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An effort expenditure perspective on cancer-related fatigue

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ABSTRACT

While fatigue is the most common and debilitating side effect of cancer and cancer treatment it is still poorly understood, partly because it is usually characterized by patient-reported outcomes. As patient-reports are inherently subjective, behavioral correlates of the symptom of fatigue are needed to increase our understanding of the symptom. We focused on motivational effort expenditure as a crucial behavior in cancer-related fatigue, using a validated computerized task contrasting high effort/high reward and low effort/low reward choices under different probabilities of success. Effort expenditure-choices were analyzed in 47 cancer patients differing by their status; current evidence for disease (n = 17) or post-treatment survivors with no evidence for disease (n = 30). In addition, patient-reported fatigue, negative and positive affect, and biomarkers of inflammation were assessed. Patient-reported general and motivational fatigue, negative affect, and plasma concentrations of pro-inflammatory biomarkers were related to higher effort expenditure while positive affect was associated with lower effort expenditure. As all four measures interacted with patient status, exploratory models were computed for patients and survivors separately. These analyses indicated that the effects of fatigue and negative affect were predominantly seen in survivors. In patients still under or shortly post treatment, general fatigue, but not motivational fatigue, was associated with lower effort expenditure but only in the most favorable reward condition. Negative affect did not have an effect. Thus, the effects observed seemed primarily driven by cancer survivors in whom both fatigue and negative affect were associated with higher effort expenditure. These findings are tentatively interpreted to suggest that a tendency to invest more effort despite feelings of fatigue is a vulnerability for developing chronic fatigue. Inflammation and negative affect might contribute to fatigue in some survivors through this effort investment pathway.

1. Introduction

Fatigue is the most common, debilitating side effect of cancer and cancer-treatment. Up to 99% of patients report some fatigue during cancer therapy (Servaes et al., 2002) and between 44% and 66% report moderate to severe fatigue (de Jong et al., 2004; Servaes et al., 2002). Although fatigue usually abates after cessation of cancer therapy, it becomes chronic in 22–39% of cancer survivors (Goedendorp et al., 2013). Severe fatigue affects quality of life by hampering daily activities and interfering with return to work. Furthermore, it is strongly related to mood disturbances such as depression (Ho et al., 2015). Thus, the emotional and financial consequences of cancer-related fatigue are severe.

To date, no efficacious treatment options for cancer-related fatigue exist, although evidence is accumulating that some patients may benefit from physical, psychosocial, or mind-body interventions (Bower et al., 2014). The lack of evidence-based treatment options might be largely due to our poor understanding of the symptom of fatigue. Fatigue is a multi-dimensional construct including physical, mental, and motivational dimensions. These dimensions are usually quantified by patient-report, thereby inadvertently subjected to psychosocial influences on symptom experience. Subjective symptom reports do not always correlate with objective assessments as illustrated in chemotherapy-induced cognitive dysfunction where self-reported cognitive function does not correlate with objective cognitive tests (O'Farrell et al., 2016; Pullens et al., 2010). To our knowledge, the only used behavioral outcome in relation to fatigue is physical activity (assessed through actigraphy), which indeed shows only low correlations with reported fatigue (Ferriolli et al., 2012; Timmerman et al., 2015). Behavioral correlates of specific dimensions of cancer-related fatigue are thus far

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unknown.

Patients with cancer-related fatigue often report a lack of motivation. For example, in a qualitative study on cancer-related fatigue, lack of motivation was reported by over 80% of patients (Gledhill, 2005). Further, de Jong et al. showed consistently high scores on patient-reported lack of motivation during adjuvant chemotherapy for breast cancer (de Jong et al., 2005). For the present study, we therefore decided to focus on motivational effort expenditure as a possibly crucial element of cancer-related fatigue. Lack of motivation might express itself as an overall reduced willingness to exert effort, or as a reduced sensitivity to the reward obtained through the expenditure of effort (i.e., anhedonia), the latter being a component of depression. We hypothesized that cancer patients and survivors with higher fatigue but no depression would display decreased effort expenditure with intact reward sensitivity.

We used the Effort Expenditure for Reward Task (EEfRT), a validated computerized task designed to assess effort expenditure as well as the hedonic aspect of motivation (i.e., reward sensitivity) (Treadway et al., 2009) in cancer patients (with active disease) and in cancer survivors (post primary cancer therapy and with no evidence of disease) in a cross-sectional design. In the EEfRT, participants repeatedly choose between a high effort-high reward task and low effort-low reward task under varying reward probabilities and magnitudes. Performance on the EEfRT is related to self-reported anhedonia (Treadway et al., 2009). In addition, when compared to healthy controls, patients diagnosed with major depressive disorder show less willingness to select the high effort-high reward task and are less sensitive to changes in reward probability and magnitude (Treadway et al., 2012). The EEfRT is sensitive to inflammation as administration of endotoxin to volunteers resulted in a decrease in low effort-low reward choices when the probability to win was low and an increase in high effort-high reward choices when the probability to win was high (Lasselin et al., 2017). In this last study, the effect of inflammation was related to the level of sleepiness, suggesting a role for fatigue in inflammation-induced changes in motivated behavior. However, to our knowledge, the EEfRT has not yet been used to assess motivational changes in fatigued subjects.

