patterns have been identified in ovarian cancer patients (Weinrib et al., 2010), endometrial cancer patients (Sannes et al., 2013), and oral cancer patients (Bernabé et al., 2012) prior to treatment. In ovarian cancer patients, these patterns are significantly associated with IL-6 concentrations in the ascites fluid (Schrepf et al., 2015) and in plasma (Lutgendorf et al., 2008).

In addition to pro-inflammatory cytokines, cancer patients prior to treatment show altered patterns of tryptophan metabolism. IDO activity is associated with tumor induction and is often highly expressed in solid tumors (Munn & Mellor, 2013). Higher kynurenine/tryptophan ratios and lower tryptophan concentrations in blood compared to healthy controls have been reported in colorectal cancer, malignant melanoma, non-small cell and small cell lung cancer, ovarian cancer, endometrial cancer, vulvar cancer, and breast cancer patients (de Jong et al., 2011; Engin et al., 2010; Huang et al., 2002; Lyon et al., 2011; Sperner-Unterweger et al., 2011; Suzuki et al., 2010; Weinlich et al., 2007), although the opposite

pattern was noted in a study of primary cervical cancer patients (Fotopoulou et al., 2011). Thus, it appears that increased IDO activity in peripheral blood is associated with many malignancies prior to treatment.

3.2 Affective/Somatic Symptoms of Depression and Cognitive Impairment in Cancer Patients Prior to Treatment

Whether a clinical diagnosis of depression is associated with subsequent increased incidence of cancer in the following years remains a controversial subject (Oerlemans et al., 2007). However, for some malignancies, changes in affect and somatic symptoms are noted in the months prior to and at the time of a diagnosis of cancer, consistent with the time frame of tumor development. This review will focus on these symptoms.

In pancreatic cancer, there is strong evidence that affective symptoms of depression may manifest prior to diagnosis (Green & Austin, 1993; Joffe et al., 1986; Sebti et al., 2014). One study reported that clinically relevant depression occurs in 50% of patients in the year prior to diagnosis (Joffe et al., 1986). Among commonly reported symptoms in pancreatic cancer patients prior to diagnosis, affective symptoms like crying spells and feelings of hopelessness were common in addition to somatic symptoms like loss of appetite, fatigue, anorexia, and insomnia (Green & Austin, 1993).

Symptoms that precede a diagnosis of ovarian cancer overlap considerably with somatic symptoms of depression. Case control studies using retrospective recall of symptoms report that fatigue (O.R. 3.9, 95% CI 2.5–6.1), weight loss or weight gain (OR 14.2, 95% CI 8.2–24.5), and loss of appetite (OR 8.8, 95% CI 4.3–18.2) are much more commonly reported by ovarian cancer patients prior to diagnosis than controls visiting the same clinics (Olson, 2001; Vine et al., 2003). Fatigue and weight loss/gain are also more common amongst those with advanced (stages III–IV) versus early (stages I–II) of ovarian cancer. The onset of these symptoms was most often reported as 2–7 months prior to diagnosis, suggesting that they are not part of pre-existing condition, but rather are consistent with the timeframe of tumor development. Another study examining medical records (and hence free of recall bias) found that loss of appetite, fatigue and anxiety are all significantly more common in ovarian cancer patients compared to controls in the 6 months preceding diagnosis (Friedman et al., 2005).

In a retrospective study of symptoms prior to lung cancer diagnosis, most symptoms were reported as occurring in the 12 months prior to diagnosis, and included 68% of patients reporting fatigue, 64% change in appetite, 59% changes in sleep, and 50% weight loss (Corner et al., 2005). These results were confirmed by a case-control analysis of symptoms recorded in primary care settings in the two years prior to a lung cancer diagnosis that found fatigue, loss of appetite, and loss of weight are more commonly reported by patients than controls (fatigue OR 2.3, 95% CI 1.9–2.9; loss of appetite OR 4.8, 95% CI 3.3–7.0; loss of weight OR 6.2, 95% CI 4.5–8.6; Hamilton et al., 2005). Importantly, when the final 180 days prior to diagnosis were excluded from the analyses fatigue, loss of appetite, and loss of weight no longer distinguish cases from controls. This suggests that these symptoms manifest relatively close to the time of diagnosis.

