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Perceived Fatigue and Energy are Independent Unipolar States: Supporting Evidence

Bryan D. Loy[1], **Michelle H. Cameron**[1,2], and **Patrick J. O'Connor**[3]

[1]Department of Neurology, Oregon Health & Science University, Portland, OR

[2]Multiple Sclerosis Center of Excellence-West, VA Portland Health Care System, Portland, OR

[3]Department of Kinesiology, University of Georgia, Athens, GA

Abstract

Persistent fatigue is a common problem (~20-45% of U.S. population), with higher prevalence and severity in people with medical conditions such as cancer, depression, fibromyalgia, heart failure, sleep apnea and multiple sclerosis. There are few FDA-approved treatments for fatigue and great disagreement on how to measure fatigue, with over 250 instruments used in research. Many instruments define fatigue as "a lack of energy", thus viewing energy and fatigue states as opposites on a single bipolar continuum. In this paper, we hypothesize that energy and fatigue are distinct perceptual states, should be measured using separate unipolar scales, have different mechanisms, and deficits should be treated using tailored therapies. Energy and fatigue independence has been found in both exploratory and confirmatory factor analysis studies. Experiments in various fields, including behavioral pharmacology and exercise science, often find changes in energy and not fatigue, or vice versa. If the hypothesis that energy and fatigue are independent is correct, there are likely different mechanisms that drive energy and fatigue changes. Energy could be increased by elevated dopamine and norepinephrine transmission and binding. Fatigue could be increased by elevated brain serotonin and inflammatory cytokines and reduced histamine binding. The hypothesis could be tested by an experiment that attempts to produce simultaneously high ratings of energy and fatigue (such as with two drugs using a randomized, double-blind, placebo-controlled design), which would offer strong evidence against the common viewpoint of a bipolar continuum. If the hypothesis is correct, prior literature using bipolar instruments will be limited, and research on the prevalence, mechanisms, and treatment of low energy and elevated fatigue as separate conditions will be needed. In the immediate future, measuring both energy and fatigue using unipolar measurement tools may improve our understanding of these states and improve therapeutic outcomes.

Corresponding Author: Bryan D. Loy, Ph.D. Department of Neurology, Oregon Health & Science University, 3181 SW Sam Jackson Park Road, Portland, OR, 97239, (503) 494-8332, loy@ohsu.edu.

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Introduction

Elevated and persistent fatigue[1] is a common, costly, and poorly understood problem. Up to 45% of the United States population experiences fatigue that is persistent (1-3). Fatigue is linked to many diseases and disorders (2), but is often underreported in medical care (4). Estimates suggest fatigue costs employers over $136 billion per year in lost productivity (5), with additional costs related to driving and other accidents (6, 7), poor medical performance (8), and school absence (9). Despite the high incidence and impact of fatigue, there is no consensus on how to measure fatigue, with over 250 different instruments used (10). There are also no FDA-approved therapies to treat fatigue in most medical conditions associated with fatigue.

Sometimes fatigue is defined as “a lack of energy”, which we will argue is problematic. MedlinePlus, the National Institutes of Health web site maintained by the National Library of Medicine, defines fatigue as “a feeling of weariness, tiredness, or lack of energy” (11). Similarly, the National Cancer Institute describes fatigue as “lack of energy” (12). The terms “lack of energy” and “fatigue” are also used interchangeably within the International Statistical Classification of Diseases and Related Health Problems, version 10 (ICD-10) in the United States. For example, Code R53.83 (Other Fatigue) can refer to “fatigue” or “lack of energy” (13). The Internet site WebMD also defines fatigue as “an inability to perform everyday tasks with your usual amount of energy” (14). But, conceptualizing fatigue as the opposite of having energy is potentially problematic, and there is an ongoing debate on this issue (15). A range of evidence suggests that energy and fatigue are independent states with different underlying neurobiology. If it is true that energy and fatigue are independent, continuing to treat them as opposite rather than distinct states is likely to limit our understanding of these states and limit clinical progress.

Feelings of energy and fatigue have been conceptualized here as distinct, biologically-based constructs that probably evolved for different purposes. Feelings of energy likely evolved as part of a system that expedited approach-oriented adaptive behaviors of all kinds, from hunting and gathering to finding a sexual partner. Feelings of fatigue presumably served different, yet equally important, avoidance-oriented behavioral functions such as promoting rest and thereby enhancing recovery from injuries or illnesses. Feelings of energy and fatigue have been vital to the propagation, survival and successful adaptations of *Homo sapiens*, and these feelings continue to play an important role in most human endeavors (16).

