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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, Kuijer, & 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, & Bleijenberg, 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 & Treharne, 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; Nijs 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 decrement 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).

Finally, many – often dualistic – distinctions have been made to describe components of fatigue, for instance: physical versus mental, objective versus subjective, or central versus peripheral. Whereas these distinctions may have heuristic value in certain areas of science or in light of specific research questions, some have argued that they do not capture the multidimensional nature of fatigue when considered in isolation (Shen, Barbera, & Shapiro, 2006). Our learning perspective will transcend most of these distinctions, as the same learning processes, for instance, may affect both physical and mental fatigue. Nevertheless, we will highlight specific components of fatigue wherever relevant.

3. (Chronic) fatigue: an associative learning perspective

Humans share the capacity with a broad range of organisms to learn that two or more stimuli or events are related to one another, and that certain actions lead to certain outcomes. This learning can result from direct experience, but also from indirect observation and socially transmitted verbal information, and may exist in the form of mental propositions or beliefs (e.g., that one event precedes or causes another; Koban, Jepma, Geuter, & Wager, 2017; Mineka & Zinbarg, 2006; Mitchell, De Houwer, & Lovibond, 2009). The ability to learn associations between events (i.e., classical conditioning) has clear benefits for survival, as it makes our ever changing environment more predictable. Learning the outcomes of our actions (i.e., operant conditioning) on the other hand provides a degree of control over our environment.

A vast literature demonstrates the role of associative learning in the development of fear and anxiety responses (e.g., Bouton, Mineka, & Barlow, 2001; Duits et al., 2015; Mineka & Zinbarg, 2006); anticipatory immune modulation (e.g., Bovbjerg et al., 1990; Stockhorst et al., 2000; Vits et al., 2011); gastrointestinal symptom learning (Stockhorst, Enck, & Klosterhalfen, 2007); and other bodily symptoms such as dyspnea (De Peuter et al., 2005); nausea and vomiting (Montgomery & Bovbjerg, 2001; Stockhorst, Steingrueber, Enck, & Klosterhalfen, 2006); and chronic musculoskeletal pain (Vlaeyen & Linton, 2012). In cancer treatment, for instance, nausea and vomiting are among the most frequent side effects of chemotherapy. In individuals who already underwent chemotherapy, these symptoms may also occur prior to subsequent sessions. This anticipatory nausea and vomiting is usually explained as a conditioned or learned response, where the environmental context of the hospital and treatment setting (conditioned stimulus, CS) has become associated with the administration of cancer medication (unconditioned stimulus, US) and its undesirable side-effects (unconditioned response, UR). As a consequence, the environmental stimuli that predict the imminent onset of nausea and vomiting may come to evoke these symptoms anticipatorily (conditioned response, CR). But the impact of associative learning on human behavior is perhaps best illustrated by the development of conditioned fear and anxiety. Fear can be highly adaptive by motivating defensive reactions in the face of danger or potential harm (US), and stimuli (CS) that predict these aversive outcomes may elicit anticipatory fear that promotes protective behavior such as avoidance. However, associative fear learning may also have maladaptive consequences, as is indicated by its central role in the development of anxiety disorders (Duits et al., 2015) and chronic pain disorder (e.g., Meulders, Jans, & Vlaeyen, 2015). In individuals with chronic musculoskeletal pain, a certain context (e.g., work) or movement (e.g., bending over) may become associated with pain (US). As a result, these contexts and movements (CS) may have become threatening to the individual's body integrity and are now being avoided. This pattern characterized by fear of pain and avoidance can in turn fuel the development of chronic pain and disability. Note that the principles of both classical and operant conditioning are at play here. Classical conditioning allows stimuli such as bodily sensations and movements (CS) to acquire signal value for ensuing pain (US), whereas operant conditioning can explain how behavioral patterns aimed at avoiding or escaping from pain may develop and persist. For instance, avoidance of certain movements (or physical activity all together) may become negatively reinforced by the temporary relief or absence of pain.

In the following, we will review the literature of associative learning in relation to fatigue, and develop a model for chronic fatigue that can guide future research. Central to this model is that during the experience of fatigue, both exteroceptive (i.e., external to the body) and interoceptive stimuli (i.e., stimuli that provide afferent information from receptors monitoring the internal state of the body; Ceunen, Vlaeyen, & Van Diest, 2016) are paired with fatigue and individuals may learn that they are related (Bouton et al., 2001). As a consequence of this learning, these stimuli may acquire the capacity to evoke a conditioned response, which may be the expectancy of fatigue, fear of fatigue, fatigue-related behavior such as resting or avoidance of activity, or fatigue itself. From an evolutionary perspective, learning which stimuli are associated with or predict the onset of fatigue may be equally important to maintain homeostasis, because it allows anticipating fatigue and acting accordingly. Indeed, the early detection of bodily symptoms that represent potential threat or harm to an organism (e.g., dyspnea, pain, fatigue) may represent a crucial evolutionary advantage (Vlaeyen, 2015; von Leupoldt et al., 2009). Associative learning facilitates this early detection by awarding *signal value* to stimuli that precede symptom onset.

However, despite this adaptive signaling function, the same learning processes may also contribute to the development of a chronic state characterized by long-term fatigue complaints, avoidance of activity, and eventually, disability and impaired social and professional functioning. In burnout syndrome, for instance, previously neutral work-related stimuli may develop into powerful triggers of stress and fatigue, and can elicit long-lasting avoidance of the work environment (Bianchi, Schonfeld, & Laurent, 2015). Whereas the subjective fatigue experience and related behavior may initially be triggered by autonomic responses to significant environmental events (Hockey, 2013), associative learning may come to loosen this link (Van den Bergh et al., 2001). That is, stimuli associated with fatigue may evoke behavioral change in anticipation of fatigue and hence also in the absence of fatigue or in the presence of only mild fatigue. Thus, learning processes also increase the risk of 'false alarms', when anticipatory action is taken in the absence of actual threat to homeostasis.

In this section, we will discuss different types of associative learning in relation to fatigue. First, we discuss the evidence for associative *learning about* fatigue. Here, fatigue is conceptualized as a *stimulus* (either conditioned or unconditioned) about which learning can take place – through direct experience, but also through verbal transmission, observation, and inferential reasoning. Individual learning differences may in turn result in different fatigue-related behavior. In our case illustration, fatigue has become an aversive and fearful experience (US), which has led Lea to avoid physical and mental effort as much as possible. Moreover, she has learned to recognize bodily warning signs of fatigue (CS) that may predict fatigue and that, when present, trigger immediate resting behavior. Again, whereas the principles of classical conditioning can explain how stimuli such as bodily sensations become associated with fatigue, operant conditioning can explain how these stimuli may trigger instrumental behavior aimed at avoiding, postponing, or escaping from fatigue. Second, we will discuss evidence for associative *learning of* fatigue. That is, when fatigue itself becomes the conditioned *response,* triggered by stimuli that were previously paired with fatigue. As illustrated by Lea, certain situations such as doctor visits or her work environment have acquired the capacity to evoke (increases in) fatigue (CR).

