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PAPER

The reciprocal relationship between daily fatigue and catastrophizing following cancer treatment: Affect and physical activity as potential mediators

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Abstract

Objective: Fatigue is a distressing symptom many cancer patients experience even after completion of treatment. Although theory and empirical evidence indicate that negative cognitions perpetuate fatigue after completion of treatment, insight into how this process unfolds in daily life is limited. This study used an intensive longitudinal design to investigate the reciprocal relationship between catastrophizing and fatigue in daily life and whether affective and behavioral processes mediate these relationships.

Methods: Post-treatment colorectal cancer patients ($n = 101$) completed daily diaries (14 days, 3 times daily) regarding their fatigue, catastrophizing, positive and negative affect, and physical activity. Multilevel modeling was applied to investigate within-person associations within days.

Results: Analyses revealed a positive reciprocal relationship between fatigue and catastrophizing throughout the day. That is, high levels of catastrophizing were associated with increases in fatigue within patients. In turn, but to a lesser extent, high levels of fatigue predicted increases in catastrophizing at the next assessment. Low positive affect and high negative affect mediated the effect of catastrophizing on increases in fatigue. Only negative affect mediated the reverse relationship. Physical activity did not mediate either relationship.

Conclusions: This study provides evidence for a mutually reinforcing relationship between catastrophizing and fatigue in daily life, which might explain the perpetuation of fatigue after completion of cancer treatment. Fatigue-specific cognitive behavior therapy could be improved by educating patients about this daily reciprocal relationship, train them to quickly replace catastrophizing thoughts in daily life, and help them to cope with affective changes induced by fatigue.

KEYWORDS

affect, cancer, catastrophizing, colorectal neoplasms, diary, fatigue, intensive longitudinal design, oncology, physical activity, survivorship

1 | BACKGROUND

Fatigue is a prevalent and highly distressing symptom in cancer patients that can persist for years after treatment completion in a substantial number of patients.¹ In support of cognitive-behavioral models, psychosocial factors, particularly catastrophizing thoughts about fatigue, have been found to perpetuate cancer-related fatigue after treatment completion.^{2,3} However, current insights into how

the perpetuating effect of catastrophizing unfolds in daily life are limited. This study applied an intensive longitudinal design⁴ to test whether catastrophizing and fatigue are mutually reinforcing in daily life and whether affective and behavioral processes can explain this reciprocal relationship. Identifying mechanisms that perpetuate fatigue in daily life can help advance current interventions aimed at improving cancer-related fatigue, and thereby benefit the well-being of the growing population of patients treated for cancer.

Catastrophizing and fatigue might be mutually reinforcing in daily life, which may explain persistent fatigue after completion of cancer treatment. Catastrophizing is defined as a set of maladaptive cognitions characterized by focusing on and exaggerating the somatic symptom and a perceived inability to cope with it.^{5,6} Although catastrophizing has mostly been studied as a maladaptive response in coping with pain,⁷ longitudinal studies in cancer patients have demonstrated that catastrophizing is also a major predictor of post-treatment fatigue.^{3,8} These studies, however, were not designed to capture dynamic within-person processes between catastrophizing and fatigue in daily life. Daily diary methods are needed to look beyond between-person differences and investigate how catastrophizing's perpetuating effect on fatigue unfolds *within individuals in daily life*. While we currently lack research investigating the daily reciprocal relationship between catastrophizing and fatigue within cancer patients, diary studies in the field of pain demonstrated that the longitudinal association of catastrophizing predicting pain is also evident in daily life. That is, daily fluctuations in catastrophizing have been found to positively predict pain severity within individuals.⁹⁻¹¹ Similarly, high levels of fatigue catastrophizing might predict high levels of fatigue severity within cancer patients. In turn, high levels of fatigue might trigger catastrophizing in everyday life. Experiencing severe fatigue might lead to increases in catastrophizing given that the fatigue may seem to confirm and thereby fuel maladaptive beliefs and worries characteristic of catastrophizing. To date, only a few studies among pain populations investigated whether severe symptoms can in turn trigger catastrophizing thoughts and yielded inconclusive results.^{9,12-15} Even though the research to date is limited to pain populations and resulted in mixed evidence, it seems plausible that daily catastrophizing predicts daily fatigue which in turn triggers catastrophizing thoughts.

