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Cognitive Frailty: Frontiers and Challenges

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An international consensus group comprised of investigators from the International Academy of Nutrition and Aging (IANA) and the International Association of Gerontology and Geriatrics (IAGG) recently convened in Toulouse, France to establish a definition for cognitive frailty in older adults. This effort was motivated by growing awareness that many people with physical frailty are also prone to cognitive problems. In "Cognitive Frailty: Rationale and Definition" [1], an initial working definition was developed, and a framework proposed for future studies of cognitive frailty.

This group should be commended for addressing the construct of cognitive frailty and an obvious gap in the clinical gerontology literature. Physical frailty is a widely recognized problem in the elderly. While age-associated cognitive dysfunction has been studied for many years, for the most part it was not conceptualized in a manner that is consistent with current definitions of physical frailty. In fact, cognition has typically not been conceptualized in this manner, and only recently has the term cognitive frailty been employed. Rockwood et al published one of the first studies to examine factors associated with frailty in the elderly [2]. Frailty was conceptualized as multidimensional construct with both physical and cognitive origins. Panza et al. used the term cognitive frailty in the title of their review of pre-dementia syndrome vascular risk factors [3]. In a subsequent paper, Panza et al, attempted to specify different models of frailty in pre-dementia and dementia syndrome [4]. The prognostic accuracy of frailty assessment inventories for mortality among hospitalized elderly people was examined subsequently, with results suggesting that both cognitive and physical factors were important in predicting outcome [5]. We reviewed 199 manuscripts cited in PubMed in which cognitive frailty was mentioned in either the title or as a keyword. In the vast majority of these manuscripts, frailty was examined as a manifestation of cognitive dysfunction. Only recently has cognitive frailty itself become the focus of inquiry.

The term cognitive frailty is attractive as it suggests a parallel with physical frailty. The concept of physical frailty is relatively well understood in the context of aging, and has been operationalized in studies conducted over the past two decades [6–8]. However, as Kelaiditi et al. point out, the operational definition of physical frailty remains unresolved [1]. The situation is even more problematic for cognitive frailty, as past investigators have focused on a variety of different phenomena. The term has often been used as a general descriptor

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for cognitive impairment occurring as people reach advanced age. Sometimes cognitive frailty refers to cognitive disturbances or pre-dementia occurring in association with other medical conditions [9]. However, Kelaiditi et al. state that cognitive frailty must be considered as being independent of dementia or pre-existing brain disorders [1]. Accordingly, there seems to be several different perspectives on the nature of cognitive frailty. The fact that the construct is ambiguous and lacking a precise operational definition clearly reinforces the author's effort to establish a common language for future studies of cognitive frailty.

An obvious question emerges. How is cognitive frailty different from cognitive reserve? Cognitive reserve refers to the capacity of a given individual to resist cognitive impairment or decline. Educational level and prior cognitive abilities have been shown to be important determinants of cognitive reserve [10–12]. Cognitive reserve has been linked with resilience of brain function and structure in the presence of disease, injury, or other factors that alter physiological functioning [13]. While cognitive and brain reserve undoubtedly have some common underpinnings, the relationship between these types of reserve is still not fully understood.

Kelaiditi et al maintain that "cognitive frailty is characterized by reduced cognitive reserve". Accordingly, cognitive frailty could be viewed as simply the inverse of cognitive reserve. The authors indicate that while cognitive reserve is an important element of cognitive frailty, it is also dependent on the existence of physical frailty; i.e., "the simultaneous presence of both physical frailty and cognitive impairment". They distinguish this category of older non-demented adults from cognitive impairment in the absence of physical frailty. The importance of this categorization is that it emphasizes an important and often under-recognized relationship between systemic physical illness, brain dysfunction, and cognitive impairment. It is now well established that cognitive disturbances occur secondary to various medical conditions, such as cardiovascular disease, diabetes and HIV [14–19].