3.1. Learning about fatigue

On the one hand, learning can relate to the aversive properties of fatigue as an unconditioned interoceptive stimulus or event (US). This subjectively learned information about fatigue may in turn fuel the development of fear and avoidance. For instance, an individual with

persistent fatigue may have developed the belief that fatigue is harmful to the body and that is better to avoid exercise, because his general practitioner previously advised to take it easy for a while and have sufficient rest. On the other hand, learning about fatigue can relate to the interoceptive precursors – 'warning signs' (e.g., mild somatic sensations) – of fatigue or of the feared outcomes of fatigue (e.g., deterioration of disease). These learned interoceptive precursors may elicit similar anticipatory behavior such as avoidance of activity; thus effectively functioning as conditioned stimuli (CS). These two forms of learning about fatigue – as US and as CS – find support in a broad range of both quantitative and qualitative evidence.

3.1.1. Fatigue as unconditioned stimulus

Fatigue can be described as a US if it changes responding to another stimulus that has been paired with fatigue. In other words, a stimulus may come to elicit responding that was not evoked by this stimulus prior to its association with fatigue. For instance, certain activities that resulted in fatigue in the past (e.g., exercise) or certain contexts that have become associated with fatigue (e.g., work environment) may now elicit the *expectancy* of fatigue. To the extent that fatigue sensations are experienced as aversive or threatening, anticipatory responding may also consist of *fear of fatigue*, *avoidance of activity* or *resting behavior*.

In order to understand how fatigue may influence responding to stimuli that become associated with fatigue, it is important to identify what about the fatigue experience may make it an undesirable or feared outcome (US). This may differ greatly between individuals and may codetermine the nature of responding to or in anticipation of fatigue. In individuals suffering from chronic illness and/or chronic fatigue complaints, fatigue sensations may be laced with negative meanings and implications. For instance, daytime fatigue represents one of the main feared outcomes in individuals with insomnia, because it interferes or is believed to interfere with daytime functioning (Hood, Carney, & Harris, 2011). In chronic disease, fatigue has been associated with a subjective lack of energy, depressive symptomatology, and physical disability (e.g., Bol et al., 2010; Goretti et al., 2012; Lewis et al., 2011; Matcham, Ali, Hotopf, & Chalder, 2015). And as discussed earlier, research has shown that fatigue may be associated with subjective or objective decreases in cognitive functioning. It is clear that when these subjective or objective negative consequences become part of (the mental representation of) fatigue as an aversive US, anticipatory avoidance behavior may be affected accordingly.

This is supported by in-depth interview studies in populations suffering from chronic disease. These reports show that fatigue may be experienced as a marker of disease progression, and may offer a sense of the body's general vulnerability. Individuals with multiple sclerosis who participated in an eight-week exercise program reported recognizing the difference between 'healthy' or 'normal' fatigue and 'unhealthy' or 'bad' fatigue – the latter resulting from not 'listening to your body' and 'going beyond the edge' (Smith, Hale, Olson, & Schneiders, 2009). Participants associated this 'unhealthy' fatigue with a sense of physical deterioration. In another study, individuals with multiple sclerosis reported experiencing a fine line between benefit and harm during exercise, with harm conceptualized as a worsening of fatigue symptoms (Kayes, McPherson, Taylor, Schlüter, & Kolt, 2011). In response to previous experiences where physical activity resulted in a worsening of fatigue, patients often feared physical activity in the future. Further, in a sample of outpatients suffering from chronic heart failure, fatigue was experienced as a distressing symptom that reflected a person's vulnerability (Jones, McDermott, Nowels, Matlock, & Bekelman, 2012). The experience of fatigue was even reported to influence the perceived proximity to death.

Qualitative evidence from different clinical populations for fatigue as an aversive US and its impact on behavior is corroborated by experimental research in chronic fatigue syndrome. Here, fatigue represents an aversive experience that greatly affects daily functioning and quality of life. Exercise or a sudden increase in physical activity may trigger fatigue and other symptoms (e.g., negative mood, muscle pain; Bazelmans, Bleijenberg, Voeten, van der Meer, & Folgering, 2005; Black, O'Connor, & McCully, 2005). As a consequence of such prior learning experience where exercise resulted in undesired symptoms, the prospect of physical activity and the anticipation of symptoms may now evoke fear of fatigue and physical activity, and may ultimately lead to avoidance of physical activity altogether. In a series of studies (Heins et al., 2013; Nijs et al., 2012a), individuals with chronic fatigue syndrome were requested to climb and descend two floors of stairs without resting. Prior to this task, participants rated their anticipated fatigue (or fatigue expectancy) and completed measures of fatigue catastrophizing, fear of fatigue, and fatigue-related fear of physical movement (i.e., kinesiophobia). Interestingly, higher anticipated fatigue (Heins et al., 2013), and higher levels of fatigue catastrophizing, fear of fatigue, and kinesiophobia (Nijs et al., 2012b) all predicted poorer stair-climbing performance (i.c., more time required to complete the 'threatening' activity). Poorer stair-climbing performance may constitute a learned avoidance response modulated by fatigue expectancies and fear of fatigue. Taking longer to complete the physically demanding task (underperformance) may constitute an instrumental avoidance/escape response to diminish its feared effects (e.g., increase in fatigue and other CFS symptoms). This is in line with the findings of Silver et al. who asked individuals with chronic fatigue syndrome to ride an exercise bicycle for as long as they felt able (Silver et al., 2002). Results showed that behavioral persistence was unrelated to symptom severity, emotional distress, maximal heart rate or resting heart rate, but was strongly and negatively correlated with fear of physical movement. Especially negative, fearful beliefs about activity (e.g., 'I am afraid that I might make my symptoms worse if I exercise') predicted poorer performance.

These experiments nicely illustrate how classical and operant conditioning processes may co-operate. Stimuli that become associated with fatigue such as exercise may trigger the expectancy that fatigue may follow. To the extent that fatigue is perceived as an aversive outcome, these stimuli may trigger instrumental avoidance or escape behavior to gain control over fatigue or to reduce fatigue-related fears. In chronic fatigue syndrome for instance, behavior (e.g., exercise) that is followed by the aversive experience of fatigue may be conceptualized as being punished. Behavior followed by fatigue may thus be expected to decrease in frequency through negative reinforcement, in that avoiding or limiting physical exercise may result in temporary relief of fatigue-related fear or in postponement of fatigue. In summary, these findings show that the *fatigue representation* as a threatening outcome or aversive US, and individual differences therein, may explain variance in fatigue-related behavior that may be aimed at gaining control over fatigue. Although the evidence discussed here mainly stems from clinical populations, it should be noted that a negative, threatening fatigue representation can also exist in absence of a medical diagnosis. This representation may have developed through prior aversive fatigue-related experiences, but also socially transmitted information, observation, and inferential reasoning.