The reciprocal relationship between catastrophizing and cancer-related fatigue might be driven by subsequent affective and behavioral processes. Some studies among patients with pain indicate that next to catastrophizing, changes in affect and reduced physical activity predict severe symptoms.^{10,11,16} These studies are in line with the Fear-Avoidance model of pain,¹⁷ stating that catastrophizing maintains pain through affective distress and reduced physical activity. The processes driving the reverse relationship, that is how severe symptoms trigger catastrophizing, are less well studied. Some studies suggest that similar affective and behavioral processes might also drive this reverse relationship. That is, among populations other than cancer, diary studies found evidence for a reciprocal relationship between fatigue and mood¹⁸ and fatigue predicting reduced subsequent physical activity.^{19,20} While none of these studies was conducted among cancer patients and none has examined the full mediational pathway, these studies suggest that catastrophizing might predict increased fatigue through daily changes in affect and physical activity. Increased fatigue might in turn trigger catastrophizing through the same affective and behavioral processes. Investigating the full mediational pathway of the reciprocal relationship will help us understand the mechanisms through which catastrophizing and fatigue unfold their maladaptive effects in daily life.

We investigated the daily reciprocal relationship between catastrophizing and fatigue within individuals and examined affective

and behavioral processes as mediators of this relationship. We expected (1a) catastrophizing to positively predict increases in fatigue and, in turn, (1b) fatigue to positively predict increases in subsequent catastrophizing. Second, we hypothesized that (2a) low positive affect, (2b) high negative affect, and (2c) low physical activity mediate the positive association between catastrophizing and increases in fatigue. Similarly, we hypothesized that (3a) low positive affect, (3b) high negative affect, and (3c) low physical activity mediate the positive association between fatigue and subsequent increases in catastrophizing (see Figure 1).

2 | METHODS

2.1 | Participants

This study draws on data from colorectal cancer patients and their intimate partners collected to investigate dyadic coping with cancer. Only patient data were used in the current study. Patients were eligible if they (1) completed cancer treatment at least 6 months ago, (2) were not terminally ill, (3) were married or in a cohabiting relationship for at least 1 year, and (4) scored at least a 1 on average fatigue during the previous week on a scale from 0 (*no fatigue*) to 10 (*as fatigued as I could be*) during the telephone screening. Couples in which 1 or both partners were (1) younger than 18 years, (2) not able to understand Dutch, (3) cognitively impaired, or (4) diagnosed with chronic fatigue syndrome or fibromyalgia were excluded.

2.2 | Procedure

Colorectal cancer patients were recruited via 4 Dutch hospitals. They were recruited either by their nurse during their follow-up visit or received a letter inviting them and their partners to participate in the study. Of the 607 potentially eligible patients approached, 569 received study information, consent forms and prepaid envelopes (reasons for not providing the study information were mainly patient's lack of interest, 55%). After contacting interested patients and reviewing their demographic and clinical characteristics, 88 patients appeared

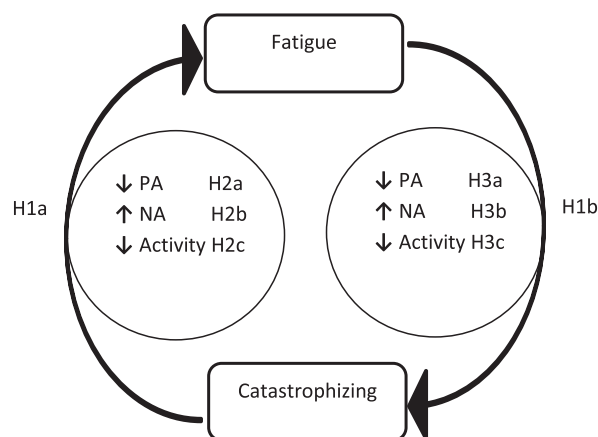


FIGURE 1 Conceptual model testing the reciprocal relationship between fatigue and catastrophizing and its mediators within individuals in daily life. PA, positive affect; NA, negative affect; Activity, physical activity

