The influence of nocebo information on fatigue and urge to stop: An experimental investigation

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Abstract

Background and objectives: Fatigue is an adaptive state after prolonged effort and often goes hand in hand with changes in behavior and motivation, such as the urge to stop exerting further effort. However, fatigue may become chronic in nature, as seen in multiple psychiatric disorders and chronic diseases, thereby losing its adaptive function. The etiology of fatigue symptoms remains poorly understood. We aimed to investigate whether nocebo information about the fatigue inducing nature of a cognitive task may contribute to the experience of fatigue and the motivational urge to stop.

Methods: Participants (*N*=46) repeatedly rated currently experienced fatigue while engaging in cognitive effort (working memory task). Crucially, half of participants received nocebo instructions prior to this task, whereas the other half only received neutral information.

Results: Over the entire sample, results showed an increase in fatigue and urge to stop as the task progressed. Crucially, participants in the nocebo condition reported a higher urge to stop throughout the task relative to participants in the neutral condition. No significant effects were found for fatigue. Interestingly however, after controlling for baseline differences between conditions in negative affect, there was a significant Condition*Task block interaction effect on fatigue.

Limitations: Limitations include the relatively short experimental protocol and the underrepresentation of male relative to female participants.

Conclusions: These findings suggest that heightened awareness among clinicians and therapists about potential nocebo effects in their communication is warranted.

Keywords: Fatigue, nocebo, motivation, urge to stop, working memory

Introduction

After physical or cognitive effort or in the presence of acute illness, the experience of fatigue is normal and promotes rest and recovery (de Ridder, Geenen, Kuijer, & van Middendorp, 2008). Fatigue thus constitutes a short term adaptive state that may involve changes in behavior, motivation, and emotion. Correspondingly, one influential view conceptualizes fatigue as a motivational state urging disengagement from effortful goal-directed behavior (i.e., 'urge to stop') in a cost-benefit trade-off (Thorndike, 1900; Van Damme, Becker, & Van der Linden, 2018). From this perspective, fatigue and an experiential urge to stop occur when the costs of maintaining current goal pursuit outweigh the perceived benefits.

However, fatigue can also persist and become more chronic in nature, and may be experienced in the absence of prior effort or acute illness, thereby losing its adaptive function. Chronic fatigue symptoms are highly prevalent in the general population (Jason et al., 1999; Loge, Ekeberg, & Kaasa, 1998; van 't Leven, Zielhuis, van der Meer, Verbeek, & Bleijenberg, 2009), as well as in multiple psychiatric disorders, including major depressive disorder, generalized anxiety disorder, and attention deficit hyperactivity disorder, and chronic diseases (e.g., cardiovascular, immunological, neurological diseases, chronic fatigue syndrome, fibromyalgia) (Kluger, Krupp, & Enoka, 2013; Rogers, Dittner, Rimes, & Chalder, 2017; Stebbings & Treharne, 2010). However, their etiology remains poorly understood. There is currently little evidence connecting fatigue symptoms to markers of chronic disease (e.g., Afari & Buchwald, 2003; Brys et al., 2020; Kos, Kerckhofs, Nagels, D'hooge, & Ilsbroukx, 2008; Kutlubaev, Duncan, & Mead, 2012). Moreover, similar to other somatic sensations such as pain and dyspnea, fatigue symptoms may exist in the absence of (evidence for) physiological or neurobiological dysregulation, indicating that other variables need to be taken into account to explain the occurrence of fatigue (Brown, 2004; Lenaert, Boddez, Vlaeyen, & van Heugten, 2018; Rief & Broadbent, 2007). More research is needed on psychological and social or contextual variables that may contribute to fatigue symptoms becoming chronic. In this study, we aimed to experimentally investigate the role of verbal nocebo information in the experience of cognitive fatigue.

