Am J of Geriatric Psychiatry 31:2 (2023) 152–161

Available online at www.sciencedirect.com

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journal homepage: www.ajgponline.org

Special Communication

A Multi-Dimensional Model of Fatigue in Old Age: Implications for Brain Aging

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ARTICLE INFO

Article history:
Received June, 15 2022
Revised October, 13 2022
Accepted October, 31 2022

Keywords:
Fatigue
brain circuit
dimensions of fatigue
brain aging

ABSTRACT

As the most reported symptom in old age, fatigue is understudied in terms of both mechanisms and measures. Population heterogeneity and methodological inconsistency makes understanding the relationship between fatigue and brain aging challenging. The present article comprehensively reviews existing conceptual and operational frameworks of fatigue, as well as mechanistic heterogeneities of fatigue that exist in the aging literature. Then, I propose a Multi-Dimensional Model of fatigue to provide theoretical cohesion to the study of fatigue in old age, along with a "fatigue circuit" addressing brain profiles across dimensions of fatigue. The potential relationships between fatigue dimensions, the fatigue circuit, and brain aging are discussed to inform the direction of future research. (Am J Geriatr Psychiatry 2023; 31:152–161)

AN OVERVIEW OF CLINICAL SIGNIFICANCE AND RESEARCH GAP OF FATIGUE IN OLD AGE

Fatigue, defined as "extreme and persistent mental and/or physical tiredness, weakness or exhaustion",[1] is one of the most reported symptoms in old age.[2] Fatigue appears to be an age-dependent phenomenon, with prevalence highest among those 90+ years old.[3] Although the incidence of fatigue can be attributed to specific conditions (e.g., chronic sleep disorder, major depression, neurological diseases, etc.), a large proportion of fatigue cases, or "idiopathic fatigue", that occur in old age cannot be explained by such secondary factors,[2,4]. Unlike chronic fatigue syndrome,[5] other psychosomatic symptoms (e.g., pain, insomnia, or depressive symptoms) or fatigue in neurologic disorders,[1,4,6] the measures and mechanisms of which are more recognized, fatigue in old age is understudied. Older adults with fatigue symptoms are often subject to deteriorating neurological, physiological, sensorimotor, cognitive, emotional, and/or physical processes (e.g., loneliness, hippocampal abnormalities, increased acute inflammation, peripheral homeostatic disruptions, reduced stress adaptation, increased

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https://doi.org/10.1016/j.jagp.2022.10.007

neuropsychiatric symptoms, and faster cognitive decline or more cognitive impairment).[7–9] Fatigue interferes with older adults' everyday activities and predicts physical vulnerability, falls, disability, and mortality.[10–13] Whether processes linked to fatigue are causes or consequences of fatigue or "byproducts" from a third factor that occur in parallel with fatigue, is also unclear.

Fatigue in old age may reflect a holistic outcome of brain aging that can provide insight into why some older adults are more vulnerable to select brain pathophysiology or neurodegeneration, while others remain resilient. One avenue of literature indicates that engagement in everyday activities becomes more effortful with increasing age or pathophysiology. Emerging studies suggest that older adults with mild cognitive impairment perceive more severe fatigue than healthy older adults, and this difference in perceived fatigue can be linked to higher brain energy expenditure when performing everyday activities.[14] Fatigue has also been linked to metabolic abnormalities in insula and posterior cingulate cortex in older adults with Parkinson's disease.[15] In the literature to date, there does not appear to be a simple relationship between degree of fatigue and level of beta-amyloid in older adults.[16] However, means for characterizing fatigue in these studies are inconsistent and narrow. To leverage fatigue as a framework for uncovering novel neural pathways involved in brain aging and its functional outcomes, we need to first better conceptualize and operationalize fatigue in the context of brain aging.

In the current paper, by referring to published review articles, I first briefly discuss existing theoretical, mechanistic, and symptomatic complexities of fatigue. I then propose a new, Multi-Dimensional Model of fatigue in old age, and conclude by suggesting ways emerging brain connectome approaches can inform our understanding of the role of fatigue in brain aging.

HISTORICAL CONCEPTUAL AND OPERATIONAL HETEROGENEITIES IN THE FATIGUE AND AGING LITERATURE

Fatigue in old age has conventionally been studied as a symptom or process via various neurobiological or psychosocial mechanisms across disciplines. Characterizing fatigue is therefore substantially influenced by these considerations.