3.1.2. Fatigue as conditioned stimulus

Fatigue has the function of a CS when the behavioral response to fatigue is changed due to co-occurrence with another (aversive) stimulus. This co-occurrence need not be experienced directly and can exist in the form of a proposition 'if P → Q' (e.g., 'If I feel fatigued, then *X* will follow'). For instance, in a focus group study by Flinn & Stube (2009), community-dwelling stroke survivors reported that, when feelings of fatigue emerged, they were concerned about having some other physical problem such as a heart attack or another stroke. The perceived relation between fatigue and potential health problems was also reported to promote illness behavior, such as seeking advice from health professionals to deal with fatigue or to alleviate worry. Thus, cognitions about fatigue indicating or predicting health problems may trigger worry and fear reactions. This is akin to the notion of

catastrophic misinterpretations of bodily sensations described in cognitive theories of panic disorder (e.g., "I am going to have a heart attack"; Clark, 1986), and to the role of pain catastrophizing in the etiology of chronic pain (Vlaeyen & Linton, 2012). It remains unclear however, to what extent these cognitions about the relation between fatigue and health problems developed as a consequence of stroke (e.g., in a one trial fatigue-stroke conditioning event) or already existed prior to stroke.

Further, interoceptive precursors of fatigue can also come to function as CS for more intense fatigue. Interoceptive conditioning experiments demonstrate that initial, mild somatic sensations can become a CS for more intense somatic sensations, which is an instance of 'homoreflexive' conditioning where CS and US belong to the same sensory modality. Interoception refers to the sense of the physiological condition of the body. Through afferent neural pathways representing the status of all aspects of the body, thalamocortical representations are generated that are crucial for somatic feelings such as temperature, pain, itch, or fatigue (Craig, 2002). Interoception thus allows the conscious evaluation of 'how we feel'. During interoceptive conditioning, low-level somatic sensations of an interoceptive event are paired with higher levels or the full expression of that interoceptive event (De Cort, Griez, Büchler, & Schruers, 2012). In other words, a strong interoceptive event can become associated with a weaker version of the same event (Bouton et al., 2001). As a consequence, these low-level or mild bodily sensations may function as CS capable of evoking anticipatory behavior and may even come to evoke higher levels of the associated interoceptive event.

Although conditioning in which the onset of an interoceptive event signals the rest of the event clearly blurs the distinction between a CS and a US, it is very common nonetheless (Bouton et al., 2001). Interoceptive conditioning effects have for instance been demonstrated extensively in homeostatic regulation processes including drug tolerance (e.g., Sokolowska, Siegel, & Kim, 2002), and blood pressure regulation (i.e., barorelfex; Dworkin & Dworkin, 1995), and have been implicated in the development of fear of pain in chronic pain (De Peuter, Van Diest, Vansteenwegen, Van den Bergh, & Vlaeyen, 2011). Further, interoceptive conditioning processes are nicely illustrated by their central role in the development of panic disorder (Bouton et al., 2001; De Cort et al., 2012). The occurrence of a panic attack represents a conditioning episode where initial interoceptive precursors (e.g., sweating, palpitations) become associated with the rest of the attack. As a result, these precursors may provoke fear and anxiety as conditioned responses, which in turn produce higher arousal and more interoceptive symptoms, spiraling into a full-blown panic attack.

Similarly, mere exposure to fatigue inevitably allows interoceptive stimuli that correspond to its early onset to become associated. These stimuli can be any bodily sensation preceding severe fatigue, such as mild levels of fatigue, elevated distractibility (e.g., lack of attentional control), or a general feeling of discomfort. As a consequence, these early or low-level sensations may acquire the capacity to elicit higher levels of fatigue solely by virtue of their (learned) association with fatigue, and may trigger anticipatory behavioral change (e.g., resting; cf. our case illustration of Lea). Remarkably, interoceptive fatigue conditioning experiments have not been conducted systematically. Nevertheless, there is good evidence to ascribe a central role to interoceptive conditioning in the development of conditioned fatigue responses. First, interoceptive stimuli can be expected to produce strong associative learning because the signaling value of a CS for the occurrence of a US increases with CS-US relatedness, for instance when the CS is a feature of the US or is a natural precursor of the US (i.e., homoreflexivity; Dworkin, 1993; De Peuter et al., 2011). For instance, because palpitations are often an early feature of a panic attack, they are more likely to become a CS than other normally unrelated stimuli (e.g., itch). Thus, early precursors of fatigue such as mild fatigue or a sense of increasing distractibility are good candidates to produce strong associative learning with fatigue. Second, the notion of bodily sensations becoming interoceptive CSs for fatigue on the basis of prior learning is again supported by self-reports from populations with chronic disease. These reports also show that these interoceptive CSs or 'warning signs' of fatigue are capable of eliciting avoidance behavior, which may be used as a strategy to gain control over fatigue (instrumental behavior). In an interview study in individuals with chronic heart failure, Jones et al. (2012) described this as follows, using quotes of participants as illustration:

> Patients with HF [heart failure] described a sense of "knowing" and anticipating the symptom of fatigue. They knew this symptom based on past experience. They recognized the warning signs and anticipated the symptom. Patients with HF read their body like a barometer upon waking. This sensation of "knowing" indicates that fatigue is not necessarily related to tasks or activity: "Usually you can tell right away whether you are or aren't going to have a bad day. I mean you kind of know." Knowing the symptom of fatigue is to understand the signs that can warn of the symptom, and understanding the consequences of not heeding those signs. Using caution or watchful waiting is a way of responding to "knowing" the symptom of fatigue: "Your body will tell you, a person has to be in tune with their body to learn." The learning can take months to years for some patients as they make some adjustments in terms of what they can do, what helps, and what does not. (p. 487)

Similar findings have been reported in individuals suffering from multiple sclerosis, who describe 'listening to your body' as a key strategy used to ensure fatigue is minimized during exercise (Smith et al., 2009). This selective attention for internal signals of fatigue (e.g., 'reading the body like a barometer') serves as a strategy to make fatigue onset more predictable, but may have unfavorable effects. For instance, experimental evidence has shown that individuals who are asked to focus their attention internally (on the posture of the body) rather than externally (on a schematic drawing of the required posture) during a fatiguing isometric task reported higher perceived exertion and exhibited poorer task-performance (Lohse & Sherwood, 2011).

Finally, internal cues other than somatic sensations, such as mental images, may also become associated with an aversive interoceptive event. In an experiment by Stegen and colleagues, healthy participants were randomly assigned to one of two conditions where they were exposed to 5.5% CO_2 enriched air (US) known to produce somatic symptoms such as dyspnea (Stegen, De Bruyne, Rasschaert, Van de Woestijne, & Van den Bergh, 1999). In the fear relevant condition, CO_2 exposure was paired with a fear relevant image (fear relevant CS+; e.g., being stuck in an elevator), whereas another fear relevant image was not paired with CO_2 (fear relevant CS-). In the neutral condition, a fear irrelevant image (neutral CS+; e.g., reading a book) was paired with CO_2, whereas another fear irrelevant image (neutral CS-) was not. At test, all participants were asked to imagine the previously described situation; while no more CO_2 was administered (participants were not informed about this). Results showed a selective conditioning effect: CS + imagery produced more symptoms and altered respiratory behavior compared with CS- imagery, but only in the fear-relevant script condition. Thus, merely imagining a (fearful) situation that was previously paired with a respiratory challenge sufficed to evoke similar symptoms. With respect to fatigue, this implies that a mental image that has become associated with fatigue (e.g., imagining a fatiguing task or retrieving a memory associated with fatigue) may be sufficient to provoke fatigue in and of itself. Interestingly, Caseras et al. (2008) provided experimental evidence in line with this. Individuals suffering from chronic fatigue syndrome and healthy controls watched a series of 30s video-clips previously selected to induce fatigue (e.g., a person carrying home heavy grocery bags), anxiety, or relaxation. Participants received the instruction to imagine themselves in that situation (e.g., "imagine yourself doing your shopping at the supermarket and then carrying home heavy bags"). Results showed that participants reported higher levels of fatigue after having imagined a fatiguing situation,