The placebo effect refers to psychological or physiological changes attributable to receiving a substance or undergoing a procedure, but not as a result of the actual components of that substance or procedure (Stewart-williams & Podd, 2004). When this effect is unfavorable, it is commonly referred to as a nocebo effect (Colloca & Finniss, 2012). Placebo and nocebo effects are often explained on the basis of expectancies about the received substance or procedure. That is, a substance or procedure produces an effect because the recipient expects it to in either positive (placebo) or negative (nocebo) respect. These expectancies may be the result of verbal information, conditioning experiences, or causal inference.

Previous research has shown that information disclosure, for instance about potential side effects of a treatment, may create expectancies which may contribute to adverse effects (Colloca & Miller, 2011). There is ample research on placebo and nocebo effects on physical performance (e.g., Carlino, Piedimonte, & Frisaldi, 2014; Hurst et al., 2020). In contrast, few studies have investigated such effects on perceived fatigue. Some clinical evidence comes from placebo controlled clinical trials. In a review of clinical pharmacology studies in healthy individuals, 19% of participants receiving placebo treatment reported adverse side effects, including symptoms associated with cognitive fatigue such as drowsiness and impaired concentration (Rosenzweig, Brohier, & Zipfel, 1993). In a recent review on placebo and nocebo effects across different symptoms, Wolters and colleagues discuss two experiments investigating nocebo effects on physical or motor fatigue from verbal suggestion alone (Wolters, Peerdeman, & Evers, 2019). One study (Bottoms, Buscombe, & Nicholettos, 2014) found that suggesting that an ingested drink was fatigue-inducing increased perceived exhaustion, but did not affect objective performance or physiological measures. However, the reverse pattern has also been reported in another experiment, where fatigue suggestion reduced physical performance but not perceived exhaustion (Pollo, Carlino, Vase, & Benedetti, 2012). Only one previous experiment investigated nocebo effects in fatigue unrelated to physical performance and exhaustion. Fletcher and colleagues investigated nocebo effects related to exposure to ultrasound, the emission of which by machinery or devices in public places has been reported by workers to cause subjective symptoms such as fatigue, headache or dizziness. After expected (but not actual) exposure to ultrasound in this experiment, there was no evidence for increased fatigue but some evidence for small nocebo effects in other somatic symptoms (Fletcher et al., 2018). Given the scarcity of nocebo

The current study focused on cognitive fatigue and experimentally examined the effect of receiving nocebo information about a cognitively demanding activity. In clinical settings, clinicians and therapists routinely make prognoses about various conditions and share this information with their patients, such as the likely or expected development of symptoms. For instance, in the treatment of psychopathology, patients may receive information during psychoeducation about the high prevalence of fatigue in psychological disorders or about fatigue as a common side effect of pharmacological treatment. Similarly, one of the most common symptoms in neurological conditions (e.g., stroke, traumatic brain injury, multiple sclerosis) is fatigue, often lasting up to months or years after brain injury (Cumming, Packer, Kramer, & English, 2016; Mollayeva, Kendzerska, & Mollayeva, 2014). Patients are usually informed during rehabilitation that daily tasks and activities may require more effort or may lead to fatigue more quickly than before the injury. Although health professionals aim to create realistic expectancies about recovery, providing such information may contribute to nocebo effects on fatigue (e.g., a situation where fatigue would not have occurred or not as intensely if these expectancies would not have been created). Moreover, because cognitive effort is required in daily activities that vary from working, doing groceries, watching television or playing sports, the impact of such nocebo effects may be far-reaching.