Associations between cancer-related fatigue and personality characteristics related to a more negative mood as well as state negative mood have been repeatedly found (Shun et al., 2011; Wang et al., 2013). In addition, inflammation has repeatedly been associated with cancer-related fatigue (Bower, 2007; De Raaf et al., 2012). Therefore, we also measured affect and circulating levels of biomarkers of inflammation to assess their associations with motivational effort expenditure.

2. Materials and methods

2.1. Participants

Patients were recruited at the Cancer-Related Fatigue Clinic and the Head and Neck Clinic at The University of Texas MD Anderson Cancer Center. The Cancer-Related Fatigue Clinic sees patients who are referred by oncologists at MD Anderson because of severe cancer-related fatigue. We included patients presenting for initial consult, at which stage they report high levels of fatigue, and for follow-up, at which stage fatigue is often of low or moderate severity. Patients recruited at this clinic could be under active cancer treatment, maintenance treatment, or no treatment. Patients recruited at the Head and Neck Clinic were between 6 weeks and 12 months post treatment for head and neck cancer and cancer free at the time of assessment. For both clinics, exclusion criteria were presence of major depressive disorder or severe depression (patients taking antidepressants and not showing signs of severe depressive symptoms were allowed), presence of pain, severe confusion, or cognitive impairments.

2.2. Study design

In a cross-sectional study design, participants were tested for incentive motivation and self-reported mood and fatigue. During testing, participants filled out questionnaires as described below, followed by the EEfRT (see below). A blood sample was drawn for plasma levels of inflammatory markers on the day of testing. Participants received a gift card of $10 plus their winnings on the EEfRT (see below) after completion of the assessments. The protocol was approved by the MD Anderson internal review board (2015–0500 and 2014–0511) and all patients provided written informed consent.

2.3. Self-report measures

Fatigue was measured with the General Fatigue subscale of the Multidimensional Fatigue Symptom Inventory-Short Form (MFSI-SI), a 30-item questionnaire assessing five empirically derived dimensions of fatigue (i.e., general fatigue, physical fatigue, emotional fatigue, mental fatigue, and vigor) (Stein et al., 2004). The General Fatigue subscale included six items which were rated for the extent to which they were true on a 5-point Likert scale (range 0 “not true at all”–4 “extremely”). Items included statements such as “I am worn out”, “I feel fatigued”, and “I feel run down”. Answers were summed resulting in score range of 0–24 with higher scores representing greater fatigue severity. The motivational aspect of fatigue was assessed with the motivation subscale of the Checklist Individual Strength (CIS), a 4-item scale with items answered on a 7-point Likert scale (range 1 “yes, that is true”–7 “no, that is not true at all”). Items included statements as for example “I don’t feel like doing anything” and “I have a lot of plans”. Higher scores (after reversed scoring when necessary) represent greater motivational fatigue (range: 4–28) (Vercoulen et al., 1994).

To monitor self-reported fatigue during the assessments, participants also filled out a fatigue visual analogue scale (VAS) before, in-between, and after the computerized tests indicating their momentary fatigue on a continuous 10-cm long scale from “not fatigued at all” to “very severely fatigued”.

Depression was assessed with the depression subscale of the Depression, Anxiety, and Stress Scale (DASS) (Antony et al., 1998; Lovibond and Lovibond, 1995) (for participants recruited at the Cancer-Related Fatigue Clinic) or the Hospital Anxiety and Depression scale (Zigmond and Snaith, 1983) (for participants recruited at the Head and Neck Clinic). Both subscales are comprised of seven items which are to be answered for the past week on a 0–3 Likert scale, resulting in sum scores with a range of 0–21.

Negative and positive affect were measured with the Positive and Negative Affect Scale (PANAS) (Watson et al., 1988). Both subscales (i.e., positive and negative affect) comprise 10 mood adjectives and the extent to which they are experienced during the last month is rated on a 5-point Likert scale.

Anhedonia was assessed with the Snaith-Hamilton Pleasure Scale (SHAPS) (Snaith et al., 1995). This 14-item scale assesses hedonic tone and its absence, anhedonia. Participants rate the degree to which they agree or disagree with statements describing situations that generate pleasure.

2.4. Markers of inflammation

Blood samples were typically drawn immediately after completion of assessments. Most participants were assessed between 12:00 and 6:00 P.M, except for ten participants who were assessed between 10:00 A.M. and 12:00 P.M. Blood samples were not drawn for three participants due to time constraints in the participant’s schedule. Blood was immediately spun down at 3000 × g for 10 min and plasma was frozen at −80 °C until batch-wise analyses of inflammatory markers previously associated with cancer-related fatigue in both patients and survivors (Saligan and Kim, 2012; Xiao et al., 2017).