compared with an anxiety provoking or relaxing situation. Although this effect was found in both groups, individuals with chronic fatigue syndrome reported higher levels of fatigue than controls. This study demonstrates that observing an effortful task while merely forming a mental image of performing that task may be sufficient to provoke fatigue. These results also suggest that these mental imagery effects may be restricted to situations that are plausibly causally related, in that only fear relevant images produced anxiety and respiratory symptoms in Stegen et al. (1999), and imagining a fatiguing task was more fatigue inducing than an anxiety provoking or relaxing task in Caseras et al. (2008).

In summary, the discussed evidence in this section suggests that somatic sensations – and even mental images – associated with fatigue may become powerful triggers (CS) of fatigue and fatigue-related behavior. More research on interoceptive conditioning of fatigue is warranted (see also De Peuter, Put, Lemaigre, & Demedts, 2007).

3.2. Learning of fatigue: fatigue as a conditioned response

Fatigue may represent a naturally occurring (unconditioned) response to prolonged physically or cognitively demanding tasks. Accumulating evidence from experimental and clinical studies in humans suggests that fatigue may also be a conditioned response to stimuli or contexts that have become associated with fatigue. In an experimental study in healthy individuals, Ishii et al. (2013) investigated whether fatigue sensations could be conditioned to an acoustic stimulus: the sound of a metronome. On the first day of the experiment, both the experimental and the control group were pre-exposed to the metronome sound for 6 min. Mental fatigue was then induced in the experimental group by subjecting participants to a 60 min demanding working memory task. Because this task had been shown in earlier studies to induce fatigue sensations after 30 min, the metronome sound was presented during the second half of the conditioning session. Fatigue was successfully induced as evidenced by a significant pre-to-post task increase in fatigue levels. On the second day, all participants were exposed to 6 min of the metronome sound again. Self-reported fatigue levels were measured immediately afterwards. Results showed that fatigue increased significantly from the first to the second day in the experimental group, but not in the control group. This is an intriguing observation, because it suggests that a contextual, exteroceptive stimulus may become fatigue-inducing by itself, merely due to its prior association with fatigue. Further, a study in individuals with asthma revealed that asthma-related symptoms, including fatigue, can be successfully induced in the laboratory after a conditioning procedure (De Peuter et al., 2007). Using a standardized histamine provocation (Cockcroft's protocol), participants inhaled progressively increasing concentrations of histamines (US) until they showed an objective decrease of lung function values and an increase in self-reported asthma symptoms (UR), including airway obstruction, dyspnea, and fatigue (e.g., tired, no energy). Crucially, prior to histamine provocation, participants inhaled a neutral substance that does not induce significant airway changes (i.c., saline), which served as CS. The following day, participants returned to the laboratory and inhaled four times saline only. Whereas measures of lung function remained unaffected, self-reported fatigue and airway obstruction increased significantly from pre-to-post saline inhalation. These results show that fatigue may be elicited by neutral stimuli that co-occurred with asthma symptoms previously.

In addition to laboratory-based evidence, fatigue conditioning in daily life situations is supported by more ecologically valid data as well. Clinical evidence comes from chemotherapy treatment in cancer patients, who experience fatigue, in addition to hair loss, nausea and vomiting, as the most prevalent side-effect. Bovbjerg, Montgomery, and Raptis (2005) followed breast cancer patients during their first four cycles of chemotherapy, and investigated whether pre-infusion fatigue increased with repeated pairings of the clinic environment (CS) with chemotherapy administration (US). Prior to each treatment session, patients rated their fatigue as experienced 'right now' in the outpatient clinic. Results showed that pre-infusion fatigue levels increased over treatment sessions, consistent with the development of a conditioned response. Further, fatigue levels prior to the fourth infusion (CR) were predicted by previous post-infusion fatigue (UR). This observation is in line with another central assumption of associative learning theory and a robust finding in classical conditioning studies: stronger unconditioned responding predicts stronger conditioned responding (Domjan, 2005). Although these results accord with fatigue as a conditioned response, other explanations cannot be ruled out. For instance, increases in pre-infusion fatigue may have resulted from a general cumulative increase in fatigue as treatment progressed. Interestingly however, post-infusion fatigue levels did not increase with repeated treatment sessions in this study. Only anticipatory fatigue increased.

4. Individual differences in vulnerability to chronic fatigue

The presented evidence supports the role of associative learning in the etiology of (chronic) fatigue and fear-related avoidance behavior. However, future research is needed, and predictive precision is still lacking when it comes to individual differences in chronic fatigue. With associative learning occurring on a virtually continuous basis, how come only a minority of individuals develop chronic fatigue? Below, we propose several factors that may increase the probability of associative learning eventually leading to chronic fatigue and maladaptive behavior. Additionally, individual differences in learning histories (e.g., about fatigue representation; about precursors of fatigue) may affect behavioral responses to fatigue. In that respect, medical histories and precipitating medical events also represent associative learning episodes that may influence the trajectory towards chronic fatigue. Further, individuals may differ, for instance, in the ease by which the contingent presentation an interoceptive or exteroceptive CS and fatigue will lead to a conditioned response to that CS (i.e., conditionability; but see Servatius et al., 1998).

4.1. Perceptual-cognitive biases

Because the subjective fatigue experience is the result of a complex integration of bottom-up and top-down processes, the same somatic sensations may or may not be perceived and interpreted as fatigue – or as equally aversive – by different individuals. Part of the input may come from bottom-up afferent signals indicating physiological or neurobiological dysregulation (Lambert et al., 2005), but top-down cognitive processes of symptom perception and interpretation are the final route to all subjective symptoms (Van den Bergh et al., 2001). In relation to fatigue, a number of interesting studies – mainly in chronic fatigue syndrome – provide evidence for perceptual-cognitive biases, which may also augment symptom experience. For instance, in a visual probe experiment, individuals with chronic fatigue syndrome showed an attentional bias towards health-threat stimuli (e.g., the word 'hospitalized') relative to stimuli that lacked threat content, whereas this attentional bias was not found in a healthy control group (Hou, Moss-Morris, Bradley, Peveler, & Mogg, 2008). In a subsequent experiment, Hou et al. (2014) showed that attentional bias was primarily evident in individuals with impaired attentional control, suggesting a relation between bias toward health-threat and basic executive control processes. Moss-Morris and Petrie (2003) showed that individuals with chronic fatigue syndrome, when presented with ambiguous cues in a word association test, exhibited a somatic interpretation bias compared with matched healthy controls. Interestingly, the number of somatic and illness-related interpretations also predicted the number of currently reported symptoms. A recent systematic review concluded that these cognitive biases may contribute to fatigue symptoms and may maintain illness beliefs in chronic fatigue syndrome (Hughes, Hirsch, Chalder, & Moss-Morris, 2016). This is in line with the earlier discussed experiment in healthy subjects showing that focusing attention

internally on the body during a fatiguing task led to more fatigue and poorer performance than an external focus (Lohse & Sherwood, 2011).