We experimentally tested this possibility by requesting all participants to perform the same working memory task. Crucially, participants in the nocebo condition received information about the cognitively demanding and fatiguing nature of this task beforehand, whereas participants in the control condition only received neutral instructions. Emergent between-group changes as a result of these instructions were examined using a self-report measure of fatigue expectancy. Fatigue was subsequently measured throughout the task using self-report measures of currently experienced cognitive fatigue and the motivational urge to stop exerting further effort (Van der Linden, 2011), administered after each of four task blocks and at baseline. Task performance was measured as well. First, we predicted that receiving verbal nocebo information about the task, relative to neutral information, would lead to higher fatigue expectancy prior to the task. Second, we predicted that receiving nocebo information relative to neutral information would result in higher self-reported cognitive fatigue throughout the working memory task, as well as a higher urge to stop. Finally, we also investigated the impact of nocebo information on task performance although there were no prior predictions. This is because research has shown that there is no simple correspondence between fatigue and observable performance decrements (Bryant, Chiaravalloti, & Deluca, 2004; Hockey, 2013). For instance, fatigue or the urge to stop may be overruled in order to uphold task performance. In such cases, no clear performance decrements may be observed, but the effort needed to overrule fatigue may in turn contribute to an even stronger urge to stop or a stronger increase in fatigue (Van der Linden, 2011).

Methods

Participants

Forty-six participants (35 women) with a mean age of 23.0 (*SD* = 4.6; age range: 18-44) were recruited at [Blinded for review]. Power calculation was based on [Blinded for review]. In order to be able to detect the Block*Condition interaction effect size or larger than reported there, with 80% power and an α error probability of .05, 22 participants were required. In order to detect a similar effect size between conditions (main effect), a sample size of 44 was required. Participants had to be 18 years or older to be included in the study, and were excluded if they reported to be currently suffering from (or diagnosed with) depression, chronic fatigue syndrome, dyslexia, or ADHD, as our fatigue induction requiring prolonged cognitive effort was likely to be too burdensome. The study was approved by the Ethical Review Committee [Blinded for review]. All participants provided written informed consent and received a monetary reward or course credits.

Working memory task

A dual 2-back task with visual and auditory cues was administered using Presentation® software, version 19.0, Neurobehavioral systems (California, USA), on a Dell Desktop computer. During this working memory task, two sequences of stimuli had to be actively monitored (Fig. 1). Auditory stimuli, numbers ranging from 1 to 9, were presented through headphones and participants had to judge whether the number they heard was identical to the number presented two numbers back (i.e., auditory target). Visual stimuli were presented simultaneously, which were black squares presented on the computer screen in one of eight possible places in a three-by-three grid (a fixation cross was presented in the center square of the grid). Similarly, participants had to monitor whether a square was presented in the same place as two presentations before (i.e., visual target). Stimuli were presented for 500 ms. The inter stimulus interval was set to 2500 ms. The task consisted of four blocks of five minutes (100 stimulus presentations per block), preceded by a short practice phase. Previous experimental work has shown that this task is capable of inducing cognitive fatigue over a relatively short period of time (i.e., within four 5-min consecutive task blocks or less; Lenaert, Jansen, & van Heugten, 2018). Each block contained eight visual targets, eight auditory targets, four dual targets with an auditory and visual target presented simultaneously, and 80 non-target stimulus presentations.