Disease Versus Symptom Model-Oriented Fatigue Taxonomy

Historically, fatigue has been most studied in through the lens of specific diseases as "**fatigue due to secondary factors**", such as neurologic diseases (e.g., multiple sclerosis, Parkinson's disease, traumatic brain injury).The disease-oriented model of fatigue is motivated by the frequency with which disease-afflicted patients report fatigue symptoms compared to their unaffected counterparts.[4] However, it does not mean that these diseases cause fatigue. Instead, more severe neurophysiological changes associated with these diseases compared to the counterparts may explain the more frequent fatigue complaint in the patients. Compared to fatigue due to secondary factors, **idiopathic fatigue** refers to fatigue that is not dominated by a disease. Idiopathic fatigue is commonly seen in old age compared to other age groups since older age is often accompanied by comorbidities.[2] Notably, both idiopathic fatigue and fatigue due to secondary factors can be explained by commonly rooted, neurophysiological changes. For example, both with rigorous statistical corrections, our group and Kluger and colleagues reported fatigue-associated changes in the putamen in typical older adults and Parkinson's diseases, respectively.[17,18] In contrast, the symptom-driven model emphasizes the persistency and severity of selected symptoms related to fatigue, which resulted in the Institute of Medicine's recommendation on the diagnostic criteria of **Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome**[19] However, the symptoms of fatigue can stem from heterogeneous neurophysiological changes and/or additional pathophysiological changes indicative of other diseases (see the "Neurophysiological mechanism" section below), which may explain the inconsistent findings in a recent systematic review on brain changes associated with chronic fatigue syndrome.[20]

Theories

There are several conceptual or operational frameworks of fatigue relevant to understanding fatigue in old age. 1) **Energy expenditure theory:** Imbalanced energy availability and expenditure in the brain and

muscles for maintaining interoceptive regulation leads to increased likelihood of fatigue. Relevantly, low-grade inflammation influences the efficiency of cellular energy expenditure, and mitochondrial disorders affect cellular energy generation efficiency [21,22] 2) **Effortfulness, attention, or motivation theories:** Fatigue can manifest as the failure to initiate and/or to sustain voluntary effortfulness (e.g., attention, motor control) in mental and physical tasks. For example, the Attention Network Test, a model originally developed for understanding domains of attention (i.e., alerting, orienting, and executive control) has been used to understand the involvement of attention in fatigue [23] There is also research on sensation of force and motor control in relation to fatigue in physical tasks.[24] Interrelatedly, there has been an emphasis on the imbalance of effort and reward underpinning changes of motivation and the appearance of fatigue.[25] 3) **Central versus peripheral fatigue**: It has been suggested that pathological changes in selective cortical and subcortical brain regions (central), or peripheral nerve or lower motor function (peripheral) can accelerate the generation of fatigue.[26] These models have respectively given rise to a debate on whether fatigue is a holistic concept or whether it can be dissociated into physical and mental domains. 4) **Fatigue versus fatigability**: The differentiation between fatigue and fatigability mirrors discussions on the relationships between traits versus states. Fatigability refers to the process of becoming fatigued via different types of fatigue manipulation tasks. This theory suggests that fatigability, in a single instance or repeatedly, drives older adults to report fatigue and can serve as a mechanistic target for modifying fatigue.[27]