Thus, perceptual-cognitive variables such as attentional bias toward signs of fatigue may influence the processing of somatic information and may impact the frequency and intensity of fatigue experiences. Moreover, this selective attention may also increase awareness of benign bodily sensations that would otherwise escape consciousness. Consequently, individuals who perceive and interpret somatic input as fatigue more frequently than others – or as more aversive – will also experience fatigue more often or more intensely. Crucially, more frequent and more intense fatigue sensations due to perceptual-cognitive bias in turn increase the number of occasions for associative learning to take place; allowing increasingly more interoceptive and exteroceptive stimuli to become associated with fatigue (De Peuter et al., 2007). Inversely, fatigue has also been shown to negatively affect perceptual discrimination capacities and may thus further facilitate this process (Han, Park, Jung, Choi, & Song, 2015; Moore, Romine, O'Connor, & Tomporowski, 2012).

4.2. Sensitization and sustained arousal

Sensitization is a non-associative learning process whereby repeated presentations of a stimulus lead to a progressive increase in responding to that stimulus (Overmier, 2002). There is accumulating evidence for central sensitization or hyperresponsiveness of the central nervous system to interoceptive and exteroceptive stimuli in the development of chronic fatigue (Nijs et al., 2012a; Wyller et al., 2009; as well as chronic pain:; Woolf, 2011). Repeated enhanced responding to a variety of input, including physical effort, heat, and histamines, has been causally linked to higher levels of fatigue; especially if it leads to a state of sustained arousal or stress (Eriksen & Ursin, 2004; Wyller et al., 2009). Moreover, it has been shown that sensitization and associative learning may have mutually reinforcing effects. On the one hand, increases in arousal from various sources can facilitate sensitization and may augment sensitized responses (Brown, Kalish, & Faber, 1951). In that respect, interoceptive and exteroceptive stimuli that have become associated with fatigue may trigger increased arousal (e.g., anticipation of aversive outcomes; fear of fatigue); thus contributing to sensitization directly (Overmier, 2002; Wyller et al., 2009). On the other hand, through sensitization, the same interoceptive or exteroceptive input can result in more frequent and intense fatigue, thereby creating more associative learning opportunities. Additionally, sensitized responding to interoceptive and exteroceptive stimuli associated with fatigue (e.g., physical activity) may further enhance anticipatory fear and avoidance of these stimuli. Thus, individual differences sensitization and sustained arousal may affect associative learning and avoidance behavior.

4.3. Fatigue catastrophizing

In the context of subjective symptom experience, catastrophizing refers to an exaggerated negative evaluation of and attention to symptoms (e.g., Pavlin, Sullivan, Freund, & Roesen, 2005; Quartana, & Edwards, 2009), and may be closely related to negative affectivity or the disposition to experience negative emotional states (Kolk et al., 2003; Van Diest et al., 2005). Catastrophizing thoughts may manifest as rumination about symptoms, magnification of symptoms, or helplessness, and may lead to more intense symptom experience and more emotional distress (Sullivan et al., 2001). A recent systematic review evidenced a robust relation between catastrophizing and fatigue symptoms in healthy individuals as well as in individuals suffering from chronic illness (*i.c.*, multiple sclerosis; cancer; chronic fatigue syndrome; fibromyalgia; Lukkahatai & Saligan, 2013). Two longitudinal studies included in this review also showed that fatigue catastrophizing before cancer treatment was a predictor of post-treatment fatigue, underlining its role as risk factor for fatigue.

Catastrophizing may impact associative learning in at least two ways, which may also provide a mechanistic explanation for the relationship between catastrophizing and fatigue. First, individuals characterized by higher levels of fatigue catastrophizing may experience fatigue as more aversive (e.g., magnification of symptoms; more emotional distress). This may contribute to a more negative fatigue representation (US), which may increase conditioned fatigue and avoidance of stimuli associated with fatigue. Second, an exaggerated negative evaluation of and attention to bodily sensations may lead individuals to experience more sensations as fatigue and to associate more bodily input with fatigue. Similar to perceptual-cognitive biases, catastrophic (mis)interpretations of fatigue-like sensations may result in more fatigue and more associative learning opportunities. Especially in ambiguous situations (e.g., in the presence of mild somatic sensations), individuals prone to catastrophizing may be biased to interpret this input as fatigue or as a signal for ensuing fatigue. This is supported by De Peuter, Lemaigre, Van Diest, and Van den Bergh (2008), who exposed individuals with asthma to merely rebreathing 100% oxygen for 2 min. However, because participants wore a nose clip and had to rebreathe an air mixture through a mouthpiece, they found themselves in an ambiguous situation where asthma symptoms could occur. Results showed that individuals who had more catastrophizing thoughts about asthma in daily life reported more fatigue (and other) symptoms after oxygen rebreathing. From an associative learning perspective, catastrophizing may represent a risk factor contributing to both the intensity (fatigue as aversive US) and frequency (more sensations experienced as fatigue) of fatigue, thereby creating more interoceptive conditioning opportunities.

4.4. Generalization

Finally, the potentially maladaptive consequences of associative learning of and about fatigue may be greatly multiplied by generalization on the basis of prior learning. Generalization occurs when behavioral change (e.g., avoidance) is elicited by a stimulus different from – but often similar to – the stimuli involved in prior learning experiences (Boddez, Bennett, van Esch, & Beckers, 2017; Dunsmoor & Murphy, 2015). Although usually adaptive, generalization can become detrimental when it occurs excessively. With respect to fatigue, this means that a certain context or activity that bears some form of (perceptual or non-perceptual) resemblance to a context or an activity previously paired with fatigue may come to evoke behavioral change as well. Individuals who felt fatigued after receiving chemotherapy in the hospital, for instance, may come to experience fatigue during future visits to *any* treatment setting. Or, after an individual with chronic fatigue syndrome experienced an increase of symptoms induced by exercise, fear of fatigue may fuel future avoidance of *any* form of physical effort. A growing amount of research highlights the role of excessive generalization in different psychological and health problems, including anxiety disorders (e.g., Lissek et al., 2010, 2014) and chronic pain disorders such as fibromyalgia (Meulders et al., 2015). Despite the functional similarities between chronic pain and chronic fatigue disorders, generalization has not been studied systematically in (chronic) fatigue. One interesting experiment (Servatius et al., 1998) investigating associative learning in individuals with chronic fatigue syndrome found evidence for learning deficits relative to healthy controls. In an eye-blink conditioning protocol where an auditory stimulus (CS) was paired with an aversive air-puff to the eye (US), individuals with chronic fatigue syndrome displayed an impaired ability to learn the contingency between CS and US compared with healthy controls. An inability to learn which stimuli predict an outcome may facilitate the development of excessive generalization. That is, if a person fails to learn the relation between an aversive outcome and a good predictor of that outcome, anticipatory behavior (e.g., expectancy of the outcome, fear, avoidance) may not be restricted to situations where that predictor is present. Future research is warranted to further assess whether individual differences in generalization are associated with risk for