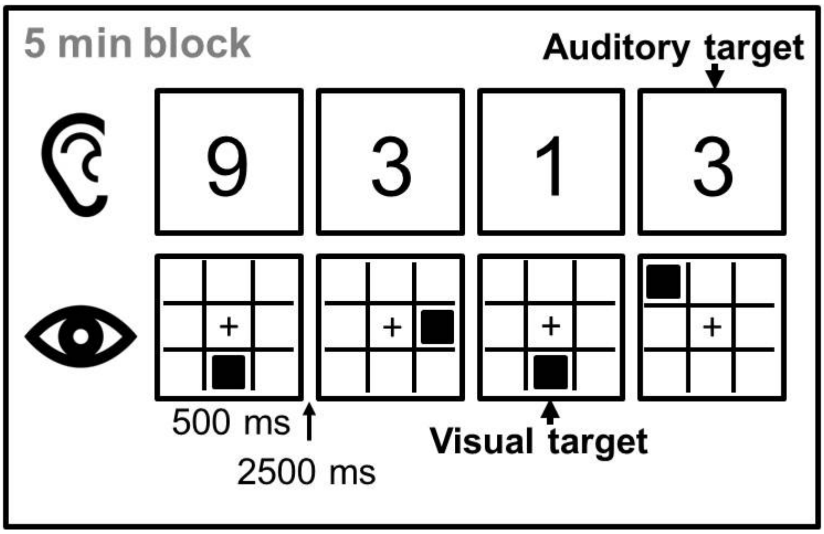

Fig. 1. One of four identical blocks of the dual 2-back task, consisting of a visual and auditory sequence of stimuli presented simultaneously. Note: Pictograms of ear and eye created by Jens Tärning; source: thenounproject.com.

Participants were instructed to click the left mouse button when either a visual target or an auditory target – or both – was presented, or do nothing when no target was presented. Similar to Lenaert, Jansen, & van Heugten (2018), we looked at the number of targets hit (correct responses), and the number of correct rejections when no target was presented (correct non-responses).

Self-report measures

Visual analogue scales. After each of the four blocks and before the first block (baseline), participants rated their current fatigue (i.e., “How tired do you feel right now?”) on a horizontal Visual Analogue Scale (VAS) presented on the computer screen, ranging from “not at all” to “extremely”.

Subsequently, a second VAS scale was presented measuring participants' urge to stop exerting further effort, and was accompanied by the question: "To what extent do you want to stop doing this task?" The next task block was immediately presented after these ratings to prevent participants from taking a break. Prior to the task but after receiving (either nocebo or neutral) task instructions, a single VAS scale on fatigue expectancy was presented as a manipulation check: "To what extent do you expect this task to be fatiguing?" Responses for all VAS scales were recorded as scores ranging between 0 and 100.

Manipulation awareness. At the end of the experiment, participants were specifically asked if they could name a possible relationship between their responses throughout the task and the instructions they received prior to the task. If participants were able to explain this relationship accurately in their own words, they were classified as 'aware of manipulation'.

Questionnaires

The Fatigue Severity Scale assessed pre-existing group differences in fatigue in daily life (Krupp, Larocca, Muir-nash, & Steinberg, 1989). This scale consists of nine statements (e.g., 'I am easily fatigued') rated on a 7-point Likert scale. Total scores are calculated as the mean score per item (range: 1-7), with lower values indicating greater fatigue severity. We also assessed negative affect, or the disposition to experience negative mood states, because previous research has shown that higher negative affect is associated with increased subjective symptom reporting, including fatigue (Van Diest et al., 2005). Negative affect was measured using the Dutch translation of the Positive and Negative Affect Schedule (PANAS) – trait version (Watson, Clark, & Tellegen, 1988). This questionnaire consists of ten positive (e.g., 'enthusiastic') and ten negative (e.g., 'distressed', 'irritable', 'disappointed') adjectives that describe different mood states. A 5-point Likert scale is used to indicate to what extent individuals experience a certain mood state throughout daily life. The total negative affect score is obtained by adding the scores of the negative mood state items (range: 10-50), with higher values indicating higher negative affectivity.

Procedure

After screening for inclusion and exclusion criteria and obtaining informed consent, participants were randomly assigned to one of both conditions and filled in the questionnaires. Participants were then instructed that they would complete a working memory task on the computer that consisted of several blocks, and that the study investigated working memory performance (cover story). In addition to neutral task instructions about the dual 2-back task, participants in the nocebo condition received both verbal and written information about the fatiguing nature of this task. More precisely, the experimenter told participants that previous studies had shown that this task is cognitively demanding, and that it would be normal if participants experienced fatigue as a result of the task. This information was presented again on the computer screen prior to the start of the task. Participants in the control condition only received neutral task instructions about the dual 2-back task. Participants then rated to what extent they expected the task to be fatiguing and started completing the dual 2-back task. Afterwards, participants were asked about their awareness of the true goal of the experiment. Finally, participants were fully debriefed and received monetary reward or course credits for their participation.

