



## Learning to feel tired: A learning trajectory towards chronic fatigue

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### ABSTRACT

Chronic fatigue complaints are frequently reported in the general population and fatigue ranks among the most commonly reported symptoms in chronic disease. In contrast to its high prevalence and impact on quality of life, relatively little is understood about the etiology of chronic fatigue. We present a cognitive-behavioral framework, the ‘ALT + F’ model, that conceptualizes fatigue from an associative learning perspective, and we will evaluate the current evidence for this position. Central to this framework is the notion that interoceptive and exteroceptive stimuli can become associated with the fatigue experience. Consequently, these stimuli may acquire the capacity to elicit fatigue as well as anticipatory fear-related avoidance behavior. We will argue that associative learning processes may contribute to the development of chronic fatigue, fear of fatigue, avoidance of fatigue and activity, and eventually, functional disability. The extent to which associative learning processes give rise to chronic fatigue and fear-related avoidance behavior may depend on a number of risk factors, including perceptual-cognitive biases, sensitization, fatigue catastrophizing, and excessive generalization. The presented framework offers a new window on treatment and intervention options for chronic fatigue.

### 1. Introduction

*Lea (44) has been struggling with chronic fatigue for over three years. She first went on sick leave due to acute illness, but has not returned to work since. What is more, she avoids any kind of physical or mental effort and tries to rest as much as possible, out of expectation that her fatigue will get worse. Her greatest fear is that she will not be able to function at all anymore, making fatigue an aversive and fearful experience. Whenever she is not resting, Lea is constantly screening her body for warning signs of fatigue, and stops all activity as soon as she feels fatigue setting in. Certain situations seem to evoke even more fatigue, such as doctor visits or her work environment. Her general practitioner finds no evidence of somatic illness or dysfunction, but believes that her behavioral pattern of avoidance of activity and excessive fear and worrying may be important factors standing in the way of recovery.*

Fatigue is a highly common and recurrent experience throughout the course of life. It is essential for survival, in that fatigue is associated with behavioral tendencies that promote homeostasis – such as installing a recovery-resting period after prolonged wakefulness or after physically or mentally demanding tasks. In response to acute illness, fatigue and concomitant inactivity is often beneficial by conserving

limited energy resources and facilitating healing processes (de Ridder, Geenen, Kuijjer, & Middendorp, 2008). Crucially, either in health or in acute illness, fatigue is usually alleviated after a period of recovery. Nevertheless, as is illustrated by the case report of Lea, fatigue may also persist over longer time periods, despite attempts to recover from illness or exertion. Community studies (Jason et al., 1999; Kluger, Krupp, & Enoka, 2013; Loge, Ekeberg, & Kaasa, 1998) estimate 2%–11% of the general population report substantial fatigue lasting at least 6 months. In one large study ( $N = 9375$ ) this estimate is even 31% of the general population, possibly due to over half of individuals with long-term fatigue in this sample suffering from a medical condition that may partially explain fatigue symptoms (van 't Leven, Zielhuis, van der Meer, Verbeek, & Bleijenbergh, 2009). Indeed, fatigue is also an extremely common complaint in chronic disease, and is often identified as one of the key factors that negatively impact quality of life in chronically ill individuals (Jason, Evans, Brown, & Porter, 2010; Swain, 2000). Long-term fatigue features prominently in cardiovascular disease, in several neurological, immunological disorders (Cumming, Packer, Kramer, & English, 2016; Heesen et al., 2006; Kluger et al., 2013; Stebbings & Trehanne, 2010), and is a defining characteristic of chronic fatigue syndrome and fibromyalgia. In psychopathology, fatigue is for instance

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listed as a symptom in the DSM-V diagnostic criteria for major depressive disorder and generalized anxiety disorder, and often features in somatic symptom disorder. Recent evidence also points to greater fatigue in attention deficit hyperactivity disorder relative to healthy controls (Rogers, Dittner, Rimes, & Chalder, 2017).