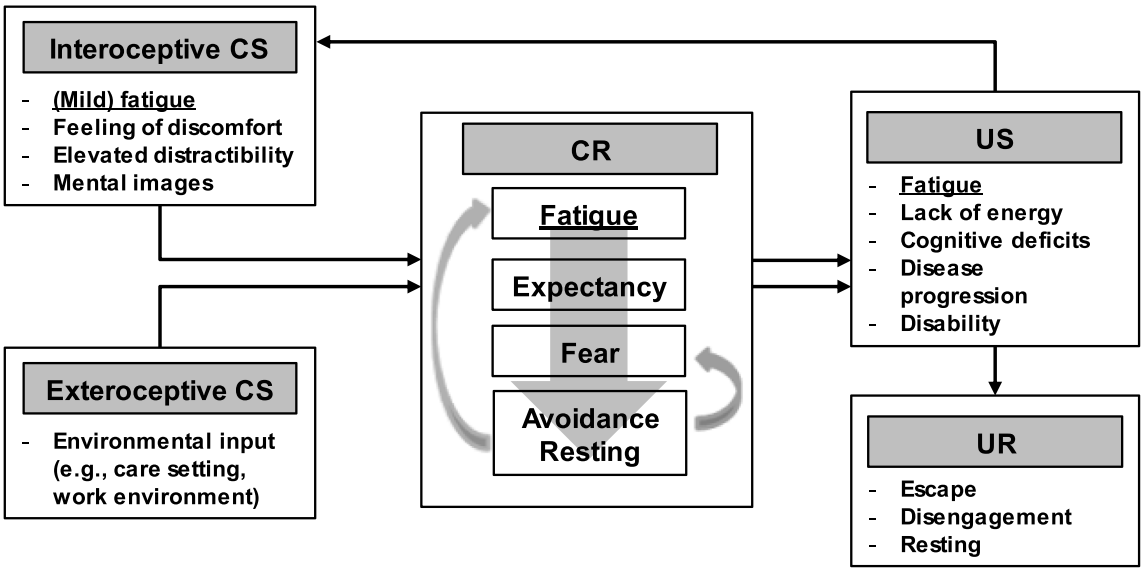

Fig. 1. The ALT + F model. In this associative learning model for chronic fatigue, fatigue can have distinct functional roles. Central to ALT + F is that somatic and environmental input may become associated with fatigue and may come to function as respectively interoceptive and exteroceptive conditioned stimuli (CS). For instance, mild fatigue sensations acquire the function of a CS when the behavioral response to these sensations is changed due to their co-occurrence with intense fatigue or another aversive stimulus. This behavioral response may consist of increased expectancy of fatigue, but also fear of fatigue, which may trigger avoidance/resting behavior. Interoceptive and exteroceptive CSs may also come to elicit fatigue itself, in which case fatigue can be considered a conditioned response (CR). Fear and avoidance may depend on the mental representation of fatigue as an aversive outcome with potentially negative consequences (e.g., impaired cognitive functioning, depressive symptoms, disease progression). Here, fatigue has the function of an unconditioned stimulus (US) in that changes responding (e.g., elicit fear) to interoceptive and exteroceptive stimuli that have been paired with fatigue. The unconditioned response (UR) to fatigue may for instance consist of disengagement or escape from ongoing activity and resting. Eventually, associative learning processes may contribute to a perpetuating cycle characterized by chronic fatigue and fear-related avoidance behavior. This may lead to increases in depressive symptoms, physical deconditioning and disability that in turn function as novel interoceptive input. The influence of the discussed vulnerability factors on associative learning in relation to chronic fatigue is not presented in the figure but is described in the text.

chronic fatigue.

5. The ALT + F model: an associative learning trajectory towards chronic fatigue

Combining the evidence listed above, we present a working model of an associative learning trajectory towards chronic fatigue. The aim of the 'ALT + F' model is to predict how associative learning processes contribute to chronic fatigue and avoidance behavior, as well as to understand individual differences in chronic fatigue and avoidance.

Central to this model is that somatic and contextual, environmental input may turn into interoceptive and exteroceptive CSs associated with fatigue (Fig. 1). Evidence from experimental and clinical research shows that these CSs may acquire the capacity to evoke fatigue as a CR. Moreover, whereas the (unconditioned) response *in reaction to* fatigue may consist of resting and disengagement or escape from ongoing activity, these CSs may acquire the capacity to elicit behavioral change *in anticipation of* fatigue and therefore also in the absence of fatigue or in the presence of only mild fatigue. Learned anticipatory behavior may manifest as an increased expectancy of fatigue, and may also consist of fear of fatigue and physical or mental effort if fatigue is experienced as an undesirable outcome, rather than as a benign or innocuous experience. This is determined in great part by the mental representation of fatigue as an aversive US with potentially negative consequences (e.g., impaired cognitive functioning, depressive symptoms, disease progression). Fatigue catastrophizing may affect this fatigue representation and may promote the development of fatigue-related fear in individuals characterized by high catastrophizing. Inversely, the well-established relationship between catastrophizing and fatigue symptoms may be mediated by the effect of catastrophizing on perceptual-cognitive processing of somatic information. These hypotheses need to be further tested in future research.

Further, the association of interoceptive and exteroceptive CSs with fatigue and fatigue-related behavior may be influenced by individual differences in medical history, perceptual-cognitive processes, sensitization, and generalization. Although they represent different mechanisms, sensitization (and sustained arousal) and perceptual-cognitive bias may lead to the same outcome: more frequent or more intense fatigue experiences; allowing increasingly more stimuli to become associated with fatigue. Generalization, finally, allows stimuli different from those involved in prior learning to gain control over behavior. Excessive generalization may represent a central factor in the spread of fatigue symptoms in daily life.

Subsequently, a negative fatigue US representation and fear of fatigue and fatigue-evoking stimuli may lead to covert and overt instrumental avoidance behavior aimed at preventing (or postponing) fatigue or its feared consequences. In that respect, ALT + F also incorporates a fear-related avoidance model originally developed in the context of chronic pain (Vlaeyen & Linton, 2012). In addition to the evidence presented earlier, several investigations targeting elements of this model support its validity for the development of chronic fatigue (e.g., Bol et al., 2010; Nijs et al., 2012b; Heins et al., 2013; Wijenberg, Stapert, Köhler, & Bol, 2016; see also; Surawy et al., 1995). If behavioral patterns of anticipatory avoidance and resting are maintained over longer time periods, they may paradoxically perpetuate fatigue complaints (presented in Fig. 1 as a reverse arrow from avoidance and resting to fatigue). Fatigue levels may even increase in these circumstances through physical deconditioning or increased negative mood, for instance due to loss of social interaction and rewarding activities. First, a lack of physical activity has indeed been associated with physical deconditioning. Sandroff, Klaren, & Motl (2015) showed that daily time spent engaging in moderate-to-vigorous physical activity was associated with aerobic capacity during an exercise test in individuals with multiple sclerosis as well as in healthy controls. Further, skeletomuscular, cardiovascular or respiratory indicants of physical deconditioning have been associated with higher levels of fatigue in different populations, including breast-cancer survivors (Neil, Klika, Garland, McKenzie, & Campbell, 2013), stroke survivors (Lewis et al., 2011), and individuals with chronic fatigue syndrome (De Lorenzo et al., 1998). Thus, inactivity due to avoidance and resting behavior may lead to