not to be eligible. After both partners of eligible and interested couples signed and returned the consent form ($n = 185$), each partner was mailed a baseline questionnaire. Couples were invited to participate in the diary component of the study if the patient scored above the cut-off score for elevated fatigue as measured with (1) the Checklist Individual Strength^{21,22} or (2) the Fatigue Symptom Inventory^{23,24} or (3) reported at least 2 days of fatigue during the previous week on the Fatigue Symptom Inventory. Of those couples invited to participate in the diary component ($n = 137$), 36 couples refused. The main reason for refusal was lack of interest (39%). According to the Dutch law for medical research involving human subjects (WMO), a waiver for ethical assessment was provided by the Medical Ethical Committee of the Medical University of Groningen (METc 2013/158). The study was conducted according to the declaration of Helsinki.

Diary data were collected between September 2014 and July 2016. A research assistant visited the couples at home to explain the diary procedure. Participants were asked to complete brief questionnaires 3 times daily for 14 consecutive days on a tablet provided to each partner of the couple. The morning assessment was completed within approximately 1 hour after waking, the noon assessment approximately 1 hour after lunch, and the evening assessment approximately 1 hour prior to going to bed. Participants received a reminder-signal to fill in each assessment. They could manually start any assessment they could not respond to following the signal. Participants were instructed to respond to the assessments separately without discussing their answers.

None of the patients dropped out during the diary period, and adherence to the protocol was excellent. Sixty-six percent of the patients completed all 42 assessments, and 91.1% completed at least 40 assessments. Thirty-seven diary assessments were excluded from analyses, mostly due to mistakes in manually starting assessments after/before the reminder-signal ($n = 20$).

2.3 | Measures

2.3.1 | Demographic and clinical variables

Gender, age, relationship duration, occupational status, and cancer-related variables were assessed by self-report in the baseline questionnaire. The cancer site was dichotomized into a carcinoma located in (1) the colon and (2) the rectum, or anus. Treatment was dichotomized into (1) surgery only and (2) surgery and additional treatment (chemotherapy and/or radiotherapy). Patients with a stoma (permanent or temporary) were categorized as having a stoma (yes). The cancer stage was dichotomized into (1) good prognosis (stage I, stage II) and (2) poor prognosis (stage III, stage IV).

2.3.2 | Fatigue severity

In each diary assessment, patients were asked to report their momentary fatigue severity with the item: "How fatigued do you feel right now?". Responses ranged from 0 (*not at all*) to 10 (*as fatigued as I could be*).

2.3.3 | Catastrophizing

In each diary assessment, patients were asked to report their catastrophizing during the hours preceding the diary. Catastrophizing

was measured using 3 items derived from the Pain Catastrophizing Scale²⁵ with each item representing 1 of the 3 subscales (rumination, magnification, helplessness; eg, "Tonight, I worried about my fatigue"; "Since rising, I was anxious my fatigue would become worse"; "Since this afternoon, I thought I could not bear the fatigue any longer"). Responses ranged from 0 (*not at all*) to 4 (*extremely*). Mean scores were calculated with higher scores indicating higher levels of catastrophizing.

2.3.4 | Affect

Momentary affect was measured 3 times daily with items derived from the Circumplex Model of Affect.²⁶ Six items assessed positive affect (eg, "Right now, I feel happy") and 6 items assessed negative affect (eg, "Right now, I feel nervous"), to which the item "depressed" was added to assess depressive feelings. Responses ranged from 0 (*not at all*) to 4 (*extremely*). Higher mean scores indicate more positive or more negative affect.

2.3.5 | Physical activity

Physical activity in the hours preceding the diary assessment was measured with 1 item (eg, "Since this morning, have you been physically active (eg, biking, vacuum cleaning, lifting objects, sports, hiking)?") with responses ranging from 0 (*not at all*) to 10 (*very much*).

2.3.6 | Sleep

Quality of sleep was assessed every morning with 2 items ("I have slept well tonight"; "This morning, I felt rested after rising"). Responses ranged from 0 (*not at all*) to 4 (*extremely*). Higher mean scores indicate better sleep.