Neurophysiological Mechanisms

Mechanistic understanding of fatigue has focused on normal changes of molecular and cellular levels. For example, the role in mitochondrial dysfunction (related to the previously mentioned energy expenditure theory) in chronic fatigue has been well studied.[28] More recent work has divided its attention to diverse neurophysiological mechanisms associated with fatigue, which is briefly summarized here to highlight the heterogeneity of fatigue in old age: 1) **Sympathetic versus parasympathetic branch of the autonomic nervous system:** the importance of hypothalamic −pituitary−adrenal axis function. The constant "fight or flight" response (i.e., sympathetic hyperactivity) along with a lack of adaptative regulation (i.e., parasympathetic inactivity) may lead to chronic fatigue.[29] In our recent work, older adults who perceived different levels of fatigue in response to an acute mental fatigue manipulation task had different degrees of parasympathetic response.[30] 2) **Serotonin versus dopamine:** Dopamine and serotonin are neurotransmitters often studied in fatigue but under different manipulations or disease models. For example, serotonin has been associated with physical exercise-induced fatigue [31] or chronic fatigue syndrome without Parkinsonism,[32] while dopamine imbalance plays an essential role in explaining fatigue in multiple sclerosis.[33] Selected studies have also compared the two neurotransmitters' roles in fatigue. Through studying Parkinson's disease patients with versus without fatigue, reduced serotonergic function in the basal ganglia and limbic structure, in addition to reduced insular dopaminergic function, has been associated with fatigue.[34] The nigrostriatal dopaminergic and raphe nuclei serotonergic pathways both modulate, although potentially in opposite directions, the functional configuration and activity of selected brain networks (e.g., sensorimotor, default mode, salience networks) with circuits concerned in fatigue.[35] 3) **The central nervous system's regulation:** Literature is largely inconsistent in this area, especially concerning the heterogeneity across brain structure versus function.[20] However, some literature suggests that the basal ganglia acts as a "fatigue hub", by top-down monitoring whole-body internal state and governing effortful exertion, or by interacting with selected cortical regions (e.g., prefrontal cortex) to regulate fatigability.[36] Section 4 will further specify the relationships between the brain and fatigue. One emerging line of work has examined **the pathophysiological mechanisms commonly observed in fatigue in old age**; that is, abnormal changes in biological systems that potentially accompany diseases. For example, in cognitively typical older adults, higher Alzheimer's disease pathology (i.e., cerebrospinal fluid ptau/abeta biomarker or hippocampal abeta deposition) was related to higher fatigue symptoms.[16,37] Vascular pathologies, such as white matter hyperintensity, are also consistently related to fatigue.[38] However, existing work has yet to examine these pathophysiological mechanisms beyond correlational associations.

Comorbid Psychosomatic Symptoms

Several psychosomatic symptoms often co-occur, or they are confused with fatigue in aging populations: 1) **Insomnia or sleepiness:** in a recent structural MRI study of over 1,300 older adults, excessive daytime sleepiness was related to global and regional brain atrophy, whereas fatigue was related specifically to frontal and temporal structural changes.[39] 2) **Depression- and anxiety-related symptoms:** individuals with late-life depression have higher fatigability than controls.[40] 3) **Cognitive symptoms:** attention, speed of processing, and cognitive control are highly interrelated with fatigue or fatigability.[23] 4) **Sensorimotor symptoms:** the relationships between physical or perceived fatigue and sensorimotor symptoms are often highly correlated, but notably more prevalent in patients with Parkinson's disease.[41] Together, it is unclear whether it is important to differentiate fatigue from sensorimotor symptoms due to its unique contribution to brain aging, or whether it is more clinically meaningful to identify symptom clusters that reflect abnormalities of brain aging. There are individual differences in the extent to which older adults are affected by these symptoms or perceive/cope with them. Two important unanswered questions may help better clarify the role of fatigue in old age: 1) why do older adults attribute fatigue to other symptoms, or *vice versa*? 2) why are older adults more tolerant of fatigue than other symptoms? Better profiling fatigue in old age, as well as the specific versus shared neurophysiological mechanisms, may help address these questions.

A MULTI-DIMENSIONAL MODEL (FIG. 1A) FOR BUILDING AN INDIVIDUALIZED MODEL OF FATIGUE

Existing literature seems to focus on selected aspects (e.g., causes, organs, behaviors) of fatigue, overlooking the fact that aging-related fatigue − idiopathic or due to secondary factors − can be attributed to multiple causes and manifest as highly diverse forms under different scenarios within an individual, as well as within the same scenario between individuals. Considering these taxonomies, theories, mechanisms, and comparisons with comorbid psychosomatic symptoms in fatigue, I suggest four dimensions that, together, capture the context and content of fatigue. These dimensions, in turn, may clarify the long-standing complexities in the fatigue and aging literature.