Hypothesis

We propose that energy and fatigue are two individual and separate but related psychological states, rather than opposites on a single bipolar continuum. As distinct states, energy and fatigue are hypothesized to have unique biological mechanisms, each of which contributes to human health and performance.

[1]For the sake of parsimony, the words energy and fatigue are used throughout the paper to mean “perceived feelings of energy” and “perceived feelings of fatigue”.

Hypothesis Evaluation

Definitions

Here, energy is defined as “an individual's potential to perform mental and physical activity” (17) and synonyms include “vigor”, “vitality”, “lively”, and “full of pep” (18). Definitions for fatigue are more varied as they at times have been tied to specific diseases (19), but refer to subjective perceptions of reduced mental or physical capacity (20) or a “persistent sense of physical, emotional, and/or cognitive tiredness or exhaustion” that can interfere with function and be disproportionate with prior activity (21-23). Common fatigue descriptors include “exhausted”, “sluggish”, “weary”, “tired” or “feeling worn out” (18).

Measurement

There is reasonable consensus that, as symptoms, energy and fatigue should be measured using self-report questionnaires that have strong evidence for validity (10). A systematic review identified the seven most common fatigue questionnaires used in original disease-related fatigue research (10). Few of these questionnaires include both energy and fatigue as distinct subscales. The European Organization for Research and Treatment of Cancer-Quality of Life Questionnaire 30 (24) and the Fatigue Severity Scale (25) have no energy items. The Chalder Fatigue Scale (26), the Piper Fatigue Scale (27), and the Multidimensional Fatigue Inventory (28) do not have sufficient energy items for a subscale. Although the commonly used SF-36 vitality scale (29) includes both energy and fatigue items, the standard scoring assumes bipolarity.

Of the most common fatigue measures used in medical research (10), only the Profile of Mood States (POMS)(18), has a sufficient number of energy and fatigue indicators for factor analysis. The POMS includes 8 vigor (that is, energy) and 7 fatigue items in the 65-item original form and 5 vigor and 5 fatigue items in the 30-item short form. Both exploratory (18) and independent, confirmatory (30, 31) factor analyses have found independence of the POMS vigor and fatigue subscales. And, the fatigue subscale is more strongly correlated with the confusion subscale of the POMS than it is inversely correlated with the vigor subscale, further supporting that the vigor and fatigue subscales are independent and not opposite ends of a single continuum (18, 32).

Research fields outside of medicine have also developed instruments to measure energy and fatigue (33). The Activation-Deactivation Adjective Check List (AD ACL) (34) and the Exercise-induced Feeling Inventory (EFI) (35) have energy and fatigue subscales shown by factor analysis to be independent. Moreover, a confirmatory factor analysis of all items from 9 of the most common fatigue scales (which include some energy items), found that two separate factors accounted for 48% of the total variance: energy and fatigue (36). Since factor analysis studies support independent energy and fatigue factors, and because our hypothesis cannot be tested without unipolar measures of energy and fatigue with similar sensitivity to change, the remainder of the paper focuses on studies measuring energy and fatigue independently.

Differences Only in Energy

Some studies across various disciplines have measured energy and fatigue using separate unipolar scales and found differences in energy, but not fatigue. Sedentary behaviors (e.g., sitting at desks, watching television) have a stronger tendency to decrease energy than increase fatigue—for example, participation in sedentary comparison conditions (e.g., quiet sitting, reading) in exercise studies has been found to reduce energy but not change fatigue (37, 38). Similarly, completing computerized cognitive tasks while sedentary has a greater effect on reducing energy than on increasing fatigue (39). Office workers who increased sedentary time after removal of a standing workstation had decreased energy and no significant change in fatigue (40).

In addition, exercise has a larger effect on increasing energy than on reducing fatigue. People meeting U.S. government recommendations for physical activity report greater energy, independent of their sedentary time (41). A meta-analysis of 16 acute exercise studies found that vigorous intensity exercise increases energy but does not decrease fatigue (37). Another study found that moderate-intensity acute exercise increases energy, which was partially mediated by changes in brain posterior theta activity, but no effect was found on fatigue (42). A study of 226 twin pairs and 38 siblings also found that energy changes in response to moderate exercise were influenced by genetic factors, but fatigue changes were not (43). When regular exercisers reduce their level of physical activity, they also experience significantly decreased energy with no change in fatigue (44). In summary, moderate or vigorous intensity exercise appears to increase energy while having less impact on reducing fatigue, and these energy changes appear to be mediated by biological variables.

