
Psychological Frailty in the Aging Patient

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Abstract

There is little written in the geriatric literature about the concept of psychological frailty which encompasses cognitive, mood, and motivational components. The concept is intended to consider brain changes that are beyond normal aging, but not necessarily inclusive of disease, that result in decreased cognitive or mood resilience in the presence of modest stressors, and may eventually lead to negative health outcomes in a manner parallel to physical frailty, an entity well known to clinicians. Most work exploring the interface between cognition, mood, and physical frailty has demonstrated a bidirectional association between the two domains. Psychological symptoms or deficits have been described as either worsening the degree of physical frailty, or physical frailty has been viewed as a risk to a worsening cognition or depression. However, psychological frailty, a consequence of age-altered brain function, has not been studied for itself. By what possible mechanism does the brain reveal its loss of resiliency under modest stress and how can this be visualized? Are there markers that predate a psychological decline that might permit a preventive intervention which could delay the appearance of negative health outcomes such as reduced functional capacity or increased dependency? The present review will explore these concepts and possibilities.

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Introduction

There is little reference in the medical literature to the term ‘psychological frailty’ in the context of aging adults. The term ‘psychological’ is taken to refer to particular products of brain function that result in conscious and unconscious

experiences and complex, usually directed behavior. There are, of course, other important aspects of brain activity which are critical to the individual but are not deemed to be psychological per se. These include multiple autonomic regulations of body functions needed to maintain homeostasis and activity. In the following discussion, we will consider the concept of frailty as it specifically pertains to three important psychological functions: cognition, mood, and motivation.

Frailty

The concept of frailty has been broadly characterized as a multisystem geriatric syndrome involving an increased vulnerability to stressors and loss of resilience in the face of internal or environmental challenges in different but interlinked physiological systems. This enhanced vulnerability to challenge, beyond that seen in usual aging, is believed to be linked to a higher risk for poor health outcomes such as falls, hospitalizations, institutionalization, and death. After more than 15 years of clinical research, no consensus operational definition has been reached nor have definitive assessment tools or biological markers been established. In landmark research, Fried et al. [1] developed the concept of a physical frailty phenotype, offering an operational definition of the condition based on an assumed state of negative energy balance, sarcopenia, diminished strength, and low tolerance for exertion. The phenotype originally consisted of five practically measurable clinical symptoms: exhaustion, weight loss, weak grip strength, and slow walking speed, three of which had to be present for the frail diagnosis. Cognition and mood were excluded. In subsequent studies, the phenotype was able to predict consistently various negative clinical outcomes such as falls, low mobility, hospitalization, and death in vulnerable populations [2]. Other groups using adapted phenotype criteria predicted similar outcomes. Recently, gait speed has become the most used marker of frailty among many clinicians due to its simplicity and predictive power [3, 4].

Other researchers have argued for a broader, more inclusive account of frailty which in addition to physical factors would include cognitive, emotional, motivational, and social characteristics given the multisystem nature of biological changes underpinning the frail condition [5]. These workers have emphasized a cumulative deficit approach which incorporates a large number of candidate factors ranging from disease states, symptoms, signs, to abnormal laboratory values. When combined and divided by the total number of deficits, these yield a frailty index. Although longer to administer, this approach offers some advantages over the frail phenotype method because it is more comprehensive and has the ability to produce a graded version of frailty rather than the bicategorical characterization of the

phenotypic model. Rockwood et al. [6] and others have produced a frailty index that has been highly predictive of the outcomes of death and institutionalization in identified frail subjects [7]. However, in spite of the considerable progress to date in the development of both the phenotypic and index models, the observational identification of frailty in the absence of the demonstrated pathophysiological mechanisms and biologic markers may occur too proximal to poor health outcomes to permit earlier, more effective interventions.