Statistical analysis

Statistical analyses were run in SPSS version 25 and α error probability was set at 0.05. To assess differences between conditions, we used independent samples *t*-tests and repeated measures analysis of variance (ANOVA). For the analyses of variance, Task Block (1–4) was used as within-subjects factor and Condition (Nocebo vs. Control) as between-subjects factor. Greenhouse-Geisser corrections were applied wherever Mauchly's test of sphericity indicated that the sphericity assumption had been violated.

Results

Group statistics

The nocebo (n = 23; 18 female; mean age = 23.5; SD = 5.7) and control group (n=23; 17 female; mean age = 22.6; SD = 3.2) did not differ significantly in age, $t(44) = 0.71$, $p = .484$, Cohen's d = 0.19. There was also no significant difference in fatigue severity in daily life, $t(44) = 0.14$, $p = .989$, Cohen's d = 0.01, between the nocebo group (M = 3.74, SD = 1.29) and the control group (M = 3.73, SD = 1.09). However, we did find a significant difference in negative affect, $t(44) = -2.58$, $p = .013$, Cohen's *d* = 0.76, with the control group reporting higher negative affect (*M* = 20.57, *SD* = 5.79) than the nocebo group (*M* = 16.70, *SD* = 4.27).

Fatigue expectancy

Prior to the dual 2-back task, the between-groups manipulation resulted in significantly higher fatigue expectancy ratings in the nocebo (*M* = 58.26, *SD* = 22.74) relative to the control group (*M* = 41.70, *SD* = 24.86), *t*(44) = 2.36, *p* = .023. Over the entire sample, fatigue expectancy also correlated significantly with the average fatigue reported over the four task blocks, *r* = .45, *p* = .002, as well as with the average urge to stop reported over the four task blocks, *r* = .34, *p* = .020.

Nocebo effects on Fatigue and Urge to Stop

There were no significant differences in fatigue at baseline (before the first block) between the nocebo group (*M* = 24.65, *SD* = 19.15) and the control group (*M* = 28.83, *SD* = 22.80), *t*(44) = -0.67, *p* = .505. Neither did the nocebo group (*M* = 4.65, *SD* = 6.39) differ significantly from the control group (*M* = 8.43, *SD* = 21.59) in baseline urge to stop, *t*(44) = -0.81, *p* = .428. The left panel of Fig. 2 shows the average increase in subjective fatigue after each block of the dual 2-back task relative to baseline. Visual inspection suggests that both groups became more fatigued during the task, but more so in the nocebo group. Mean increases in fatigue ratings in the nocebo group were 5.22 (*SD* = 20.97) points on the VAS scale after block 1, 16.00 (*SD* = 24.60) after block 2, 24.61 (*SD* = 30.95) after block 3, and 30.91 (*SD* = 34.71) after block 4. For the control goup this was 5.57 (*SD* = 23.01) after block 1, 14.26 (*SD* = 27.50) after block 2, 16.61 (*SD* = 25.87) after block 3, and 16.61 (*SD* = 28.46) after block 4. Repeated measures ANOVA with reported Fatigue (difference from baseline) as dependent variable revealed a significant main effect of Block , *F*(1.6,70.4) = 17.34, *p* < .001, partial $\eta 2$ = .283, indicating that fatigue increased throughout the task. However, there was no significant main effect of Condition, *F*(1, 44) = 0.65, *p* = .423, partial $\eta 2$ = .015, and the Condition*Block interaction effect was no longer significant after Greenhouse-Geisser correction was applied, *F*(1.6,70.4) = 2.93, *p* = .071, partial $\eta 2$ = .062.