Energy also is more strongly impacted than fatigue in a number of medical conditions and diseases. Among people with human immunodeficiency virus (HIV), energy is more strongly related to functional status and quality of life than is fatigue (45). When mental and physical aspects of energy and fatigue were measured in individuals with Friedreich's ataxia, low physical energy was found while no differences were observed for mental energy or mental or physical fatigue (46). This type of information appears logical and is potentially useful because Friedreich's ataxia is a disease that targets pyramidal nerves, causing muscle incoordination and reduced physical activity that worsens over time yet largely preserves mental functioning (47). In women with breast cancer, prior to surgery, 50% reported clinically meaningful low energy, whereas only 32% reported elevated fatigue (48). In a separate study, 66 women with breast cancer reported reduced energy without clinically elevated fatigue, whereas a different 40 women had higher fatigue and no reduced energy (49). Different genetic polymorphisms have also been linked to the time of day that people with cancer experience reduced energy (50). Several single nucleotide polymorphisms, including SLC6A1 (encoding GABA transporters), SLC6A3 rs37022 (a dopamine transporter gene), and TAC1 rs2072100 (encoding substance P) were related only to changes in energy among women recovering from breast cancer surgery (21). Differences in findings between energy and fatigue in various medical conditions underscore a need to view energy and fatigue independently.

Differences Only in Fatigue

A separate body of research has found differences in fatigue, but not energy. This appears to be especially true in the cancer fatigue literature. A meta-analysis of studies in cancer-related fatigue found that psychological interventions significantly reduced fatigue but did not increase energy (51). In people with breast cancer, differences in gene expression are related to the circadian variation of fatigue (52). Cancer-related pain is also correlated with fatigue, but there is no relationship with energy (53).

Fatigue is also affected by environmental changes independently of energy. In an analysis of microblogs (i.e., tweets) from August 1 – December 20, 2008 in the United States, fatigue increased during the stock market crash on September 29th, but markedly decreased two days before the November 4th presidential election in the absence of reciprocal changes in energy (54). In another study of 250 Boston, Massachusetts residents, fatigue changed seasonally, peaking in late fall and decreasing in early spring, while energy did not change (55). Even altering the color of paper on which questionnaires were printed changed reporting of fatigue but had no effect on reporting of energy. Specifically, fatigue was reported highest on red paper and lowest on green, with little difference between yellow, blue and white (56).

There is also evidence that some types of alcohol and food (specifically carbohydrate) consumption more reliability alters fatigue than energy. In a study of almost 30,000 people in 21 different countries, red wine was found to be more fatiguing than white, with no difference in energy between wine types (57). When participants ate a complex carbohydrate (rye bread, cheese spread) or a simple carbohydrate breakfast (white bread, fruit-flavored sprinkles) equal in calories, fatigue was lower after the complex carbohydrate breakfast than the simple carbohydrate breakfast, but there was no difference in energy (58). In another study, when participants were fed either high-fat, low-carbohydrate or low-fat, high-carbohydrate meals, high-fat meals were associated with significantly greater fatigue three hours later, but energy was not affected by the type of meal (59). Similarly, when people are sleep-deprived, there is increased tendency to consume food high in carbohydrate (60). Total sleep deprivation, when compared to an 8-hour sleep condition, also results in increased fatigue with no change in energy (61). Another study that measured sleep hours, energy, and fatigue for an entire calendar year also found that sleep hours were related to fatigue, but not energy (55). Taken together, these studies suggest that fatigue is increased when carbohydrate consumption is low or during sleep deprivation, whereas perceived energy is less impacted.

Mechanisms

Evidence related to the biological mechanisms underlying energy and fatigue states lying along different continua are now discussed.