In women awaiting surgery for suspected ovarian cancer, symptoms of somatic and affective depression are more prevalent in those subsequently diagnosed with ovarian cancer than in those with tumors of low malignant potential, despite facing presumably similar levels of distress and no differences in levels of interpersonal difficulties (Lutgendorf, 2008). Nonetheless, it is possible that symptoms of invasive disease (e.g. bowel distension) may have contributed to suspicion of ovarian cancer and consequent symptoms of depression, though this possibility warrant further investigation. One study of women presenting at an outpatient clinic subsequently diagnosed with breast cancer found that 28% met criteria for state anxiety and depression prior to diagnosis though the prevalence of these affective disturbances were not reported for women who were subsequently found to be free of cancer (Van Esch et al., 2012). In contrast, another report using assessment of affective symptoms in women prior to diagnosis either with breast cancer or benign disease found that neither anxiety nor depression were higher in cancer patients than women with benign disease in the two years prior (Eskelinen & Ollonen, 2011). Similarly, another study that examined physical and mental well-being in the year before a prostate cancer diagnosis found no differences between men that were subsequently diagnosed with prostate cancer and matched healthy controls (Reeve et al., 2012). Therefore, increased symptoms of depression, and specifically affective symptoms, are not universal prodromal features of cancer.

That somatic symptoms may be more pronounced in cancer patients prior to treatment is unsurprising. In a large-scale mixed cancer population (n=213) post-diagnosis but pre-treatment somatic symptoms are responsible for most of the variance in Beck's Depression Inventory scores when compared to healthy controls (Wedding et al., 2007). More specifically, the effect sizes (Cohen's D) for the difference in affective symptoms averaged 0.12 between cancer patients and controls versus 0.34 for somatic items. Interestingly, some affective items are considerably less pronounced in cancer patients (i.e. sense of failure, d= −2.35, guilt, d=−1.00), while every somatic item except loss of libido is more prevalent in cancer patients. Comparing patients with solid tumors to those with haematological malignancies reveals no differences in affective items or total depression scores, but significantly higher somatic scores in patients with solid tumors (Wedding et al., 2007).

A relatively small number of published studies have examined neuropsychological test performance in cancer patients prior to treatment. Eleven total studies were identified: 5 in breast cancer samples (Ahles et al., 2008; Hermelink et al., 2007; Hurria et al., 2006; Mandelblatt et al, 2014; Wefel et al., 2004), and 1 each in samples of prostate cancer (Green et al., 2004), ovarian cancer (Mayerhofer et al., 2000), testicular cancer (Wefel et al., 2011), head and neck cancer (Bond et al., 2012), lung cancer (Meyers et al., 1995), and leukemia (Meyers et al., 2005). Of these, five were in samples prior to the receipt of any treatment and five were samples in which some patients had completed surgery but not chemotherapy or radiation. Sample sizes ranged between 18 and 110 participants.

Reviewing the areas of cognitive impairment tested across studies resulted in enough crossover in several domains by percent of sample impaired to warrant comparison across studies: global impairment (6 studies), verbal learning -- both total recall (5 studies) and delayed recall (4 studies), manual dexterity (4 studies), executive function (5 studies), visual scanning (5 studies), verbal fluency (5 studies), processing speed (4 studies) and auditory

attention (3 studies) (Table 2). Some studies that did not report percentages of impaired patients are discussed but could not contribute to mean and median calculations. Mean and median percentages of cognitive impairment in cancer patients across studies were as follows: global impairment, 32% (median: 33%); total verbal learning 31.7% (median 37.7%); delayed recall 39.3% (median 33%); executive functioning 23.3% (median 22%); manual dexterity 24.5% (median 24.5%); visual scanning 18.9% (median 16%); verbal fluency 10.6 % (median 10%); processing speed 7.8% (median 6.2%); auditory attention 5.4% (median 5%). Several studies also compared cancer patients prior to treatment to controls or normative means using group means rather than percentage of sample impaired, and these generally revealed fewer differences. These results reveal a broadly consistent pattern of impairment. Approximately one-third of patients demonstrated impairment in total recall and delayed recall on verbal learning tasks, and one-quarter demonstrated impairment on manual dexterity and executive functioning tasks. Approximately 20% demonstrated impairment on visual scanning tasks, while approximately 10% or fewer were impaired on verbal fluency, processing speed, and auditory attention tasks. The percentages of impaired patient in the verbal learning, executive function, manual dexterity, and visual scanning domains were considerably higher than what would be expected were the samples drawn from a healthy population, while verbal fluency, processing speed and auditory attention did not appear to differ substantially from normative expectations. Verbal learning (either total recall or delayed recall) was the most impaired domain in every study in which it was assessed, while processing speed and auditory attention were the least impaired domains in all but one study.

Methodological differences appeared to play a large role in the differential findings. For instance, studies which examined sample means in comparison to healthy controls or normative means appeared to find fewer differences than studies which determined if individual participants met criteria for impairment. For instance, one 2007 study of breast cancer patients found no significant difference in verbal learning using group means compared to normative means (Hermelink et al., 2007) while a 2004 study of breast cancer patients using individual scores compared to normative means found that the number of patients impaired on verbal learning tasks was twice what would be expected in a normal, healthy population (Wefel et al., 2004). As it would appear that many of the sample means studied would fall within a normal performance range according to normative means, group means likely mask individuals with impaired performance. This further suggests that cognitive impairment affects a particular, vulnerable subsample of cancer patients prior to treatment.