Psychological Frailty

Cognitive Frailty

The use of this construct is relatively new in the geriatric literature, having to date attracted little attention from clinicians and gerontologists. The term ‘cognitive frailty’ suggests a parallel to physical frailty, a loss of resilience and adaptability in the domain of brain function and implies a linkage to physical frailty. Numerous studies on expanded physical frailty have implicated cognition as a possible factor influencing health outcome [8, 9]. Furthermore, in many of these studies, frailty was explored as a manifestation of some class of cognitive impairment or, more frequently, frailty was viewed as a predictor of cognitive impairment. The concept of cognitive frailty is not examined in and of itself. What then is it and how can its presence be determined? In the recent literature, only Panza et al. [10] and Keleiditi et al. [11] have attempted to develop the construct, albeit in different clinical contexts. Most recently, Keleiditi et al. [11] made a direct attempt to open a dialogue about what cognitive frailty should comprise, of what should constitute a basic operational definition of the condition? They raised important considerations and suggested that cognitive frailty should be (1) linked to a reduction in cognitive ‘reserve’; (2) independent of specific brain diseases but at the same time coexist with the presence of physical frailty (in this concept, cognitive frailty is to be distinguished from the presence of cognitive impairment found in individuals without physical frailty), and (3) represented by a score of 0.5 on the well-established Clinical Dementia Rating (CDR) Scale, a score that is often associated with predementia, but not dementia conditions. These framing concepts deserve further consideration.

Cognitive Frailty as a Reduction in Cognitive Reserve. The link between the notion of cognitive reserve and the emergence of cognitive frailty would benefit from further development. As used by Keleiditi et al. [11], cognitive reserve implies a passive process similar to the concept of brain reserve capacity first proposed by Katzman [12] and Satz [13] where reserve is defined in terms of the amount of brain damage that can be sustained before reaching a threshold of

clinical expression. Analogously, per Keleiditi et al. [11], the appearance of cognitive frailty would be established with a CDR score of 0.5. In contrast, an active model of cognitive reserve would suggest that the brain actively attempts to manage brain damage or age-related changes by either using preexisting cognitive processing approaches or by using compensatory mechanisms [14, 15]. That is, an active model of cognitive reserve implies that underlying it are neural networks and neuronal connectivity that are more efficient, have a greater capacity, or are more flexible in individuals with greater reserve than those with less, thus high-reserve persons may be better capable of coping with challenges imposed by age-related brain changes or systemic or brain disease. Significant variability exists in cognitive reserve among individuals, and epidemiologic studies have suggested that good proxies for the amount of cognitive reserve include measures of economic attainment, level of education, IQ, and degree of literacy [16].

With the recent development of more sophisticated brain imaging techniques such as functional MRI, diffusion tensor imaging, and optical imaging, for example, and in combination with the application of new, highly sensitive cognitive tasks during imaging, there has been accelerating activity in the functional imaging of cognitive reserve and compensatory cognitive operations in healthy younger and older persons. Functional neuroimaging is providing many useful insights into the field of cognitive aging besides improving information on the localization of particular cognitive operations. It has furnished evidence in aging for increased recruitment of the prefrontal cortex in diverse cognitive tasks, probably the area with most plastic capacity in the brain [17]. It has also revealed that functional interactions between the prefrontal cortex and other brain regions, such as the mesial temporal lobe, which are important in encoding new information, are associated with better memory performance in older adults [18]. These changes are likely compensatory in nature. Reuter-Lorenz and Cappell [19] have shown evidence supporting the observation that older adults display regions of greater prefrontal activity than younger adults when task demands are low, suggesting that older adults recruit more neural circuits than younger adults at lower levels of task demand. As demand increases, younger adults also begin to engage additional circuitry, whereas older adults plateau and then begin to decline, probably because they are no longer able to engage task-related circuitry, that is, they can no longer compensate for the challenge of the added cognitive load.

One could possibly consider then, as a more biologically based marker of cognitive frailty, the inability to exhibit a minimal level of compensation for a cognitive task that had been previously established to produce a compensating response in most healthy older persons. From a more practical standpoint, an office proxy for the imaging evidence could be a successful completion of that image-linked task in a given amount of time. An approach of this type would

have improved validity over the more arbitrary selection of a particular CDR score as a cutoff point for cognitive frailty. Its prognostic value would need to be determined in subsequent longitudinal studies, but it could have the advantage of a longer lead time before negative health outcomes became imminent.

It can already be foreseen that through the future use of state-of-the-art cognitive testing and imaging techniques, improved understanding of the neural mediation of various aspects of cognitive reserve can be attained. The imaging approach to measuring cognitive reserve could be important for understanding an aged individual's true clinical status which would reflect a combination of underlying age-related brain changes and that individual's cognitive reserve in the context of those changes. Individuals with similar clinical appearances could differ substantially in their neural measures of reserve and this could have significant implications for a timely prognosis and treatment.