Dopamine—Evidence from psychopharmacology and genetics suggests altering brain dopamine does not change fatigue but can influence energy. D-amphetamine, which blocks dopamine reuptake, increases energy but does not change fatigue (62). Other dopaminergic drugs used clinically have not decreased fatigue in randomized controlled trials, further

suggesting that dopamine function may impact energy. When methylphenidate was evaluated as a treatment for cancer fatigue in trials, no significant differences were found using the Brief Fatigue Inventory, which has only fatigue items. On the other hand, methylphenidate was found to improve scores on the Functional Assessment of Cancer Therapy-Fatigue, a measure which includes several energy items (63). Methylphenidate has also been found to not reduce fatigue in people with multiple sclerosis (64), even though methylphenidate is frequently used off label for fatigue in multiple sclerosis (65). The dopamine precursor drug levodopa also does not improve fatigue in people with Parkinson's disease who are drug-naïve, although it is unclear if levodopa impacts energy (66). Caffeine, which is known to act by blocking adenosine receptors, also works in part by increasing dopamine transmission and D_2 receptor binding (67, 68). In a study of low caffeine consumers (< 400 mg/day), single doses of 64 and 128 mg of caffeine significantly increased energy but did not reduce fatigue (69). Others have similarly found that caffeine has a greater effect on energy than on fatigue (70, 71). Genetic polymorphisms in the dopamine DRD4 receptor gene are related to decreases in energy with mental work and not fatigue (72), and others have suggested additional dopamine genes underlie the effectiveness of dopaminergic drugs on increasing energy (62). Since dopamine is a precursor of the catecholamines norepinephrine and epinephrine (73), it is possible that all three influence energy. Catecholamine synthesis is elevated during stress, when high amounts of energy would contribute to survival, such as during the fight or flight response (74). Depletion of catecholamines via the drug alpha-methyl-p-tyrosine (AMPT) also results in a larger change in energy than fatigue (75).

Serotonin—Evidence also suggests that brain serotonin may be more strongly related to perceived fatigue than energy. Among females in the premenstrual phase, blood serotonin (which approximates brain serotonin (76)) was significantly correlated with fatigue but not energy (77). Serotonin also varies in accordance with season and is positively correlated with acute changes in sun luminosity (i.e., brightness) (78), and we mentioned previously that fatigue varies by season but energy does not (55). Variants in serotonin genes have also been linked to fatigue among those diagnosed with chronic fatigue syndrome (CFS) (79). One positron emission tomography study provided evidence of increased serotonergic activity in people with CFS (80). Fatigued patients with Parkinson's disease also have differences in serotonin transporter binding in caudate, putamen, striatum, and thalamus when compared to non-fatigued people with Parkinson's disease, with no difference in dopamine function (81). The data suggest that in Parkinson's disease, and in several other conditions and situations, fatigue may be more influenced by serotonin than by dopamine.

Histamine—The neurotransmitter histamine may also influence fatigue more than energy. Histamine has a known role in circadian rhythms and sleep (82). Drugs that block histamine receptors induce increases in self-reported sedation (83), and are sometimes used as sleep aids (84). In a double-blind, placebo-controlled study the histamine antagonist drug doxepin significantly increased fatigue, whereas placebo did not. Energy was affected similarly by both doxepin and placebo, suggesting histamine has a specific effect on fatigue and not energy (38). In another double-blind, placebo-controlled trial, participants given supplemental histidine, the amino acid precursor for histamine, for two weeks had reduced

fatigue and no change in energy (85). Although there is currently a small literature on histamine and energy and fatigue states, the studies reviewed here suggest that histamine has a stronger relationship with fatigue.

Proinflammatory Cytokines—Fatigue is also increased and energy is unchanged by proinflammatory cytokines. In one study where healthy participants received either the typhoid vaccination or placebo, the active vaccine doubled serum IL-6 levels and increased fatigue, but did not significantly alter energy. Further, fatigue in the active vaccine condition was significantly correlated with insula and anterior cingulate cortex activity (86), suggesting a specific link between inflammation and neural activity for fatigue that is independent of energy. Other cytokines, such as leptin, have been strongly associated with fatigue (87-89). A review article of studies where endotoxin/lipopolysaccharide was used to increase systemic inflammation also supports the conclusion that proinflammatory cytokines increase fatigue (90). In sum, evidence suggests that peripheral proinflammatory cytokines activating the brain, as occurs in sickness behavior, may be one of the mechanisms underlying fatigue in many disease states (91).