Studies that consider moderating factors reveal inconsistent results. For instance, 3 of 4 studies that considered fatigue as a moderating factor did not find it to be associated with any test results, while the fourth found it to be associated only with processing speed and global impairment. Similarly, depression was not related to neuropsychological test results in three of five studies, but was associated with processing speed in two studies and both verbal learning and global impairment in another. In one study of breast cancer, medical comorbidities were the only factor associated with worse neurocognitive performance, such that having 2 or more comorbidities was associated with a nearly 9 fold increase in the risk for cognitive impairment (Mandelblatt et al., 2014).

3.3 Inflammatory Correlates of Somatic/ Affective Symptoms of Depression and Cognitive Impairment

Elevations in peripheral markers of inflammation are linked to the elevations in somatic and affective symptoms in cancer patients prior to treatment in a variety of malignancies. In ovarian cancer patients with invasive disease, elevated IL-6 in plasma and ascites is associated with greater somatic, but not affective, symptoms of depression prior to diagnosis (Lutgendorf et al., 2008). In breast cancer patients prior to the receipt of treatment, a diagnosis of depression by structured interview (Structured Clinical Interview for DSM-IV, SCID) is associated with both elevated plasma IL-6 and abnormal dexamethasone suppression tests compared to non-depressed patients (Soygur et al., 2007). Similarly, levels of soluble IL-6 receptor (sIL-6r) and CRP are positively associated with fatigue and affective symptoms of depression in breast cancer patients prior to treatment (Courtier et al., 2013; Pertl et al., 2013). In patients with peritoneal carcinomas, serum levels of IL-6 and CRP are associated with greater fatigue and somatic symptoms of depression, but not affective symptoms (Low et al., 2014). In prostate cancer patients with non-metastatic disease elevated TNF-α levels in serum are associated with fatigue, depression and anxiety (HADS) (Dirksen et al., 2013). In malignant melanoma patients, sIL6-r levels in serum are negatively associated with self-reported combined affective and somatic symptoms (Self-Reported Depression Scale; SDS) and sTNF-r levels positively associated (Friebe et al., 2007) In metastatic colorectal cancer patients serum IL-6 levels are positively associated with loss of appetite and nausea/vomiting, TGF-β levels are positively associated with loss of appetite and fatigue (Rich et al., 2005). In advanced lung cancer patients higher Glasgow Prognostic Scores (a composite measure of abnormal albumin and CRP levels in blood) are correlated with both depression and anxiety levels (HADS) (Giannousi et al., 2012) and serum CRP levels with fatigue (Brown et al., 2005). However, in a study of colorectal cancer patients, levels of TNF-α and CRP in plasma are not associated with baseline depressive symptoms (Archer et al., 2012). Similarly, in a study of depressed versus non-depressed hepatobilary carcinoma patients, levels of TNF-α and IFN-γ in plasma did not differ between groups (Steel et al., 2007).

IDO activity has also been linked to somatic and depressive symptoms in cancer patients. Reduced serum tryptophan is associated with more severe somatic symptoms (RSC) but not anxiety or depression scales in a sample of colorectal cancer patients (Huang et al., 2002). In pancreatic cancer patients, a lower kynurenic acid:tryptophan ratio in serum is associated with worse symptoms of anxiety and depression (Botwinick et al., 2014). Regarding cognitive function, only one study has examined inflammatory correlates of impairment in cancer patients prior to treatment and found that levels of IL-6 were found to be associated with poorer executive functioning and levels of IL-8 were inversely associated with measures of memory (Meyers, et al., 2005).

4. Conclusions and Limitations

Viewed in tandem, the rodent and human literatures suggest that similar inflammatory mechanisms and behaviors, which were initially established with respect to behavioral changes following acute immune challenges (i.e. sickness behavior, cognitive impairment),

are also features of chronic disease (i.e., cancer). Differences between cancer-associated behavioral changes and acute sickness behavior are likely due to differing time scales, the magnitude of inflammation, and subtle differences in underlying mechanisms. One possibility is that tumor growth, in early stages, represents a slow-priming effect on the immune system rather than full activation of conserved sickness responses. In fact, mounting a full sickness response over the span of tumor growth would not be viable given the high energetic cost of such behaviors (fever, anorexia). The sensitized neuroinflammatory responses to LPS administration in tumor-bearing rats (Pyter et al., 2014) and microglial activation (Norden et al., 2014; Pyter et al., 2014) support this priming hypothesis.