The value of excluding brain disorders from cognitive frailty may be less well justified. By limiting cognitive frailty to people with physical frailty, Kelaiditi et al create four discrete categories of older non-demented adults, which may have some clinical value. However, with respect to the concept of cognitive frailty, there are many examples of people who are vulnerable to subsequent functional decline based on the existence of subtle cognitive and/or brain abnormalities below the threshold for clinical detection. In fact, a major thrust of current research on neurodegenerative disease focuses on the discovery of vulnerability and early markers of future functional decline. While physical disorders such as diabetes and cardiovascular risk factors contribute to this vulnerability, a variety of neurobiological and behavioral risk factors also exist that create functional vulnerability [20–22], and ultimately cognitive frailty. In fact, excluding people with brain disturbances from the definition of cognitive frailty fails to account for the fact that the effects of physical illnesses are exacerbated by the existence of a neural predisposition to cognitive decline or prior brain disturbances that reduce cognitive reserve. Furthermore, people with physical frailty who develop cognitive frailty presumably do so as their brain begins to develop neuropathological changes. Accordingly, there is value in dichotomizing cognitive frailty between people with or without pre-existing brain dysfunction, or alternatively treating brain vulnerability as a mediator of the effects of physical illness on cognitive frailty.

Defining cognitive frailty depends on determining its diagnostic criteria. Other than physical frailty, the primary criteria proposed by Kelaiditi et al. is the presence of mild cognitive impairment as defined by a clinical dementia rating (CDR) score of 0.5, without Alzheimer's disease or another progressive brain disturbance that would lead to dementia. Using these criteria, it is not clear whether people with cerebrovascular disturbances would meet these criteria or not. The authors make a point of also noting that "under different circumstances cognitive frailty may also represent a precursor of neurodegenerative processes". This is a critical point that reinforces the need to go beyond the definition of cognitive frailty as occurring in the absence of brain dysfunction. It is also likely that a CDR = 0.5 is too narrow to fully capture the heterogeneity of cognitive frailty. For example, people without cognitive impairment that rises to the level of a CDR= 0.5 may still be vulnerable to functional decline under certain conditions. This occurs commonly during hospitalization, in response to extreme stress, or to changes in the physical environment in the elderly.

In fact, it is the vulnerability to alternations in cognitive function under such conditions that may be the essential determinant of cognitive frailty. There are many people in society with cognitive limitations who would not be considered to be frail, unless they exhibit a tendency to functionally decompensate when their resources are challenged. The key to operationalizing cognitive frailty may ultimately depend of developing diagnostic challenges that would enable clinicians to determine this tendency. This will depend on determining which neurocognitive measures are most useful for detecting this vulnerability and for assessing the severity of cognitive frailty.

In sum "Cognitive Frailty: Rationale and Definition" [1] provides a valuable starting point for the development of a coherent operational definition and for future studies of cognitive frailty. While closely linked to cognitive reserve, the construct of cognitive frailty goes beyond cognitive reserve, particularly because of its association with physical frailty and the fact that it often becomes evident in the context of acute physical illness. There seems to be considerable value in distinguishing vulnerability of cognitive functional decline among people with or without physical frailty. Though there is evidence that both cognitive and physical frailty share several common pathophysiologic mechanisms and risk factors. Growing and consistent epidemiologic evidence shows that impaired physical performance, which is a component of physical frailty, measured with walking speed or the Short Physical Performance Battery (SPPB) [23], is independently associated with cognitive decline [24–36]. The SPPB tests, including walking, balance and chair stands, require the complex interplay of sensory, cognitive, and motor functions, and these systems may be altered early in the path to cognitive decline [36, 37], and possibly to cognitive frailty. Low walking speed and low SPPB score are also associated with elevated inflammatory cytokines and low Brain-Derived Natirurectic Factor (BDNF) [38–40], all of which are predictors of cognitive decline [41, 42].