2.3.7 | Statistical analysis

Multilevel modeling was used to account for the nested data structure (ie, diary assessments nested within patients).⁴ Models were run in R using the *lme4* package.²⁷ To examine the within-person associations between catastrophizing and fatigue, the diary measures (level 1 predictors) were person-mean centered, that is, each patient's mean score was subtracted from his/her raw score at each assessment. To examine between-person differences in fatigue and catastrophizing and to facilitate model estimation and the interpretation of the intercepts, these variables were also included as grand-mean centered variables (level 2 predictors). Random intercepts and slopes were included in all models unless otherwise specified. In some cases, effects were fixed to enable model convergence.

Preliminary analyses included investigation of selective non-response and confounders. First, high levels of fatigue ($P = .85$) and catastrophizing ($P = .51$) did not predict missing diary assessments. Second, we tested demographics, clinical characteristics, daily sleep, and time trends as possible confounders. We retained those that were significant predictors of fatigue and/or catastrophizing, which included patient's age, daily sleep, diary day, and assessment time.

To test our first hypothesis (H1a), we investigated whether catastrophizing in the hours prior to the assessment (t) predicted momentary fatigue severity (t), while controlling for previous levels

of fatigue ($t - 1$). To test the reverse relationship (H1b), we investigated whether previous levels of momentary fatigue ($t - 1$) predicted catastrophizing at the next assessment (t), while controlling for previous levels of catastrophizing ($t - 1$). Controlling for previous levels of the outcome variable allowed us to interpret our findings in terms of predicting change in the outcome over time. Because the items measuring catastrophizing assessed thoughts in the hours *prior*

to each assessment, the relationship between catastrophizing and subsequent momentary fatigue in our first hypothesis (H1a) was operationalized by using both measures from the same assessment (t). As is common in diary studies,^{9,10} we investigated within-day associations and did not predict fatigue and catastrophizing as assessed in the morning using the evening assessment. Data of the morning assessment were thus not used as an outcome in our analyses. However, fatigue and catastrophizing as assessed in the morning were used as predictors and covariates for models predicting the outcomes as assessed at noon. Affect as assessed in the morning was used for the mediation-models predicting catastrophizing as assessed at noon.

In order to test the lower-level within-person mediation models (H2 and H3), the approach as developed by Bauer, Preacher and Gil²⁸ was applied, using SPSS (Version 24). Unless otherwise specified, all paths of the mediation-model were allowed to vary randomly across patients. Intercepts and confounders were fixed to reach model convergence. Confidence intervals were calculated to report on the precision and significance of the average total and indirect effects. The percentage of the total effect that is explained by the mediator was calculated by dividing the average indirect effect by the average total effect.⁴

TABLE 1 Sample characteristics

Total Sample $n = 101$	
Demographics	
Age, years (SD)	64.3 (10.2)
Gender, male	67 (66.3%)
Relationship duration, years (SD)	37.7 (13.4)
Occupation	
Employed (full-time or part-time)	26 (25.7%)
Retired	44 (43.6%)
Unemployed	15 (14.9%)
Unable to work	11 (10.9%)
Unpaid work	3 (3%)
Other, unknown	2 (2%)
Clinical Characteristics	
Cancer site, colon	63 (62.4%)
Prognosis, good	78 (77.2%)
Treatment, surgery only	45 (44.6%)
Stoma, yes	50 (49.5%)
Time since diagnosis, months (SD)	17 (9)
Time since treatment, months (SD)	13 (8)

All values represent n and % unless otherwise indicated.

3 | RESULTS

3.1 | Demographics and descriptive results

The sample consisted of 101 post-treatment colorectal cancer patients (see Table 1). Descriptive statistics of the within-person variables can be found in Table S1.