Can Cognitive Frailty Exist Independently of Brain Disease and Must It Co-Occur with Some Evidence of Physical Frailty? A major question in the study of brain aging is the boundary between age-related changes and disease. More recently, the questions of what distinguishes 'normal' aging from cognitive frailty and how is frailty different from disease have arisen. Our ability to answer these questions has improved recently as a consequence of better imaging techniques and cognitive characterization of patients, but certainly is not yet complete. Many now suggest that aging is not just the aggregation of disease, but that other time-related factors and subtle but pervasive accumulation of damage to homeostatic mechanisms can account for aging changes and that some brain structures are more vulnerable than others to this process. In making the distinction between age-related brain changes and age-related brain disease, Small et al. [20] have been able to demonstrate, using human and nonhuman primate species, that memory decline is different in aging than in Alzheimer's disease (AD), and is mediated by damage to different hippocampal structures in each condition, e.g. the entorhinal cortex in AD and the dentate gyrus in normal aging. Their work supports the proposition that aging per se and AD are distinct but possibly related processes since sporadic AD appears to be age dependent with the risk of it increasing exponentially after 65 until about 95 years of age, yet there are very old individuals who do not develop AD.

Where to situate cognitive frailty in relationship to normal or 'usual' aging cognition and disease is a more complicated issue and has been viewed differently by clinicians from different disciplines. Application of emerging imaging techniques and new cognitive testing approaches should help to bring clarity and evidence of more subtle brain dysfunctions into better view. If we assume that primary cognitive frailty can develop intrinsically in the brain, perhaps from a loss of protective factors still operative in normal aging, and as a result of non-

disease-specific, age-related physiological degradation of neural network communications evidenced by a reduction in cognitive reserve and an inadequate compensatory response to a challenge, we can affirm that in at least some cases cognitive frailty can be dissociated from identifiable disease processes such as, for example, predementia AD. As we become more able to image occult brain diseases (e.g. amyloid imaging in asymptomatic AD) and confirm the presence of preclinical disease with biomarkers (e.g. amyloid β 42 and phosphorylated tau), we will be able to separate those individuals who are developing intrinsic primary cognitive frailty, as evidenced by challenge test results, from those who harbor occult disease and may also underperform during a challenge paradigm. This would have important intervention implications as the absence of disease would permit the frail brain to respond much better to cognitive and behavioral stimulation of its inherent plasticity.

Primary cognitive frailty will be worsened by the presence of brain and systemic disease, preclinical or not, as cognitive reserve and compensatory mechanisms would be additionally challenged by disease-specific neurodegenerative or vascular processes with a predilection for particular brain circuitry and areas beyond what is likely to be affected in nondiseased aging. Examples of these are the early damage in AD to the entorhinal cortex and posterior cingulate, and in systemic hypertension by the deep white and deep grey matter lesions due to damage of the thin, deep, penetrating arteries of the posterior and anterior circulation. Consequently, disease-specific damage would be additive to the physiological degradation of age-vulnerable areas such as the prefrontal cortex, a structure likely to be involved in reduced reserve and compensatory capacity in primary cognitive frailty.

Lastly, the relationship between the state of intrinsic primary cognitive frailty and disease needs to be considered. As with much of the preceding discussion, little is factually known currently and many of the ensuing comments will necessarily be conjectural, yet eventually testable. It is appealing to hypothesize that primary cognitive frailty is an intermediary between 'normal aging' and brain disease. For example, the molecular changes in neurons and glial cells that characterize the subtle loss of functionality from 'normal' aging to primary cognitive frailty are but part of a continuum of changes that as further degradation takes place permit the pathogenic mechanisms of a particular disease to become more fully activated and expressed. The additional burden of systemic disease and physical frailty may actually hasten the process. This could at least partially explain why the emergence of sporadic, late-onset AD seems to accelerate exponentially with age as individuals become more frail and ill. If this were the case, then it would be important to identify primary cognitive frailty and develop interventions to reduce it to delay the risk of acquiring age-related diseases.