Significant gaps in knowledge remain. Sleep dysregulation is clearly prevalent in human cancer patients prior to treatment, but little information is known about sleep and associated mechanisms in tumor-bearing rodents. While models of tumor-bearing rodents suggest that some anxiety-like behaviors may be enhanced, little is known about symptoms of anxiety and inflammation in human cancer patients prior to diagnosis. Methodological disparities have thus far limited inference from behavioral results in tumor-bearing rodents. For instance, models which clearly result in reduced locomotion are not ideal for behavioral tests that required considerable movement such as the tail-suspension and Porsolt forced swim test. Similarly, models which result in wasting and anorexia are not ideal for behavioral tests predicated on food/consumption rewards. Additionally, inflammatory correlates of cognitive impairment have not been established in cancer patients prior to treatment. In other clinical populations, elevated peripheral biomarkers of inflammation (CRP, IL-6) have been associated with neurocognitive decline such as delayed verbal learning tasks (Bettcher et al., 2012; Grassi-Oliveira et al., 2011; Hudetz et al., 2011) and impaired executive functioning (Hoshi et al., 2010; Mooijaart et al., 2013). Increased markers of indoleamine-2,3-dioxygenase activity in peripheral blood have been linked to poorer global cognitive performance in stroke survivors and cardiac patients following surgery (Forrest et al., 2011; Gold et al., 2011). Some of these effects may be hippocampus-dependent, as damage limited to the hippocampus has previously been associated with impaired recognition memory and verbal learning in patients suffering hypoxia-induced brain damage (Hopkins et al., 1995) and hippocampal impairments generally produce worse performance on NOR tests in rodent models, though this relationship continues to be explored (Antunes & Biala, 2012).

This work has several implications for future research. The appearance of somatic symptoms in the months prior to a cancer diagnosis again raises the possibility of early detection for some malignancies. Against this proposition is the fact that most of these symptoms appear to be non-specific and experienced by a wide swath of the population. However, this conclusion is based on the limited survey of symptoms that are discovered in clinic visits. It is unlikely symptoms of anxiety and depression are widely monitored. It is possible, therefore, that somatic, depressive, or cognitive symptoms may have utility in combination with physiologic measures to contribute algorithmically to characterizing high-risk patients.

Measures of depression in cancer patients, even those that attempt to exclude somatic symptoms, likely capture considerable influence of tumor-derived processes in some malignancies. This is an issue that has posed a considerable challenge to researchers

interested in affective disturbances in cancer patients. While depressive symptoms are sometimes modeled as a unitary construct, in cancer populations it appears that there are differential associations between somatic and affective symptoms of depression and measures of inflammation (Lutgendorf et al., 2008). Many theories of depression and sickness behavior emphasize putative shared inflammatory mechanisms, however, there is also evidence that affective and somatic symptoms do not always occur in tandem in acute and chronic illness, and that specific presentations (e.g., melancholic vs. vegetative depression) may be undergirded by independent, albeit associated, mechanisms (Maes et al., 2012). We would advocate, therefore, the use of measures or structured interviews that allow both somatic and depressive symptoms to be measured, rather than measures which aggregate both or exclude somatic symptoms. In cancer populations both affective and somatic symptoms have important and sometimes divergent associations with quality of life outcomes throughout the trajectory of treatment (Reuter et al., 2004; Teng et al., 2014).

The understanding that cancer may fundamentally alter behavioral processes prior to any treatment should challenge existing paradigms and lead to changes in rodent models of cancer treatment and protocols for observational studies of cancer patients. The physiology and behavior of pre-diagnosis cancer patients may already be compromised before the advent of other challenges associated with cancer and cancer treatment. Figure 1 represents a timeline of various factors involved in the cancer experience that may influence the associated behavioral outcomes. Notably, tumors, cancer-associated stressors, and cancer treatments can independently influence relevant neuroinflammatory pathways over chronological stages of cancer, as well, as their likely synergistic/additive biological interactions. Finally, persistent negative behavioral symptoms in cancer survivors suggest that these neuroimmunological pathways are likely altered over the long term (Figure 4D). Many rodent models of cancer treatment-related symptoms (CTRS) do not employ tumor-bearing animals. Given that there is now a substantial body of work suggesting that many of the behaviors of interest and associated physiological and CNS processes of interest to CTRS researchers are altered by the presence of tumors, this modeling approach is no longer adequate. Further, the immunologic changes secondary to cancer and the immunologic changes secondary to treatment are not necessarily additive, but may be interactive. In fact, these interactions have begun to be explored in the context of fatigue and cognitive complaints in breast cancer patients (Bower, 2014; Bower et al, 2013: Bower, 2007; Ganz, 2013). Cancer represents a state of immunologic compromise; this is demonstrated potently by the differential response to subsequent acute immune challenges (i.e., LPS) seen in tumor-bearing rodents, and by the fact that many alterations of the immune system (e.g., enhanced production of pro-inflammatory cytokines) associated with cancer-treatment symptoms are the same as those that are clearly altered by tumor-related processes. That tumor bearing rats have an enhanced neuroinflammatory signaling cascade response to LPS challenge may be an important finding for cancer treatment symptom research, as Toll-Like receptor 4, which is responsive to LPS, also responds to damage-associated molecular patterns (DAMPs) that are thought to be more prevalent following some cancer therapies (Krysko et al., 2013). It is worth considering that predisposing genetic factors may increase the risk of both cancer and worse symptoms associated with the disease and treatment. Studies of genetic polymorphisms and symptom profiles in cancer patients pre-treatment