The high prevalence of chronic fatigue in clinical and nonclinical populations together with its debilitating impact on quality of life is in stark contrast to our poor understanding of the factors involved in its etiology. Surprisingly, there is little or at best inconsistent evidence for a direct association between chronic fatigue complaints and the pathophysiology of chronic disease (e.g., chronic fatigue syndrome: Afari & Buchwald, 2003; Hampton, 2006; multiple sclerosis: Kos, Kerckhofs, Nagels, D'hooghe, & Ilsbrouckx, 2008; stroke: Kutlubaev, Duncan, & Mead, 2012), indicating that other variables need be taken into account to explain chronic fatigue in these conditions. Similarly, there is also no evidence of somatic illness or dysfunction in our case report of Lea. Moreover, the presence and severity of chronic fatigue differ greatly between individuals suffering from the same conditions, ranging from mild or no fatigue to extreme fatigue with severe limitations on daily functioning (DeLuca, 2005). Several models have been proposed to reach a better understanding of chronic fatigue symptomatology. These theoretical accounts differ substantially in the relative weight attributed to biological or disease specific variables (e.g., Chaudhuri & Behan, 2004; Pardini, Bonzano, Mancardi, & Roccatagliata, 2010), psychological variables such as cognitions about fatigue or avoidance behavior (e.g., Knoop, Prins, Moss-Morris, & Bleijenberg, 2010; Surawy, Hackmann, Hawton, & Sharpe, 1995), or environmental factors such as stress (i.e., threat to homeostasis; e.g., Wyller, Eriksen, & Malterud, 2009). Considerable progress has been made over the last decades in uncovering neurobiological and physiological factors in chronic fatigue. These include but are not restricted to hypothalamic-pituitary-adrenal axis dysregulation (Papadopoulos & Cleare, 2012), prolonged immune system activity with increased levels of pro-inflammatory cytokines (Dantzer, O'Connor, Freund, Johnson, & Kelley, 2008), and oxidative stress (Gilliam & St. Clair, 2011). Despite this progress, many questions remain largely unanswered up to date: What are the factors involved in the transition from acute, transient fatigue to chronic fatigue? How can we explain the large individual differences in chronic fatigue complaints within diagnostic categories? And how can we improve intervention options for chronic fatigue? The aim of this theoretical review is to present a cognitive-behavioral model that conceptualizes chronic fatigue from an *associative learning* perspective. We will argue that learning processes facilitate the trajectory from short-term to chronic fatigue. Whereas acute, short-term fatigue may be explained by its proximal antecedents such as prolonged effort or acute illness and their physiological correlates, chronic fatigue and individual differences therein remain largely unexplained. Our model provides an incremental step towards understanding the development and maintenance of unexplained chronic fatigue. We will discuss several risk factors related to associative learning that may explain individual differences in chronic fatigue. The presented framework is not intended as a substitute for current biomedical or psychological models of chronic fatigue. Rather, we believe it constitutes a much needed addition in an approach to chronic fatigue that integrates biological, affective, and motivational processes. This may further our understanding of chronic fatigue, paving the way for targeted prevention and more successful personalized treatment. In summary, we will argue that the evidence for an associative learning account of (chronic) fatigue is accumulating, that it adds to the explanatory power of existing theoretical models of chronic fatigue, and that it offers interesting options for its management.