Future research is needed to determine how phenotypic differences among people and the existence of a wide variety of preexisting manifestations of brain structure and function affect this vulnerability. Following the expert consensus, prospective studies will be needed to assess the reliability and predictive validity of the operational measure of cognitive frailty. We laud the efforts of the IANA/IAGG consensus group in laying the foundation for the emerging concept of cognitive frailty and strongly encourage future studies aimed at advancing this clinical domain.

References

1. Kelaiditi E, Cesari M, Canevelli M, van Kan GA, Ouset P, Gillette-Guyonnet S, Ritz P, Duveau F, Soto ME, Provencher V, Nourhashemi F, Salva A, Robert P, Andrieu S, Rolland Y, Touchon J, Fitten Vellas B. Cognitive Frailty: Rational and definition from an (I.A.N.A./I.A.G.G.) International Consensus Group. J Nutr Health Aging. 2013 in press.
2. Rockwood K, Stolee P, McDowell I. Factors associated with institutionalization of older people in Canada: testing a multifactorial definition of frailty. J Am Geriatr Soc. 1996; 44(5):578–582. [PubMed: 8617909]
3. Panza F, D'Introno A, Colacicco AM, et al. Cognitive frailty: Predementia syndrome and vascular risk factors. Neurobiol Aging. 2006; 27(7):933–940. [PubMed: 16023766]
4. Panza F, Solfrizzi V, Frisardi V, et al. Different models of frailty in predementia and dementia syndromes. J Nutr Health Aging. 2011; 15(8):711–719. [PubMed: 21968870]
5. Pilotto A, Rengo F, Marchionni N, et al. Comparing the prognostic accuracy for all-cause mortality of frailty instruments: a multicentre 1-year follow-up in hospitalized older patients. PLoS One. 2012; 7(1):e29090. [PubMed: 22247767]
6. Abellan van Kan G, Rolland Y, Houles M, Gillette-Guyonnet S, Soto M, Vellas B. The assessment of frailty in older adults. Clin Geriatr Med. 2010; 26(2):275–286. [PubMed: 20497846]
7. Abellan van Kan G, Rolland Y, Andrieu S, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging. 2009; 13(10):881–889. [PubMed: 19924348]
8. Abellan van Kan G, Rolland Y, Bergman H, Morley JE, Kritchevsky SB, Vellas B. The I.A.N.A Task Force on frailty assessment of older people in clinical practice. J Nutr Health Aging. 2008; 12(1):29–37. [PubMed: 18165842]
9. Chouliara Z, Kearney N, Stott D, Molassiotis A, Miller M. Perceptions of older people with cancer of information, decision making and treatment: a systematic review of selected literature. Ann Oncol. 2004; 15(11):1596–1602. [PubMed: 15520059]
10. Satz P, Morgenstern H, Miller EN, et al. Low education as a possible risk factor for cognitive abnormalities in HIV-1: findings from the multicenter AIDS Cohort Study (MACS). J Acquir Immune Defic Syndr. 1993; 6(5):503–511. [PubMed: 8483113]
11. Stern Y. What is cognitive reserve? Theory and research application of the reserve concept. J Int Neuropsychol Soc. 2002; 8(3):448–460. [PubMed: 11939702]
12. Stern Y, Albert S, Tang MX, Tsai WY. Rate of memory decline in AD is related to education and occupation: cognitive reserve? Neurology. 1999; 53(9):1942–1947. [PubMed: 10599762]
13. Satz P, Cole MA, Hardy DJ, Rassovsky Y. Brain and cognitive reserve: mediatoRs) and construct validity, a critique. J Clin Exp Neuropsychol. 2011; 33(1):121–130. [PubMed: 20680883]
14. Okonkwo OC, Cohen RA, Gunstad J, Tremont G, Alosco ML, Poppas A. Longitudinal trajectories of cognitive decline among older adults with cardiovascular disease. Cerebrovasc Dis. 2010; 30(4):362–373. [PubMed: 20693791]
15. Cohen RA, Poppas A, Forman DE, et al. Vascular and cognitive functions associated with cardiovascular disease in the elderly. J Clin Exp Neuropsychol. 2009; 31(1):96–110. [PubMed: 18608677]