Cognitive Frailty May Indicate a Higher Risk for Adverse Long-Term Health Outcomes. Based on the assumption that frailty is driven by the same basic age-related processes in all organs and systems in the body, its presence in the brain is bound to have functional consequences as it develops and these will likely lead to undesirable health outcomes. However, it is important to note that all organs or systems in the body will not have developed the same degree of frailty at the same point in the individual's history. A number of recent studies have shown links between cognitive deficits and physical frailty [9]. The pattern emerging from these studies suggests that gait speed or grip strength are the components of frailty most strongly associated with cognitive function. Executive dysfunction and impaired attention are the cognitive domains most consistently linked to frailty. This may be best understood by the strong relationship of gait to the functioning of prefrontal executive and motor circuits. More subtle brain dysfunction such as a reduction in cognitive compensation mechanisms under challenge has not been examined as a predictor of gait speed or strength or longitudinally as a possible indicator of future negative health outcomes.

Mood and Motivational Frailty

As with the term cognitive frailty, the concept of 'mood or motivational frailty' in aging also suggests a parallel to physical frailty in the domain of brain function and implies a linkage between the two. The term mood describes a relatively persistent state of emotion such as depression, fear, anxiety, or anger. Motivation, the drive toward a goal, or lack thereof (apathy), is linked to mood but can be largely independent of it as is noted, for example, in nondepressed individuals with dementia. This is probably the case because reward and motivation are subserved by different but overlapping neural networks and circuits. Generally, the elaboration of emotion and mood is dependent on particular brain circuitry involving limbic and neocortical structures such as the amygdala, hippocampus, hypothalamus, anterior cingulate, ventral striatum, and orbital and medial prefrontal cortices, possibly explaining why thoughts are so colored by mood and moods influenced by thought. Single-source divergent networks primarily originating in the locus ceruleus, raphe' nuclei, and ventral tegmentum of the brain stem innervate and modulate the above networks via noradrenergic, serotonergic, and dopaminergic input. The experience of particular emotions appears dependent on the activation/suppression and modulation of key structures in a circuit. There is usually circuit overlap between emotions, but there are also differences. This may explain why in the presence of a disorder such as depression, other emotions such as anxiety and irritability can also be present. The development of mood disorders appears dependent on the interaction of genetic circuitry predispositions and a variety of stressors.

Much of the work examining the relationship of physical frailty to mood has focused on depressive symptoms. Depression and physical frailty share several clinical characteristics such as loss of energy, fatigability, poor sleep, and reduced interest. A number of clinical studies have strongly suggested a bidirectional association between depression in later life and physical frailty [21], but have not explored the possibility of the existence of a primary, intrinsic vulnerability to emotional stressors with age that might signal mood frailty, a possible precursor to depression and its negative health outcomes. A state of mood frailty could possibly be demonstrated by monitoring a subject's response to an emotional challenge test such as visualizing or imagining a sad situation, then being able to quickly revert to positive thoughts. Failure to make a rapid switch could have the potential to invite an earlier preventive intervention. As is the case with cognitive frailty, stressors, either external or internal, such as the presence of disease, will likely augment mood frailty.

The frailty and depression studies noted above also have not been able to disentangle frailty and depression, i.e. whether they are separate etiological entities or are simply variants in the expression of the same underlying pathology. Recent basic work has demonstrated that the pathophysiology of psychological stress-induced illnesses such as depression is associated with atrophy of vulnerable neurons and decreased expression of neurotrophic factors such as brain-derived neurotrophic factor [22, 23]. It has also been shown that the NMDA receptor antagonist ketamine, which has been found to produce rapid antidepressant actions in treatment-resistant depressed patients, also rapidly increases synaptogenesis and reverses the atrophy caused by depression-induced chronic stress [24]. Further studies on the clinical applicability and safety of this agent in diverse populations are needed. However, future studies using new imaging techniques combined with ketamine-stimulated synaptogenesis and brain-derived neurotrophic factor production may show differences or similarities between low-energy, fatigued, but nondepressed or demented frail elders, and others who display similar symptoms but are found to be depressed. Thus future studies involving functional neuroimaging and biomarkers to the study of cognition, mood, and frailty will help us gain greater insight into the biological similarities and differences between physical frailty and brain-based cognitive, motivational and mood frailty.

Disclosure Statement

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