## 2. The concept and measurement of fatigue

The scientific study of fatigue represents a challenging endeavor, as is evidenced by the multitude of definitions and ways to measure fatigue developed over several decades of research (Aaronson et al.,

1999; DeLuca, 2005; Shahid, Shen, & Shapiro, 2010). This may be due in large part to its inherently subjective and private nature, especially when fatigue is experienced and reported as an aversive symptom. The subjective feeling of fatigue is the essential marker of the state, as is true for other bodily symptoms such as pain or dyspnea (Auvray, Myin, & Spence, 2010; Hockey, 2013; Meek et al., 1999). Still, subjective fatigue experience may be associated with observable changes in behavior such as fatigue reporting, resting or avoidance of activity (e.g., Evering, van Weering, Groothuis-Oudshoorn, & Vollenbroek-Hutten, 2011; Nijis et al., 2011). Research has also shown that fatigue may lead to subjective or objective decreases in cognitive functions required to perform daily tasks such as attention or memory (e.g., Boksem, Meijman, & Lorist, 2005; van der Linden, Frese, & Meijman, 2003). However, changes in behavior or cognitive functioning seem to be neither necessary nor sufficient for subjective fatigue. The relation between subjective, covert fatigue and overt change in behavior or cognitive functioning is complex and may differ depending on the person and the situation. In his motivational theory of fatigue, Hockey (2013) underlines the *signal value* of fatigue for motivational control over ongoing behavior, thereby providing a mechanism for resolving conflicts between current goals and other possible or desired actions. This is closely akin to the affective-motivational dimension of pain described by Auvray et al. (2010) who emphasize that pain is not merely a percept but a motivation to act. Therefore, these accounts propose to consider pain and fatigue respectively as a kind of affection or emotion that includes a tendency to act (e.g., resting, escape behavior, disengagement). Hence, the occurrence or non-occurrence of overt behavioral change in the presence of subjective fatigue may depend on its momentary affective-motivational aspects.

In the same vein, researchers have repeatedly tried to identify objective measures of fatigue (DeLuca, 2005). In this effort, fatigue, either physical or mental, has for instance been operationalized as an observable decrease in performance after prolonged or excessive effort, such as a decrease in muscle contraction or an increase in reaction time on a certain task. Again, observable performance decrements after prolonged effort – often referred to as *fatigability* – can be related to subjective increases in fatigue, but not necessarily so (e.g., Bryant, Chiaravalloti, & DeLuca, 2004).

Fatigue can also be described in terms of its neurobiological or physiological correlates (e.g., Borghini, Astolfi, Vecchiato, Mattia, & Babiloni, 2014; Caseras et al., 2008; Cook, O'Connor, Lange, & Steffener, 2007; Dantzer et al., 2008; Gilliam & St. Clair, 2011; Ishii, Tanaka, & Watanabe, 2014, 2016; Kutlubaev et al., 2012; Lambert, Gibson, & Noakes, 2005; Lorist, Boksem, & Ridderinkhof, 2005; Papadopoulos & Cleare, 2012; Pardini et al., 2010). A synthesis of these findings primarily shows that the neurobiological and physiological correlates of fatigue can be very diverse, and may differ depending on how fatigue is defined, induced, or measured. The heterogeneity of currently available evidence corroborates the more general observation that there is often no simple correspondence between neurobiological or physiological parameters and the conscious experience of somatic sensations and symptoms. Subjective symptoms are the result of a complex integration between neurobiological or physiological bottom-up and perceptual-cognitive top-down processes (Janssens, Verleden, De Peuter, Van Diest, & Van den Bergh, 2009; Kolk, Hanewald, Schagen, & Gijsbers van Wijk, 2003; Meek et al., 1999; Moseley & Vlaeyen, 2015; Van Diest et al., 2005; Van den Bergh, Witthöft, Petersen, & Brown, 2017). Moreover, somatic symptoms such as pain, dyspnea, or fatigue may even be reported in absence of evidence for bottom-up dysregulation – often referred to as 'medically unexplained symptoms' (Brown, 2004; Rief & Broadbent, 2007). When investigating the neurobiological correlates of fatigue, it thus seems warranted to ascribe a central role to brain areas involved in the perceptual discrimination of bodily input and in the cognitive interpretation of these percepts as fatigue, which may be negatively valenced in individuals with fatigue complaints (e.g., Caseras et al., 2008).

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