may help to identify vulnerable patients. In fact, a recent investigation of breast cancer patients prior to treatment revealed that variations in cytokine genes are associated with subsyndromal depressive symptoms through the treatment trajectory (Saad et al., 2014).

Moving forward, baseline measurements and monitoring of immune processes prior to treatment are an important step in observational studies of cancer patients at risk for cancer treatment symptoms. At least one meta-analysis of cancer treatment related cognitive impairment found no evidence for treatment associated impairment in studies which included a baseline measurement of cognitive function compared to those that used non-treatment controls (Anderson-Hanley et al., 2003). The lack of studies considering inflammatory processes and cognitive function in cancer patients is an urgent concern. Future research should incorporate in vitro challenges of isolated circulating immune cells from cancer patients prior to treatment in order to provide information about facets of immune compromise not inferable from systemic markers of inflammation. Additionally, there is evidence that depressive episodes may impact inflammatory pathways, as inflammatory markers are seen to increase with greater numbers of depressive episodes (Maes et al., 2012). It is possible, therefore, that inflammatory mechanisms associated with cancer-treatment symptoms may be altered by tumor-associated inflammation and depressive episodes triggered by diagnosis prior to the impact of treatment. Non-cancer controls, particularly those facing the same pre-surgical stress but subsequently found not to have malignant disease, can provide critical information about the relationship between tumor-associated biological mechanisms and psychological comorbidities. Well-designed imaging studies may play an important role in future research, as diffusion tensor imaging techniques have been able to identify structural alterations that predict future remission of depression following antidepressant treatment (Korgaonkar et al., 2014) and transition to chronic pain (Mansour et al., 2013) suggesting that neural signatures may be an important and underused marker of vulnerable phenotypes in cancer. Structural (e.g. reduced fractional anisotropy in the hippocampal formation) or functional (e.g. reduced functional connectivity in the prefrontal cortex) changes in networks associated with executive function and verbal learning are strong candidates. In fact, a recent fMRI study found that pre-treatment dysfunction in executive networks was more strongly associated with post-treatment fatigue and cognitive dysfunction than receipt of chemotherapy in a longitudinal study of breast cancer patients (Askren et al., 2014). As it would appear that a substantial proportion of cancer patients pre-treatment suffer from deficits in memory tasks, clinicians should consider what potential impact this may have on information provided to patients at this critical juncture. Patient retention of treatment-related information should be assessed in cancer patients prior to treatment to determine if alternative strategies for communication and retention need to be developed.

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Highlights

- We review evidence of peripheral tumor-associated biological process on the CNS
- Tumors exert considerable influence on behavior via inflammatory pathways
- Cancer patients may experience affective and cognitive symptoms due to tumor