physical deconditioning, which may in turn perpetuate fatigue complaints (see also Evering et al., 2011). Second, a lack of physical activity has also been associated with depressed mood in healthy and chronically ill individuals (Galiano-Castillo et al., 2014; Matcham et al., 2015; Motl, Birnbaum, Kubik, & Dishman, 2004), and has even been shown to be a prospective risk factor for the development of depressive symptoms (Brown, Ford, Burton, Marshall, & Dobson, 2005; Camacho, Roberts, Lazarus, Kaplan, & Cohen, 1991). Given the association between depressed mood and fatigue (e.g., Kroencke, Lynch, & Denny, 2000; Schönberger, Herrberg, & Ponsford, 2014), fatigue may also be perpetuated by increased depressed mood (and vice versa) resulting from avoidance and resting behavior. This may eventually result in a perpetuating cycle characterized by chronic fatigue, fear-related avoidance behavior, and disability (e.g., Bol et al., 2010). It is noteworthy that if the mental fatigue representation also consists of non-accepting cognitions about fatigue (e.g., "If I give in to my complaints, I will not be able to do anything at all"), this may trigger opposite behavioral patterns characterized by bursts of activity and overdoing, which may also be complaint-enhancing (cf. distinction between relatively active and passive individuals in chronic fatigue syndrome; Bazelmans, Prins, & Gijs Bleijenberg, 2006).

In summary, the ALT + F model provides an associative learning account for the development and persistence of chronic fatigue and fatigue-related behavior, and incorporates several variables that may influence associative learning. This model aims to shed new light on the etiology of chronic fatigue and provides heuristic value for organizing existing knowledge and guiding future research. For instance, in their narrative review, Knoop et al. (2010) highlighted three different cognitive processes that play a role in the perpetuation of symptoms in chronic fatigue syndrome. The first is a general cognitive representation in which fatigue is perceived as negative and aversive (*i.e.*, negative fatigue/US representation). The second proposed process is focusing on fatigue (*i.e.*, attentional bias towards fatigue), and the third consists of specific dysfunctional beliefs about activity and fatigue, which is akin to fatigue catastrophizing. This illustrates how the ALT + F model allows anchoring previous research within a broader (learning-oriented) theoretical framework. Finally, the bulk of research has focused on chronic fatigue syndrome, but the ALT + F model predicts that learning processes play a central role in the etiology of chronic fatigue across multiple diseases and disorders.

5.1. Implications for treatment

A first overarching recommendation is that any cognitive or behavioral intervention targeted at fatigue should be based on a thorough functional analysis (FA) of fatigue and fatigue-related behavior. FA refers to the idiographic assessment of an objectively defined target behavior and the contextual, cognitive, and behavioral factors that control some aspect of its topography (e.g., frequency, intensity, duration; Haynes & O'Brien, 1990). Considering the large individual differences in learning histories, mental representations of fatigue, and the risk factors involved in the development of chronic fatigue and fatigue-related behavior, the data derived from FA are critical to design personalized interventions. Depending on the outcome of a FA, different interventions may be chosen for the same behavior observed in different individuals. For instance, engaging in an exercise program may be effective for someone who experiences fatigue as a result of excessive resting and physical deconditioning. In contrast, it may not have the desirable effects in someone who is constantly screening the body for signs of fatigue and who engages in overt and covert avoidance during the exercise program (e.g., underperformance to prevent feared outcomes of fatigue). In such cases, cognitive interventions aimed at attentional control and countering catastrophizing thoughts should be part of the treatment program as well. In summary, current treatment options may be insufficiently tailored to the individual. A thorough analysis of the antecedents and consequences of fatigue and fatigue-related behavior allows assessing which elements of the presented model constitute relevant targets for intervention for each individual separately.

Further, our model predicts that the expectancy of fatigue triggered by interoceptive or exteroceptive CSs may trigger anticipatory behavior (e.g., avoidance) as well as fatigue. It follows that interventions aimed at modifying fatigue expectancy – either through verbal instructions or direct experience – may have direct fatigue alleviating effects. This is supported by placebo research in healthy and clinical populations, where the expectancy of fatigue reduction induced using various placebo procedures has been shown to decrease subjective fatigue and increase behavioral performance (Carlino, Guerra, & Piedimonti, 2016; de la Cruz, Hui, Parsons, & Bruera, 2010; Piedimonte, Benedetti, & Carlino, 2015; Pollo, Carlino, & Benedetti, 2008). Carlino et al. even showed that a classical conditioning placebo procedure used to reduce pain can induce a reduction in fatigue on a motor task. This suggests that placebo effects can generalize to different stimuli and across sensory modalities.

In treatment, the expectancy of fatigue can be modified in different ways. First, creating positive expectancies about symptom development could become a more prominent element of psycho-education in different conditions. Whereas this may be at odds with the tempering role health professionals often (need to) assume when treating individuals with chronic illness, a positively framed prognosis of fatigue symptomatology may help alleviate fatigue in the long run. Second, our learning model implies that behavior such as conditioned fatigue and fear of fatigue can also be extinguished (Graham & Milad, 2011). Extinction procedures consist of repeated confrontations, in the absence of the US, with stimuli that provoke conditioned responses. In cognitive-behavior therapy, exposure is the clinical proxy of extinction (Craske, Treanor, Conway, Zbozinek, & Vervliet, 2014). For instance, in individuals who received cancer treatment, repeated exposure to the hospital environment alone is predicted to decrease anticipatory fatigue (Bovbjerg et al., 2005). In that respect, extinction may also represent one of the active ingredients of already validated cognitive-behavioral treatment protocols for chronic fatigue, such as graded activity training (combined with cognitive interventions; Zedlitz, Rietveld, Geurts, & Fasotti, 2012). Repeated exposure to physical exercise may not only alleviate fatigue complaints, but may also decrease fear of fatigue and avoidance if individuals learn that exercise is not necessarily followed by its feared expected outcomes (e.g., increase in symptoms). Indeed, the violation of existing expectancies about aversive outcomes (US) is one of the proposed mechanisms underlying exposure treatment. Exposure to interoceptive (e.g., bodily warning signs of fatigue) and exteroceptive (e.g., work environment) stimuli associated with fatigue represents a novel tool that could be combined with existing treatment options such as graded activity training. To our knowledge, there has been no research on the extinction of conditioned fatigue or fear of fatigue, in strong contrast to the rich literature on this topic in pain and anxiety research (Craske et al., 2014; den Hollander et al., 2010).