Interoception Versus Exteroception

Interoception refers to the perception and regulation of internal function, while exteroception concerns reactivity to and recovery from various environmental stressors (e.g., heat or cold, stress, pain, traumatic or threatening events, social/interpersonal interactions, cognitively demanding tasks, physical tasks, etc.).[42] Diurnal (endogenous, 24 hours) and circadian (evoked/masked from activity/rest, wake/sleep, posture, eating/fasting, social interactions, light levels) regulations are essential for interoception and selective exteroceptive regulation. Changes in domains of interceptions (e.g., accuracy, sensitivity, awareness) can cause fatigue in old age.[43] Meanwhile, older adults who develop fatigue more easily over a task often have worse regulation of exteroceptive signals (e.g., disruptive inflammatory or autonomic reactivity in response to or recovery from tasks with sustained attentional demands).[30,44]

Perception Vesus Performance

Performance in fatigue refers to the reduction of voluntary activities, while perception in fatigue refers to the feeling of tiredness. Theoretically, the field suggests that perception top-down regulates performance. That is, it is not muscle or mental vitality itself but the perception that interferes with the process via a neural failure to demotivate or disrupt behaviors involved in the performance in a top-down manner. However, empirical data suggest a discrepancy, especially in older adults. There is a possible prediction error (e.g., driven by between-individual variability in interceptive sensitivity, affective status, or past experience) toward the expected versus experienced vitality. In other cases, some individuals may be willing to compromise or ignore their perception to tolerate the tasks. Both scenarios create a between-individual discrepancy between performance versus perception related to fatigue.[45]

Laboratory Versus Real-world Environment

Fatigue, under interoceptive or exteroceptive regulation, or evaluated from perception or performance,

can be influenced by an environment. We have validated various laboratory fatigue-manipulation task protocols among older adults, by fatiguing motor function (e.g., finger tapping task, walking task),[46] prolonging mental effort (e.g., dual n-back working memory task, sustained attention task, Color-Word Stroop inhibition task),[18,30,45,46] or manipulating motivation and reward (e.g., Iowa Gambling Task, Balloon Analogue Risk Task).[18] Separately, reports of tiredness or performance limits in daily activities in the real world or naturalistic environments among older adults are critical for predicting clinically meaningful outcomes.[12] However, recall of real-world experience can be biased in old age. Fatigue diaries or experience sampling-based data acquisition approaches have been applied to overcome this bias.[47] Relevant to interoception and exteroception, physiological signals of diurnal and circadian regulation can be recorded in a naturalistic environment to monitor fatigue without compromising recall reliability.

Chronicity Versus Cyclicity

Conventionally, fatigued experienced for less than 6 months is considered short-term, and for more than 6 months is considered chronic. The use of nonspecific durations of fatigue has dominated existing literature, despite the false dichotomy that it creates in the chronicity of fatigue. Cyclicity (i.e., the periodic repetition of symptoms) is another common term in the fatigue literature that cannot be captured simply by summarizing duration. Any type of fatigue (e.g., chronic fatigue syndrome, idiopathic fatigue) can come and go in cycles. Experience in a real-world environment seems particularly relevant to clarifying the duration and dynamics of fatigue. In addition to relying on reports of perception, capturing relevant physiological signals during circadian and diurnal regulation of interoception and exteroception can help understand the dynamics of fatigue.

The dimensions, together, construct the content and context of fatigue, defining the when, where, how, and frequency of a fatigue event. For instance, a series of 60-minute education lectures can be a fatiguing event that contains different dimensions (interoception, perception, real-world environment, and cyclicity) than a series of 30-minute, monitored aerobic exercise sessions (exteroception, performance, laboratory, chronicity). These dimensions likely encompass the mental and physical intrinsic capacity, personality, and socioeconomic status of older adults, which can help differentiate between-individual experiences across structured fatigue events. I also emphasize **three attributes** that measure the magnitude of a single fatigue event: **intensity** (i.e., the intensiveness of fatigue), **persistence** (i.e., the duration of fatigue), and **valence** (i.e., the extent to which fatigue induces negative emotion). The continuality in monitoring these attributes may help extend our understanding of fatigue beyond differentiating fatigue magnitude between individuals within a given fatigue event. This extension may take the form of understanding 1) within-individual stability or change (e.g., adaptive to maladaptive changes) in a given fatigue event, and/or 2) within-individual differences when experiencing different fatigue events. Fatigue experience is unique to the individuals and scenarios. Together, by detailing the dimensions and attributes, we can build individualized model of fatigue that help address the heterogeneities seen in fatigue in old age.