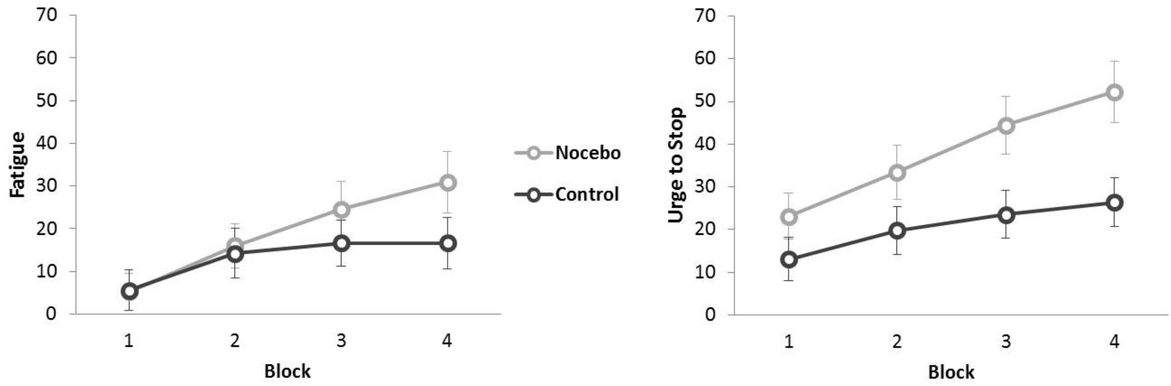

Figure 2. Left panel: Mean fatigue ratings (difference from baseline) for both conditions after each of four blocks of the dual 2-back task; Right panel: Mean Urge to Stop (difference from baseline) for each condition after each block; Error bars represent ±1 *SE*.

The right panel of Fig. 2 suggests that are differences between conditions in the urge to stop or disengage from the task. For the nocebo group, mean increases in urge to stop relative to baseline were 23.13 (SD = 26.12) after block 1, 33.43 (SD = 30.31) after block 2, 44.43 (SD = 32.16) after block 3, and 52.26 (SD = 34.59) after block 4. For the control group this was 13.09 (SD = 24.20) after block 1, 19.78 (SD = 26.91) after block 2, 23.52 (SD = 26.94) after block 3, and 26.43 (SD = 27.05) after block 4. The same repeated measures ANOVA with Urge to Stop as dependent variable showed that there was a main effect of Block, $F(1.4,60.1) = 17.73$, $p < .001$, partial $\eta 2 = .287$. Crucially, there was a main effect of Condition, $F(1, 44) = 5.41$, $p = .025$, partial $\eta 2 = .109$, indicating a higher urge to stop in the nocebo condition relative to the control condition. Planned comparisons revealed that there were significant differences between conditions after block 4, $t(44) = 2.82$, $p = .007$, and after block 3, $t(44) = 2.39$, $p = .021$, but not after block 2, $t(44) = 1.62$, $p = .113$, or after the first block, $t(44) = 1.35$, $p = .183$. Finally, although Fig. 2 may suggest that differences between conditions became larger as a function of task progression, there was no significant Condition*Block interaction effect, $F(1.4,60.1) = 2.63$, $p = .099$, partial $\eta 2 = .056$.