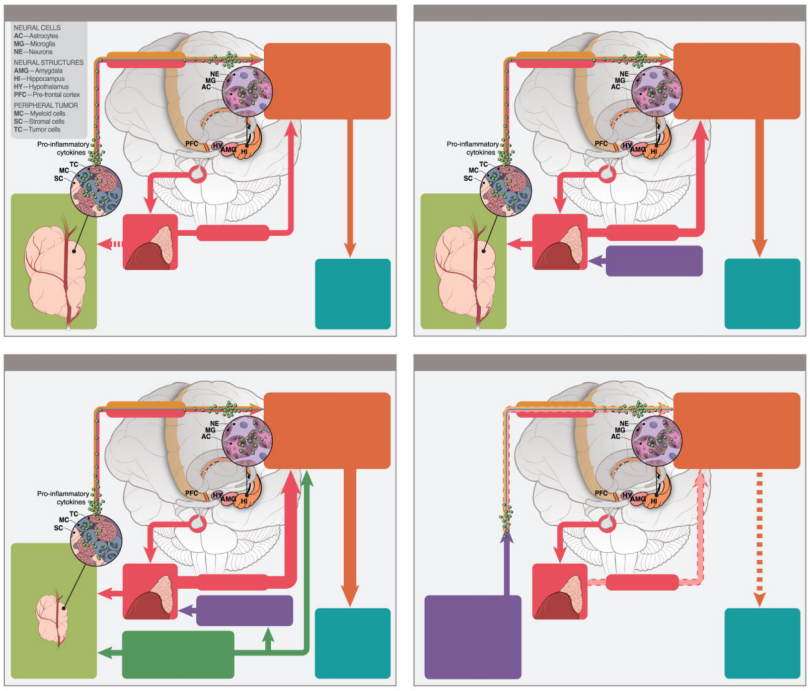

Figure 1.

Proposed causes underlying cancer-associated behavioral alterations over the cancer process: (A) pre-cancer diagnosis, (B) post-cancer diagnosis, pre-treatment, (C) during cancer treatment, and (D) post-treatment, cancer remission.

Table 1

fective-like and cognitive behavioral and inflammatory consequences of peripheral tumor growth in rodents.

ublication	Tumor model	Behavioral Tests	Putative Behavioral Correlate	Peripheral Inflammatory Measures	Central Inflammatory Measures	
ang 2012	mouse breast (SI; sc)	Tail suspension	⬆ depressive-like behavior (learned helplessness/ behavioral despair)		⬆	hippocampal COX-2 and iNOS expression
ang 2014	mouse colorectal (SI; sc)	Tail suspension	⬆ depressive-like behavior (learned helplessness/ behavioral despair)	⬆ blood IL-6	⬆	hippocampal IL-6 and TNFa mRNA
					⬇	cell proliferation and neurogenesis markers and qualitatively shorter dendrites in dentate gyrus
					⬇	hippocampal BDNF and COX-2 mRNA
ng 2012	mouse colorectal (SI; sc)	Tail suspension	⬆ depressive-like behavior (learned helplessness/ behavioral despair)	⬆ blood IL-12 (initially)	⬇	binding ratio of ^{123}I-ADAM in various SERT-rich in relevant brain regions
2009	mouse hepatoma (SI; ip)	Tail suspension	⬆ depressive-like behavior (learned helplessness/ behavioral despair)		⬇	whole brain SOD activity (reversible by fluoxetine)
					⬇	hippocampal GMFβ and BDNF mRNA (reversible by fluoxetine)
orden 2014	mouse colorectal (SI; sc)	Tail suspension	⬆ depressive-like behavior (learned helplessness/ behavioral despair)	⬆ blood IL-6	⬆	cortical microglial activation (reversible by minocycline)
		Sucrose anhedonia	⬆ depressive-like behavior (anhedonia)		⬆	hippocampal and cortical IL-1β and IL-6 (reversible by minocycline)
eWys 1974	rat breast (SI; sc?)	Sucrose anhedonia	⬆ depressive-like behavior (anhedonia)			
mkin 2010	mouse ovarian (SI; ip)	Sucrose anhedonia	⬆ depressive-like behavior (anhedonia)	⬆ blood IL-6, TNFα, IL-10		
u 2010	rat breast (SI; sc)	Sucrose anhedonia	⬆ depressive-like behavior (anhedonia)			
nith 1994	rat sarcoma (implant; sc)	Sucrose/saccharine anhedonia	⬆ depressive-like behavior (anhedonia)			

Publication	Tumor model	Behavioral Tests	Putative Behavioral Correlate		Peripheral Inflammatory Measures	Central Inflammatory Measures	
Pyter 2009	rat breast (carcinogen)	Porsolt forced swim	⬆ depressive-like behavior (learned helplessness/ behavioral despair)		⬆ tumor IL-1β and GM-CSF mRNA	⬆	hippocampal and IL-10
		Sucrose anhedonia	⬆ depressive-like behavior (anhedonia)				
Papiez 2009	rat myeloid leukemia (SI; ip)	Porsolt forced swim	⬆ depressive-like behavior (learned helplessness/ behavioral despair)			⬇	cortical and h antioxident pe
						⬆	cortical and h peroxidation, oxidative stre
						⬆	cortical and h activity (but i hippocampus
						⬆	cortical 5-HT binding affini receptors
Lebena 2014	mouse melanoma (SI; iv)	tail suspension	⬆ depressive-like behavior (learned helplessness/ behavioral despair)		⬆ blood IL-6 for large tumors	⬆	hippocampal mRNA
						⬇	striatal DOPA prefrontal 5-H HT
Vegas 2004	mouse melanoma (SI; iv)	Social defeat	⬆ potentially depressive-like behavior (social avoidance)			⬇	hypothalamic
						⬆	hypothalamic
Vegas 2004	mouse melanoma (SI; iv)	Social defeat	⬆ anxiety-like behavior (exploration)			⬇ ⬆	hypothalamic
						⬆	hypothalamic
Pyter 2009	rat breast (carcinogen)	Marble burying	⬆ anxiety-like behavior (obsessive- complusive)		⬆ tumor IL-1β and GM-CSF mRNA		hippocampal and IL-10
Qi 2009	mouse hepatoma (SI; ip)	Total locomotor activity	⬆ sickness behavior (lethargy)	⬇ anxiety-like behavior (hyperactivity)		⬇	whole brain S (reversible by
						⬇	hippocampal mRNA (rever
Fang 2012	mouse colorectal (SI; sc)	Total locomotor activity Total	⬆ sickness behavior (lethargy)	⬇ anxiety-like behavior (hyperactivity)	⬆ blood IL-12 (initially)	⬇	binding ratio various SERT brain regions