Operationalizing the Multi-Dimensional Model to Build an Individualized Model of Fatigue

To effectively operationalize the proposed model, tools for data acquisition and data analysis are needed. There are at least two types of data collection that may elicit information related to the four dimensions of fatigue. Method 1: multi-modality data collection, including 1) providing a single or a series of real-world or laboratory fatigue events; 2) collecting ambulatory electrocardiographic data continuously while probing interception/self- or body-related questions periodically; 3) record perceived fatigue (intensity, persistence, and valence) or performance in a fatigue event; and 4) analyzing the stability/change of data obtained in 2) and 3). Method 2: by applying what we learn from the semantics and aging literature,[48,49] I propose a semantic data acquisition method by combining unstructured text descriptions of personal experience of a fatigue event, along with structured probes of the attributes. Analytically, natural language processing, computer vision, along with supervised or unsupervised computational models can help extract and identify relevant features (e.g., words from the unstructured text description,[49] or physiologically meaningful

patterns of dry biomarkers [50]) for building an individualized model of fatigue.

APPLYING EMERGING BRAIN CONNECTOME APPROACHES TO UNDERSTAND RELATIONSHIPS BETWEEN THE MULTI-DIMENSIONAL MODEL OF FATIGUE AND BRAIN AGING

Existing Aging Literature on Brain Imaging and Fatigue

The literature has been broadly divided between two perspectives of fatigue and aging: localized nodes (brain region) or edges (connections between brain regions) versus large-scale brain networks. Our previous work across four mental effort-oriented fatigue manipulation tasks identified the insula and putamen as consistently related to fatigue during these tasks in typical older adults.[18] These findings are supported by evidence that highlights the insula as a region that regulates responses to salient events,[51] and the striatum in regulating motivation. Our group has also provided evidence that specific brain networks regulate different dimensions of fatigue.[52] We have found that decreased connections between the striatum, subregions of prefrontal cortex, anterior and posterior cingulate cortices are related to perception of fatigue in cognitively typical older adults[53] and those with mild cognitive impairment[30]; rostral and frontal-caudal middle frontal connections and rostral middle frontal-insula connections are shared across perception and performance-based fatigue in typical older adults.[46] More recently, using a graph theory approach, we found that fatigue is associated with a whole-brain topology property of decreased information processing efficiency.[14] Finally, the "posterior-to-anterior shift in aging" (PASA) phenomenon,[54] which is about neural compensation via frontal regions for supporting cognition in old age, only exists among older adults without fatigue.[53,55] Of note, the literature has been lacking a distinction between functional versus structural aspect of neural connections underlying fatigue. Both fatigue and Alzheimer's pathology affect the integrity of functional[56–59] and structural connectivity.[14,46,60–64]

A Fatigue Circuit: Brain Circuits Underpinning the Multi-Dimensional Model of Fatigue (Fig. 1B)

Synthesizing work on brain aging, fatigue, and brain connectome approaches, I propose that the insula, especially its role in the shift from posterior to anterior subregions, is critical for linking dimensions of fatigue. A brain circuit composed of posterior insula, ventral striatum, thalamus, and amygdala (see the **blue box**) plays a central role in interoception, which regulates the basis of fatigue; prolonged dysfunction of this circuit may result in the chronicity of fatigue. A second brain circuit consisting of posterior insula, temporal pole, and entorhinal and posterior cingulate cortices (see the **orange box**) regulates exteroceptive experience and helps integrate previous experience to evaluate the discrepancy between the expected versus actual experience during a task (including differentiating laboratory from real-world tasks), which reflects the correlation between perception and performance-based fatigue. Based on the feedback of posterior insula from these two brain circuits, anterior insula interacts with ventromedial prefrontal cortex (see the **green box**) to determine the perception of fatigue while interacting with dorsolateral prefrontal cortex and dorsal anterior cingulate cortex (see the **grey box**) to determine the performance of fatigue. The discrepancy between perception and performance across exteroceptive stimuli give rise to the cyclic experience of fatigue.