Cognitive performance

There was no significant difference in total targets hit (correct responses) throughout the task between the nocebo group (M = 58.1 out of 80 targets, 72.6% accuracy, SD = 13.5) and the control group (M = 58.1 out of 80 targets, 72.6% accuracy, SD = 15.0), $t(44) = -0.01$, $p = .992$. There was also no significant difference in the number of correct rejections when no target was presented (correct non-responses) between the nocebo group (*M* = 293.8 out of 320 non-targets, 91.8% accuracy, *SD* = 23.4) and the control group (*M* = 287.0 out of 320 non-targets, 89.7% accuracy, *SD* = 27.4), $t(44) = 0.90$, $p = .372$. Repeated measures ANOVA with targets hit as the dependent variable revealed no significant main effect of Block, $F(2.5,108.4) = 0.62$, $p = .572$, partial $\eta 2 = .014$, or Condition, Condition, $F(1, 44) = 0.00$, $p = .992$, partial $\eta 2 = .000$. There also was no significant Condition*Block interaction effect, $F(2.5,108.4) = 0.74$, $p = .508$, partial $\eta 2 = .016$. With correct rejections as the dependent variable, there was a significant main effect of Block, $F(2.0,86.9) = 7.00$, $p = .002$, partial $\eta 2 = .137$, indicating that participants became better at correctly rejecting non-targets as the task progressed. However, there was no significant main effect of Condition, $F(1, 44) = 0.81$, $p = .372$, partial $\eta 2 = .018$, and no significant Condition*Block interaction effect, $F(2.0,86.9) = 1.47$, $p = .236$, partial $\eta 2 = .032$.

Negative affect

Because the control group reported on average higher negative affectivity than the nocebo group, it was investigated whether negative affect was related to subjective symptom reporting. Correlations between negative affect and average fatigue over the four task blocks, $r = -.23$, $p = .122$, and average urge to stop, $r = -.13$, $p = .401$, were not significant. Further, we also repeated the two main repeated measures ANOVAs but now with negative affect as a covariate. Interestingly, with fatigue as the dependent variable and negative affect as covariate, the Condition*Block interaction became significant, $F(1.6,68.1) = 3.71$, $p = .039$, partial $\eta 2 = .079$, indicating that participants in the Nocebo condition showed a greater block-by-block increase in fatigue relative to participants in the Control condition. There was no main effect of Condition, $F(1,43) = .00$, $p = .965$, partial $\eta 2 = .000$. Further, with urge to stop as the dependent variable and negative affect as covariate, the Condition*Block interaction also became significant, $F(1.4,59.3) = 3.79$, $p = .043$, partial $\eta 2 = .081$, indicating that participants in the Nocebo condition showed a greater block-by-block increase in urge to stop relative to participants in the Control condition. However, the main effect of Condition was no longer significant, $F(1,43) = 3.66$, $p = .063$, partial $\eta 2 = .078$.

Awareness

No participants in the nocebo (or control) group could correctly identify the crucial manipulation of this experiment.

Discussion

In this experiment, we investigated whether receiving nocebo information about the potentially fatigue inducing effects of a task had an impact on subjective fatigue, the motivational urge to stop exerting further effort, and cognitive performance. The experimental manipulation of giving nocebo *versus* neutral task instructions was successful in creating differences between conditions in fatigue expectancy. Results showed that while all participants performed the same task, the group that received nocebo information reported a higher urge to stop throughout the task relative to the group that only received neutral instructions. We found no statistically significant differences in subjective fatigue or task performance. However, after including negative affect as covariate to control for baseline differences between conditions, we did find evidence for a greater block-by-block increase in fatigue (as well as urge to stop) in the Nocebo condition relative to the Control condition. These results may suggest that fatigue and the motivational urge to stop exerting further effort or maintaining goal-directed behavior is not merely a function of prior effort, but may be affected by prior verbal information as well.

This finding calls for heightened awareness among clinicians and therapists about the impact of information disclosure to their patients. The observation that receiving information about the potential occurrence of fatigue during a task impacted the motivational urge to stop doing that task may be relevant to everyday tasks people engage in. For instance, to the extent that information disclosure about the likelihood of experiencing fatigue negatively affects motivation to work or to exercise, this may inadvertently hamper rehabilitation or treatment progress and societal participation. This would be especially the case if a motivational urge to stop translates into the effective cessation of goal-directed behavior. In our experiment, all participants were instructed to complete the task until it was finished. Future experiments could employ a protocol where participants are allowed to stop the task when their fatigue or urge to stop exceed a certain subjective threshold. This would allow the behavioral assessment of nocebo information on fatigue-related avoidance of effort. Further research in clinical populations where fatigue is a common symptom is also warranted to corroborate the clinical validity of these findings.