Further, interventions aimed at reducing associative learning opportunities and generalization are predicted to limit the impact of fatigue and fatigue-related behavior on daily life. Attentional control training (e.g., mindfulness) may correct perceptual-cognitive biases and may lead to a decrease in internal focusing on the warning signs of fatigue (Hou et al., 2014). This may reduce opportunities for interoceptive conditioning and subsequent generalization to take place. Interestingly, in a randomized control trial on the effects of cognitive-behavior therapy in chronic fatigue syndrome, treatment gains were mediated by a decrease in focusing on fatigue (Wiborg, Knoop, Prins, & Bleijenberg, 2011). Another randomized control trial on graded exercise training in chronic fatigue syndrome also showed that treatment gains were mediated by a decrease in focusing on symptoms rather than by an increase in physical fitness (Moss-Morris, Sharon, Tobin, & Baldi, 2005). Mindfulness training has also proven to alleviate fatigue in different clinical populations (Carlson & Garland, 2005; Grossman

et al., 2010).

Finally, associative learning principles may partly explain why fatigue complaints can be so robust to change in treatment. First, avoidance behavior – once acquired – can be extremely persistent, and usually maintains fear (Nijs et al., 2011; Volders, Boddez, De Peuter, Meulders, & Vlaeyen, 2015). The non-occurrence of an expected negative outcome may provide relief and may reinforce avoidance behavior, thus maintaining it. Additionally, avoidance behavior can function as a source of information about the threat-value of a certain situation, for example: 'I am avoiding, therefore there must be danger.' (Gangemi, Mancini, & van den Hout, 2012). As depicted in our model, avoidance may thus strengthen negative fatigue representations and fear of fatigue that triggered avoidance in the first place. This type of cognitions is not standardly assessed in treatment, but may be associated with avoidance behavior that restricts treatment gains. Second, although extinction is a promising tool to treat conditioned fatigue and fear of fatigue, it is known to be a fragile and context-dependent learning phenomenon. For instance, exposure to exercise in individuals suffering from chronic illness may successfully challenge the expectancy that fatigue results in further physical deterioration or disease progression, thereby reducing fear of fatigue (Smith et al., 2009). This does not mean, however, that the association between fatigue and physical deterioration has been unlearned. Rather, during extinction, a new inhibitory association is learned (i.c., fatigue → no deterioration) that competes with the original association (i.c., fatigue → deterioration). These inhibitory associations are known to be highly context-specific. Individuals may ascribe positive effects of exposure treatment to the relative safety of the treatment setting for instance, and may still entertain maladaptive beliefs and fear of fatigue in other contexts. Therefore, attention should be given to maximizing the probability of transfer of extinction to daily life (Craske et al., 2014).

More generally, our model is based on evidence that several factors contributing to chronic fatigue may also interact and reinforce each other. Interventions may not have desirable effects when presented in isolation. Chronic patterns of fatigue and avoidance call for an integrated approach where cognitive-behavioral interventions are used simultaneously, based on a personalized analysis of the factors maintaining fatigue symptoms, maladaptive behavioral patterns, and functional disability. In order to mitigate potential patient concerns when introducing this (mainly psychological) learning explanation for chronic fatigue, introductory psycho-education about the biopsychosocial approach to somatic symptoms may be appropriate. It may be helpful to have a dialogue about the role of cognitive and behavioral variables in the maintenance of fatigue symptoms despite potentially more somatic triggering conditions (e.g., acute illness). This dialogue may be stimulated by using a graphical presentation of the associative learning model and by gauging for each individual separately which aspects of the model could be implicated in chronic fatigue symptomatology; followed by discussing the potential role of behavioral and cognitive interventions in the attainment of personal treatment goals.

6. Future research

Throughout our discussion of the model, we have made several suggestions for future research on areas where current evidence is still inadequate. Additionally, more experimental research in healthy and clinical populations on (interoceptive) conditioning of fatigue and fatigue-related behavior is needed. Especially the notion that mild fatigue can act as conditioned stimulus that predicts and that may even trigger more intense fatigue should be investigated experimentally. Further, research on the relation between perceptual-cognitive biases and fatigue in other chronic illnesses besides chronic fatigue syndrome is warranted. The influence of generalization in the development of maladaptive fear in anxiety disorders and chronic pain is well-established, but remains to be investigated more thoroughly in relation to chronic fatigue. More generally, perceptual-cognitive biases, catastrophizing, sensitization, and generalization and their status of vulnerability factors needs to further tested. Up to date, it remains largely unclear whether they precede the onset of chronic fatigue and contribute to its development, or merely develop as a consequence of chronic fatigue (possibly contributing to its maintenance) or aversive fatigue-related learning experiences. Another interesting observation is that longitudinal studies in chronic illness often if not always assess fatigue as an outcome and not as a predictor of disease progression. With respect to catastrophizing thoughts about fatigue (e.g., that fatigue signals physical deterioration), it would nonetheless be important to know to what extent current fatigue symptoms may indeed prospectively predict disease progression. Proposed procedures to alleviate fatigue and decrease fear-avoidance behavior based on our model (e.g., extinction) also need further empirical support.

The crucial test would be to investigate the validity of this model and its components in several conditions characterized by chronic fatigue, as the ALT + F model predicts that the same learning processes may play a *trans*-diagnostic role, irrespective of the initial fatigue-triggering conditions. Related to this is that associative learning processes may also help explain comorbidity. For instance, there is a much higher prevalence rate of panic disorder and other anxiety disorders in chronic fatigue syndrome (Afari & Buchwald, 2003) than in the general population, as well as among people in the general population who report fatigue complaints relative to those who do not (Walker, Katon, & Jemelka, 1993). Associative learning could be a common mechanism underlying the development and maintenance of anxiety and chronic fatigue symptoms, and perhaps also other symptoms such as chronic pain. Future research is warranted to assess this *trans*-diagnostic role of associative learning.

It is noteworthy that several biological processes implicated in chronic fatigue have also been shown to be susceptible to classical conditioning. For instance, Stockhorst et al. (2000) found evidence for anticipatory immune system modulation in individuals following cancer treatment, consistent with the development of a conditioned response. Evidence from animal studies also shows that hypothalamic-pituitary-adrenal axis responding can be classically conditioned (Amario et al., 2012). Advancing our understanding of how associative learning processes may modulate biological pathways to chronic fatigue will allow incorporating these variables in our currently predominantly cognitive-behavioral model.

7. General conclusion

Point of departure of this review was our still largely inadequate understanding of the etiology of chronic fatigue in illness and health. There is little evidence for a relation between chronic fatigue symptoms and the pathophysiology of chronic disease, and the presence and severity of chronic fatigue differ greatly between individuals suffering from the same conditions. We presented an associative learning account that can explain the development of chronic fatigue and avoidance behavior. More precisely, learning about fatigue as an aversive, undesirable experience, and about the precursors of fatigue may shape a negative and threatening mental representation of fatigue that can give rise to anticipatory fear of fatigue and avoidance behavior. Moreover, stimuli that become associated with fatigue may acquire the capacity to evoke fatigue by themselves. 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. Future research, especially experimental studies in both clinical and non-clinical populations, is warranted to further our understanding of learning trajectories toward chronic fatigue, and to assess the effectiveness of associative learning procedures in the treatment of chronic fatigue.

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