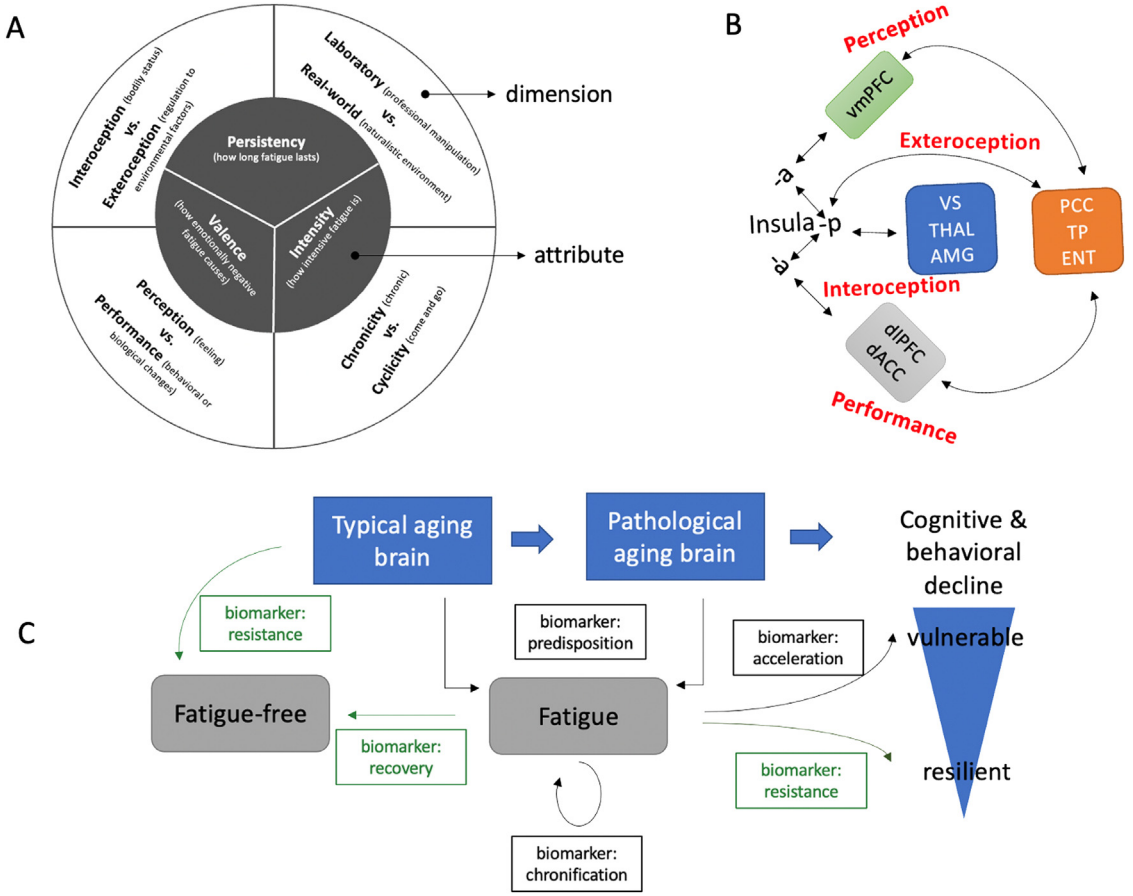
Aging-related sensitivity and vulnerability to fatigue may be explained partially by the aging-associated posterior-to-anterior shift in regulating behavior. The proposed brain circuits of fatigue that are primarily composed of anterior regions may become more involved in the regulation of day-to-day behavior. Also, older adults who have more difficulties associating their perception with performance during fatigue manipulation tasks may have worse underlying brain pathophysiology. That is, the function of the temporal lobe, entorhinal cortex, and posterior cingulate cortex (**orange box**) involved in establishing a reliable reference regarding the past may be impaired. Our group has shown that tautology can disrupt the white matter integrity between the temporal lobe, entorhinal cortex, and posterior cingulate cortex, as well as between ventromedial prefrontal cortex and these temporal regions,[65] as can amyloid deposition,[66] suggesting that abnormalities in this brain circuit's

function and structure can be exacerbated by pathological brain aging.