Implications

We present diverse evidence supporting that energy and fatigue are independent states. Our understanding of both energy and fatigue states will be enhanced if these constructs are measured using separate, unipolar scales. At present, fatigue is insufficiently assessed, inadequately treated, and consequently costly to society. Energy, while not entirely ignored, has been assessed less frequently than fatigue in medical studies. Researchers often have tacitly assumed that fatigue and energy are bipolar when the evidence supports that they are independent and this assumption could have a range of negative consequences. The estimated prevalence of fatigue in the United States population as a whole and in specific medical conditions could be inaccurate due to the use of bipolar instruments in studies. Perhaps, as a consequence of implicitly assuming that energy and fatigue are opposites, there appear to be no prevalence estimates of low energy in the United States, or in the peer-reviewed literature. Medical personnel may assess and treat only fatigue, although patients are really suffering from low energy. Patients may also want increases in energy to optimize health once fatigue is relieved. Treatments that appear clinically effective for patients (because they increase energy) could fail to produce improvement in randomized controlled trials when unipolar fatigue measurements are used and energy is not captured. Trials using bipolar fatigue outcome measures may incorrectly suggest that treatments reduced fatigue when they in fact they only increased energy without affecting fatigue. There may be disagreement between studies seeking to understand the biomarkers, correlates, and mechanisms of fatigue when unipolar and bipolar scales are used. In addition, if energy and fatigue are independent states best measured with unipolar measures, the use of bipolar instruments in fatigue research muddies the understanding of fatigue and potentially limits the recognition of low energy as a problem that could be better understood and treated.

Although we propose that energy and fatigue are independent states, we recognize that they are closely related. In some diseases and conditions, such as depression, both energy and fatigue could be improved by a singular treatment, which may continue to obscure the

possibility that energy and fatigue are independent. Some medications commonly used to treat depression (e.g., bupropion, sertraline) could also reduce fatigue and increase energy, perhaps due to multiple mechanisms of action (92, 93). Moderate intensity exercise can also increase energy, decrease fatigue, and reduce depressive symptoms (94). Exercise has numerous mechanisms of action in the central nervous system that could plausibly impact energy, fatigue, and depression (37, 95). It is not currently known how exercise induces each of these changes, and there may be multiple mechanism(s) underlying the effects on energy, fatigue, and depression.

Conclusion

If the hypothesis presented here is correct and low energy and fatigue are indeed distinct states, it follows that it could be possible to simultaneously experience high energy and fatigue. This appears to occur in the real world, such as when giving birth, finishing a marathon, or in extreme work environments (e.g., surgeons conducting emergency procedures after long shifts, soldiers responding to fighting during long periods on watch). Studies could be conducted that seek to produce states where people experience simultaneously high energy and high fatigue. To test this possibility, a randomized, double-blind study using unipolar energy and fatigue measures could evaluate the effects of administering a drug that increases dopamine, such as the dopamine transport blocker methylphenidate, which might increase energy, and an H_1 receptor antagonist such as doxepin that has been shown to increase fatigue (38, 96). Another possibility is that fatigue and energy directly interact, such that fatigue is a signal (that can either be adaptive or debilitating) to preserve resources when energy is low (97). Or, neurobiological mechanisms underlying energy and fatigue may function in a “flip-flop switch” manner, where increases in one state inhibit the other. Such a mechanism has been clearly identified to exist between sleep and wake states, with very limited transitional time between the opposing states (82). If either of these latter options were true, it does not necessarily follow that it must be possible to produce a state where both energy and fatigue are elevated to demonstrate a distinction. The possibility of energy and fatigue interactions could be tested using mediation analyses in large datasets where energy and fatigue are measured independently on unipolar scales with similar sensitivity to change.

In summary, we suggest that perceived energy and fatigue are separate states that should be measured independently with unipolar scales. Factor analyses have repeatedly identified energy and fatigue as separate factors. Experimental studies measuring energy and fatigue independently have often found changes in one, but not the other, and the findings are often consistent with specific behaviors. Finally, emerging evidence suggests that dopamine transmission is related to energy, whereas serotonin, histamine, and inflammatory cytokines are related to fatigue. Although it is still a hypothesis that energy and fatigue are distinct states, researchers should measure energy and fatigue using separate unipolar scales until these states are better understood. Ultimately, experimental studies are needed to examine whether the bipolar or unipolar models of energy and fatigue are correct. Until there is definitive evidence, questioning the assumption of energy and fatigue bipolarity may improve understanding of these states and improve treatment for people with chronic, problematic fatigue or low energy.

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