TABLE 2 Within-day associations between fatigue and catastrophizing

Predictors: Fixed Effects	Outcome Fatigue		Outcome Catastrophizing	
	B	95% CI	B	95% CI
Level 1 (within-person)				
Intercept	3.87***	[3.53 – 4.22]	0.38***	[0.30 – 0.46]
Assessment time	0.47***	[0.36 – 0.59]	0.01	[-0.01 – 0.03]
Diary day	-0.04***	[-0.05 – -0.02]	-0.001	[-0.01 – 0.00]
Fatigue ($t - 1$)	0.15***	[0.11 – 0.19]	0.02***	[0.01 – 0.03]
Catastrophizing (t)	1.03***	[0.83 – 1.22]		
Catastrophizing ($t - 1$)			0.20***	[0.16 – 0.23]
Sleep	-0.09	[-0.19 – 0.01]	-0.01	[-0.03 – 0.01]
Level 2 (between-person)				
Fatigue			0.15***	[0.10 – 0.19]
Catastrophizing	2.09***	[1.46 – 2.73]		
Age	-0.06***	[-0.09 – -0.03]	0.01	[0.00 – 0.02]
R^2/Ω_0^2 ^a	.65/.64		.68/.68	
n patients/ n diary assessments	101/2732		101/2723	

Abbreviation: CI, confidence interval.

^aExplained variance by the model.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

3.2 | Reciprocal relationship between fatigue and catastrophizing

As expected (H1a), high levels of catastrophizing significantly predicted increases in levels of fatigue within patients across the day ($b = 1.03$, $P < .001$). On average, a 1 unit increase in catastrophizing translated into a 1.03 unit increase in fatigue severity (scale 0–10), while controlling for previous levels of fatigue severity. The reverse association was also significant (H1b), that is, high fatigue significantly predicted increases in catastrophizing at the next assessment ($b = 0.02$, $P < .001$), see Table 2. On average, a 1 unit increase in fatigue severity at the previous assessment translated into a 0.02 unit increase in catastrophizing (scale 0–4), while controlling for previous levels of catastrophizing.

3.3 | Mediators between fatigue and catastrophizing

In line with hypothesis 2a, low levels of positive affect significantly mediated the relationship between catastrophizing and increases in fatigue. The average total effect was 1.02 (95% CI [0.77, 1.27]), and the average indirect effect was 0.37 (95% CI [0.20, 0.55]). It follows that 36.3% of the overall average relationship between catastrophizing and increases in fatigue was explained by low positive affect. Similarly, high levels of negative affect were found to significantly mediate the relationship between catastrophizing and fatigue (H2b). The average total effect was 1.02 (95% CI [0.79, 1.25]), and the average indirect effect was 0.35 (95% CI [0.20, 0.50]). Thus, 34.3% of the overall average relationship between catastrophizing and increases in fatigue was explained by high negative affect. As expected, catastrophizing predicted low physical activity ($b = -0.31$, $P = .04$), but physical activity in turn did not significantly predict increases in fatigue ($b = 0.03$, $P = .12$). Thus, hypotheses 2c was not confirmed. Hypotheses H3a and H3c were not confirmed either. Only the mediating effect of negative affect between fatigue and increases in catastrophizing reached significance (H3b), with an average total effect of 0.022 (95% CI [0.01, 0.03]) and an average indirect effect of 0.0076 (95% CI [0.001, 0.014]). This indicates that 34.5% of the overall average relationship between fatigue and increases in catastrophizing was explained by high negative affect. Results of the mediation models are shown in Table S2.

4 | CONCLUSIONS

This diary study investigated the reciprocal relationship between daily fatigue and catastrophizing within post-treatment cancer patients and tested whether affective and behavioral processes mediate these relationships. As expected, catastrophizing positively predicted increases in fatigue severity. While this relationship was evident in longitudinal studies among post-treatment cancer patients,^{3,8} we demonstrated that catastrophizing predicts increases in fatigue *within individuals* in *daily life*. We also found some evidence for the reverse relationship, that is, high fatigue predicting increases in subsequent catastrophizing. This reciprocal relationship between catastrophizing and fatigue was mediated by negative affect. Positive affect mediated the effect of catastrophizing on increases in fatigue, but not the effect of fatigue

on increases in catastrophizing. Even though the evidence for the prediction of catastrophizing by fatigue and its mediation through negative affect was less strong, these findings suggest that a mutually reinforcing relationship between symptoms and maladaptive cognitions, driven by high levels of negative affect, might be responsible for the perpetuation of fatigue after completion of cancer treatment.