Remaining Research Questions for Fatigue and Brain Aging

Applying the Multi-Dimensional Model may help establish a fatigue profile reflecting selected traits or states specific for research questions in brain aging. Acknowledging this role of the model, several biological mechanisms or biomarkers should be further determined to disentangle the relationship between brain aging and fatigue (Fig. 1C). 1) biomarker of predisposition: selected biomarkers or mechanisms may help explain why some cognitively typical older adults or patients with brain pathophysiologies easily generate fatigue, and the difference between these mechanisms; 2) biomarker of acceleration: selected biomarkers or mechanisms may help explain why some older adults with fatigue exhibit cognitive decline or non-cognitive behavioral disturbance more apparently than others; 3) biomarker of chronification: selected biomarkers or mechanisms may explain the development of chronic or periodically repeated fatigue; 4) biomarkers for recovery or resistance: selected biomarkers or mechanisms may explain why some older adults with brain aging easily experience fatigue but others do not, how some older adults recover to a fatigue-free status, or why some older adults with fatigue do not have concurrent cognitive deficits or behavioral disturbances.

FIGURE 1. Multi-dimensional Model of Fatigue. (A) Dimensions and attributes of fatigue; (B) "Fatigue circuit" underpinning the dimensions of fatigue (Note: a=anterior; d = dorsal; p = posterior; AMG=amygdala; dACC=dorsal anterior cingulate cortex; dlPFC=dorsolateral prefrontal cortex; ENT=entorhinal cortex; PCC=posterior cingulate cortex; THAL=thalamus; TP=temporal pole; vmPFC=ventromedial prefrontal cortex; VS=ventral striatum); (C) Proposed relationships between fatigue, the Multi-Dimensional Model, and brain aging (NOTE: green lines: protective factors; black lines: risk factors).



Related to addressing these remaining questions, we need to pay particular attention to two methodological questions: 1) Chronological age versusbiological aging. That is, older adults, even in the context of "typical" older adults, there is a wide range of biological difference,[67] which explain individual difference in functional health. Acknowledging "aging" as a two-layer construct of chronological age and biological aging may help specify the biomarkers; 2) Relationships between systemic and central mechanisms of fatigue. In relation to the previously mentioned neurophysiological and pathophysiological mechanisms of fatigue, several systemic domains in relation to the proposed fatigue circuit cannot be overlooked. The most obvious one is the overlap between the immune-brain-communication pathway[52] and central autonomic network,[68] both of which signal feedback and/or feedforward within selected subcortical and cortical regions involved in the fatigue circuit, and attend the regulation of both perception versus performance and exteroception versus interoception underlying fatigue. However, the remaining question for future research mainly concerns the directionality between these central and systemic factors. While it is known that environmental or biological stressors can trigger peripheral and central responses, both types of responses manifest as fatigue. The directionality between these responses may vary between individuals (e.g., depending on the availability of overall brain resources or coping preference); 3) Directionality between fatigue and brain/cognitive aging: similar to the directionality problem encountered in the systemic versus central responses of fatigue, we need to specify the directionality between fatigue and brain/cognitive aging. It is very possible that under certain circumstances one or the other is the cause. Novel methods on causality, e.g., cross-species model, computational counterfactual generator, experimental manipulation, etc. can be useful tools. To confirm the relationship between the proposed brain circuits, systemic factors, and the Multi-Dimensional Model of fatigue, or differentiate fatigue from its confounding symptoms, selected neurotransmitter (e.g., serotonin versus dopamine) markers, multi-modality brain imaging sequences (e.g., PET, diffusion, and functional MRI), along with multivariate brain-behavioral analysis (e.g., canonical correlational analysis [69]) can be utilized.

CONCLUSION

I suggest the Multi-Dimensional Model will help older adults, family, and healthcare providers effectively decompose and profile fatigue when fatigue becomes a complaint that requires specific healthcare attention. There are various strategies to modify fatigue. However, the heterogeneity in the dimensions of fatigue have made its management difficult. To understand the precise mechanisms and effective treatment of fatigue in aging,[1] it will be beneficial to comprehensively describe dimensions to construct an individual model of fatigue without strong assumptions or intentions of differentiating taxonomies, central versus peripheral, mental versus physical, or trait versus state of fatigue.

DISCLOSURES

Feng V. Lin has no conflict of interest.

The author wishes to acknowledge the helpful comments from Mia Anthony and Adam Turnbull during the manuscript development and revision. The paper development was supported by NIH/NIA R21/R33 AG073356 and NIH/NIA U24 AG072701 to Feng V. Lin.

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