It is interesting that we only found significant effects in fatigue after controlling for baseline differences in negative affect. Although fatigue increased over the entire sample, it is possible that nocebo information about how demanding or fatiguing a task may be mainly affects the motivation to continue the task. That is, learning from others how hard a task is may contribute to a higher urge to stop or may make it more likely for a person to quit the task prematurely (e.g., because this person thinks it is more acceptable to quit based on receiving that information), without necessarily experiencing fatigue. Alternatively, although statistical power calculation was based on [Blinded for review], it is possible that the current manipulation of a single instance of information disclosure was less strong, thereby resulting in a smaller effect. This would then require a larger sample to detect such effect. Relatedly, visual inspection of Fig. 2 (left panel) suggests that differences between conditions grew larger as the task progressed. It is possible that this pattern of increasing differences between conditions may have continued with longer task duration. However, in such case it remains to be explained why nocebo fatigue information would only lead to increased fatigue relative to neutral information after a certain amount of time spent of the task. Indeed, although task duration in this experiment was relatively short, it was sufficient to induce increases in fatigue in both conditions. Nevertheless, future studies could investigate nocebo effects on fatigue in longer experimental protocols. In daily life, cumulative experiences may lead to more drastic effects such as sick leave.

When negative affect was included as a covariate in the analyses, there was a significant Condition*Block interaction effect for both fatigue and urge to stop. That is, participants in the Nocebo condition showed a greater increase in fatigue and urge to stop as the task progressed relative to the Control group. Although this analysis was not a priori planned but included to account for baseline differences between conditions in negative affect (significantly higher in the Control condition), these results provide an interesting extension to our findings. Given the positive association that has been demonstrated between negative effect and increased subjective symptom reporting, it is interesting that our nocebo manipulation affected fatigue and urge to stop while controlling for individual differences in negative affect. These phenomena would benefit from future studies investigating whether the susceptibility to nocebo information in the context of fatigue and motivation depends on negative affect or other stable individual difference variables (e.g., personality).

A strength of this study is that the nocebo information was given about the cognitive task itself. This is different from placebo and nocebo studies where information is given about receiving a certain substance such as a placebo pill or drink or undergoing a sham procedure, which may in turn affect cognitive or physical task performance, or may evoke symptoms unrelated to effort. We believe that nocebo instructions directly related to task performance, rather than to receiving a substance or procedure which may in turn affect task performance, may be especially relevant to how nocebo effects may manifest in the flow of daily life (e.g., clinicians informing their patients that the same daily tasks may now be more fatiguing than they used to be). Relatedly, this experiment differs from more traditional placebo/nocebo studies where instructions are given about an inert substance or sham procedure. Here, participants performed a task that may elicit fatigue by its nature. Nevertheless, results showed that verbal instructions moderated the effects of the task, which we believe constitutes a nocebo effect in its own right. Limitations of this study include the relatively short experimental protocol and the small number of men relative to women in the sample, which may limit the generalizability of the results to men and also precluded testing for gender effects. Generalizability of this experiment is further limited to cognitive fatigue and the urge to stop exerting further cognitive effort. Future studies could investigate the effects of verbal nocebo information directly related to physical effort. Finally, whereas participants rated their fatigue and urge to stop after each task block on a VAS-scale presented on the screen, future studies could employ vocal ratings to prevent participants from taking short breaks during the task (e.g., Van Cutsem et al., 2018).

This study adds to the limited available experimental evidence for nocebo effects in the context of fatigue. As Wolters and colleagues (Wolters et al., 2019) have argued, studies on fatigue mainly come from the field of sport psychology and focus on improving physical performance. Therefore, placebo effects have been investigated much more than nocebo effects. Our findings may be more readily applied to how nocebo effects may manifest in clinical contexts.

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