In line with earlier diary research among post-treatment cancer patients,²⁹ we found evidence that fatigue negatively predicts physical activity in daily life. High catastrophizing was also predictive of low physical activity. Contrary to our expectations, physical activity did not mediate the reciprocal relationship between fatigue and catastrophizing. This lack of evidence for mediation might be due to the use of a self-report measurement of physical activity,²⁹ and the applied assessment schedule in our diary. That is, we currently lack knowledge on the time intervals in which psychological processes unfold in daily life.³⁰ While our 3 times daily assessment schedule might have been appropriate to capture the mediating effect of affect between catastrophizing and fatigue, investigating the mediating effect through physical activity might require another schedule.

The strengths of our study include an ecological valid design with repeated measurements within days that allowed us to reveal the reciprocal relationship between fatigue and catastrophizing within individuals. Our diary procedure resulted in a high completion rate and no drop-out. Missing diaries were not sensitive to increased fatigue and catastrophizing.

Study limitations

First, the response rate of the larger study (36%) was lower than that of other psycho-oncological studies.³¹ This low response rate might be due to the dyadic³² and intensive longitudinal design of our study. However, the demographic and clinical characteristics of the patients in our sample are comparable to those of a large population-based study among post-treatment colorectal cancer patients in the Netherlands.³³

Second, due to the operationalization of catastrophizing (“since”) and fatigue (“now”) in our study, we investigated catastrophizing as predictor of fatigue as measured at the same assessment (t). This might introduce some bias as fatigued patients might recall higher levels of catastrophizing. The design choice was based on the assumption that cognitions, as opposed to symptom severity, are not frequent enough to be assessed by a 3 times daily momentary measure. A related limitation is that the mean values of catastrophizing were rather low in our sample. The fatigue scores of our sample were comparable to another diary study among post-treatment cancer patients,²⁹ but patients with the most severe fatigue complaints were underrepresented. Future studies might need to invest extra effort to include patients with the most severe symptoms.

Further, while the formulation of the items assessing catastrophizing and physical activity (eg, “Since rising”) provided the patients a clear anchor within their individualized assessment schedule, this formulation does not allow us to state exactly how many hours the constructs have captured.

Finally, in line with our primary research question, we only included patient data to test an intra-personal model of fatigue and catastrophizing. However, as noted by Sullivan and colleagues,⁵

catastrophizing might have an inter-personal component as well. Hence, the maladaptive effect of catastrophizing thoughts might be influenced by the patient's social context, particularly by his or her intimate partner. For example, Holtzman and DeLongis⁹ found that arthritis patients satisfied with the support provided from their partner engaged in less catastrophizing in daily life and, when they did, were protected from its maladaptive effects on affect. Future studies should adapt a dyadic approach to investigate whether partner support can reduce the mutually reinforcing relationship between fatigue and catastrophizing.

Clinical implications

Cognitive behavior therapy (CBT) has been shown to be effective in reducing post-treatment fatigue.³⁴ One important module in this fatigue-specific CBT³⁵ entails educating the patient about the perpetuating effect of catastrophizing thoughts and stimulating more adaptive cognitions. First, our results indicate that the perpetuating effect of catastrophizing operates quickly within the day. Patients should be educated that even in the short term, thus within days, their catastrophizing thoughts can increase their fatigue. Being aware of this fast maladaptive process, patients should be trained to quickly identify and immediately replace their catastrophizing thoughts with adaptive cognitions that have been developed during the CBT sessions. Second, patients should be educated to avoid interpreting currently feeling fatigued as confirmation of their (former) maladaptive thoughts as this interpretation might in turn perpetuate catastrophizing. Learning how to cope with negative feelings induced by fatigue might foster this adaptive change. Integrating these strategies might increase the beneficial effect of CBT targeting fatigue and hence foster the well-being of the growing population of patients treated for cancer.

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CONFLICT OF INTEREST

None declared.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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