Publication	Tumor model	Behavioral Tests	Putative Behavioral Correlate		Peripheral Inflammatory Measures	Central Inflammatory Measures	
Xiu 2010	rat breast (SI; sc)	locomotor activity	⬆ sickness behavior (lethargy)	⬇ anxiety-like behavior (hyperactivity)			
Lamkin 2010	mouse ovarian (SI; ip)	Total locomotor activity	⬆ sickness behavior (lethargy)	⬇ anxiety-like behavior (hyperactivity)	⬆ blood IL-6, TNFα, IL-10		
Papiez 2009	rat myeloid leukemia (SI; ip)	Total locomotor activity	⬆ sickness behavior (lethargy)	⬇ anxiety-like behavior (hyperactivity)		⬇	cortical and h antioxident p
						⬆	cortical and h peroxidation, oxidative stre
						⬆	cortical and h activity (but i hippocampus
						⬆	cortical 5-HT binding affini receptors
Yang 2014	mouse colorectal (SI; sc)	Novel object recognition	⬇ cognition (temporal lobe-dependent learning and memory)			⬆	hippocampal mRNA
						⬇	cell proliferat neurogenesis qualitatively dentate gyrus
						⬇	hippocampal mRNA
Pyter 2010	rat breast (carcinogen)	Radial arm maze	⬇ cognition (hippocampal-dependent learning and memory - aversive)			⬆	hippocampal
		Novel object recognition	⬇ cognition (temporal lobe-dependent learning and memory)				
Bernstein 1985	rat leydigcell and breast (both implant; sc)	Taste aversion (in advanced disease)	⬇ cognition (classical conditioning with tumor as unconditioned stimulus)				
Treneer 1987	rat leydig cell (implant; sc) and tumor resection	Taste aversion (reversal learning)	⬇ cognition (classical conditioning with tumor as unconditioned stimulus)				

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Publication	Tumor model	Behavioral Tests	Putative Behavioral Correlate	Peripheral Inflammatory Measures	Central Inflammatory Measures
Bernstein 1980	rat sarcoma (implant; sc)	Taste aversion	↑ cognition (classical conditioning with tumor as unconditioned stimulus)		
Bernstein 1983	rat leydig cell (implant; sc)	Taste aversion	↑ cognition (classical conditioning with tumor as unconditioned stimulus)		

N/C = No change

SI = syngeneic inoculation

sc = subcutaneous

iv = intravenous

ip = intraperitoneal

OVX = ovariectomized

Table 2

Study characteristics and results of neuropsychological tests in cancer patients prior to chemotherapy/radiation.

First Author, Year	**Ahles 2008**	**Bond 2012**	**Green 2004**	**Hermelink 2007**	**Hurria 2006**
Sample	Breast cancer	Head and Neck cancer	Prostate cancer	Breast cancer	Breast cancer
Time	Post-surgery/Pre-chemotherapy/radiation	Pre-Treatment	Pre-Treatment	Pre-treatment	Post-surgery/Pre- chemotherapy/radiation
Inclusion criteria	Stage 1–3A, 18–70 years	21 or older	Non-localized prostate cancer	Non-metastatic breast cancer	Newly diagnosed Stage 1–3 breast cancer, age 65 or older
Exclusion criteria	CNS disease, previous cancer/cancer treatment, neurologic disorder, substance abuse, brain injury, psychiatric disorder	Brain metastases, intracranial radiation, previous cancer	Previous hormonal therapy, severe LUTS, abnormal serum testosterone	None listed	Metastatic disease, psychiatric disorder, previous cancer treatment
n	110	70	77	109	31
Definition of Global Impairment	2 domains below 1.5 S.D. of healthy controls, or 1 domain 2.0 S.D. below*	Average Global Deficit Score ≥ 0.5	N/A	≤ 5% normative mean on 2 or more domains	2 domains below 2.0 S.D. below normative means
Global Impairment	22%	47 %	N/A	31%	11%
Definition of Impairment on individual tests	Below 1.5 S.D. of healthy controls*	T-score <40 By normative means	Comparison to healthy control	Mean comparison to HC	N/A
Verbal Learning	n/a	25%	< Healthy controls	Not different from norms	n/a
Test	n/a	RAVLT total	N/A		n/a
Delayed Recall	n/a	21%	N/A	N/A	n/a
Test	n/a	RAVLR DR	N/A	N/A	n/a
Auditory Attention	n/a	N/A	N/A	Not different from norms	n/a
Test	n/a	N/A	N/A	Digit Span	n/a
Processing Speed	n/a	19%	<Healthy controls	>Norms	n/a
Test	n/a	SDMT	N/A	N/A	n/a
Executive	n/a	22%	Marginal < Healthy Controls	<Norms	n/a
Test	n/a	TMT-B	Stoop Inhibitory	TMT-B	n/a
Verbal fluency	n/a	17%	N/A	<Norms	n/a
Test	n/a	AVF	N/A	RWT	n/a
Visual Scanning	n/a	16 %	N/A	Not Different from Norms	n/a

First Author, Year	Ahles 2008	Bond 2012	Green 2004	Hermelink 2007	Hurria 2006
Test	n/a	TMT-a	N/A	TMT-A	n/a
Dexterity	n/a	N/A	N/A	N/A	n/a
Test	n/a	N/A	N/A	N/A	n/a

First Author, Year	Mayerhofer 2000	Meyers 2005	Meyers 1995	Wefel 2011	Wefel 2004
Sample	Epithelial ovarian cancer	Myelogenous Leukemia/ Myelodysplastic Syndrome (AML/ MDS)	Small cell lung cancer	nonseminomatous germ cell tumors (NSGCT)of the testis	Breast cancer
Time	Pre-treatment	Pre-treatment	Pre-treatment	Post-surgery/pre-chemotherapy	50% pre-surgery, all pre-chemotherapy/radiation
Inclusion criteria	Newly diagnosed EOC, normal blood panel	Newly diagnosed AML/MDS	Newly diagnosed limited sclc, ≥ 8th grade education	Newly diagnosed NSGCT, age 18–50	Breast carcinoma, 18 + years, ≥ 8 years of education
Exclusion criteria	Neurologic disorder, psychiatric disorder, brain metastases, substance abuse, cognition altering medication	N/A	psychiatric disorder, substance abuse	Neurologic illness, brain injury, psychiatric disorder, brain metastasis	evidence of metastases, psychiatric disorder, previous cancer, cognition altering medication
n	28	54	21	69	18–84**
Definition of Global Impairment	n/a	n/a	n/a	2 domains below 1.5 S.D. of normative means, or 1 domain 2.0 S.D. below	2 domains below 1.5 S.D. of normative means, or 1 domain 2.0 S.D. below
Global Impairment	n/a	n/a	n/a	46 %	35%
Definition of Impairment on individual tests	Median values compared to normative means	2 S.D. below normative mean	1.5 S.D. below normative mean	1.5 S.D. below normative mean	1.5 S.D. below normative means
Verbal Learning	n/a	44%	38%	37.7%	14%
Test	n/a	HVLT	VSRT	HVLT	HVLT, VSRT
Delayed Recall	n/a	41%	70%	N/A	25
Test	n/a	HVLT-DR	VSRT-DR	N/A	VSRT-DR
Auditory Attention	n/a	7%	5%	4.3%	N/A
Test	n/a	Digit Span	Digit Span	Digit Span	N/A
Processing Speed	Not different than norms	8%	0%	4.3%	N/A
Test	Alphabet cross-out test	Digit Symbol	Digit Symbol	Digit Symbol	N/A
Executive	n/a	29 %	38 %	21.7%	6%
Test	n/a	TMT-B	TMT-B	TMT-B	TMT-B

First Author, Year	Mayerhofer 2000	Meyers 2005	Meyers 1995	Wefel 2011	Wefel 2004
Verbal fluency	n/a	17 %	10 %	2.9%	6%
Test	n/a	COWA	COWA	COWA	COWA
Visual Scanning	n/a	28 %	33 %	4.3%	13%
Test	n/a	TMT-A	TMT-A	TMT-A	TMT-A
Dexterity	< than norms	37 %	31.5 %	17.4%	12%
Test	Fine motoric test	Pegboard	Pegboard	Pegboard	Pegboard

* Estimated by Monte Carlo simulation

** employed a mixed sample ranging in size from 18–84 participants