16. Gunstad J, Cohen RA, Paul RH, Tate DF, Hoth KF, Poppas A. Understanding reported cognitive dysfunction in older adults with cardiovascular disease. Neuropsychiatr Dis Treat. 2006; 2(2):213–218. [PubMed: 19412466]
17. Devlin KN, Gongvatana A, Clark US, et al. Neurocognitive effects of HIV, hepatitis C, and substance use history. J Int Neuropsychol Soc. 2012; 18(1):68–78. [PubMed: 22132928]
18. Cohen RA, de la Monte S, Gongvatana A, et al. Plasma cytokine concentrations associated with HIV/hepatitis C coinfection are related to attention, executive and psychomotor functioning. J Neuroimmunol. 2011; 233(1–2):204–210. [PubMed: 21146232]
19. Cohen RA, Harezlak J, Schifitto G, et al. Effects of nadir CD4 count and duration of human immunodeficiency virus infection on brain volumes in the highly active antiretroviral therapy era. J Neurovirol. 2010; 16(1):25–32. [PubMed: 20113183]
20. Elie M, Cole MG, Primeau FJ, Bellavance F. Delirium risk factors in elderly hospitalized patients. J Gen Intern Med. 1998; 13(3):204–212. [PubMed: 9541379]
21. Robertsson B, Blennow K, Gottfries CG, Wallin A. Delirium in dementia. Int J Geriatr Psychiatry. 1998; 13(1):49–56. [PubMed: 9489581]
22. Woods AJ, Mark VW, Pitts AC, Mennemeier M. Pervasive cognitive impairment in acute rehabilitation inpatients without brain injury. PM R. 2011; 3(5):426–432. [PubMed: 21570030]
23. Guralnik JM, Ferrucci L, Simonsick EM, Salive ME, Wallace RB. Lower-extremity function in persons over the age of 70 years as a predictor of subsequent disability. N Engl J Med. 1995; 332(9):556–561. [PubMed: 7838189]
24. Camargo, EC.; Beiser, A.; Tan, ZS., et al. Walking Speed, Handgrip Strength and Risk of Dementia and Stroke: The Framingham Offspring Study. American Academy of Neurology; 64th Annual Meeting; April 21–28, 2012; New Orleans. 2012.
25. Dodge HH, Mattek NC, Austin D, Hayes TL, Kaye JA. In-home walking speeds and variability trajectories associated with mild cognitive impairment. Neurology. 2012; 78(24):1946–1952. [PubMed: 22689734]
26. McGough EL, Kelly VE, Logsdon RG, McCurry SM, Cochrane BB, Engel JM, Teri L. Associations between physical performance and executive function in older adults with mild cognitive impairment: gait speed and the timed "up & go" test. Phys Ther. 2011; 91(8):1198–1207. [PubMed: 21616934]
27. Fitzpatrick AL, Buchanan CK, Nahin RL, DeKosky ST, Atkinson HH, Carlson MC, Williamson JD. Associations of gait speed and other measures of physical function with cognition in a healthy cohort of elderly persons. J Gerontol A Biol Sci Med Sci. 2007; 62(11):1244–1251. [PubMed: 18000144]
28. Deshpande N, Metter EJ, Bandinelli S, Guralnik J, Ferrucci L. Gait speed under varied challenges and cognitive decline in older persons: a prospective study. Age Ageing. 2009; 38(5):509–514. [PubMed: 19549981]
29. Rosano C, Simonsick EM, Harris TB, Kritchevsky SB, Brach J, Visser M, Yaffe K, Newman AB. Association between physical and cognitive function in healthy elderly: the health, aging and body composition study. Neuroepidemiology. 2005; 24(1–2):8–14. [PubMed: 15459503]
30. Soumare A, Tavernier B, Alperovitch A, Tzourio C, Elbaz A. A cross-sectional and longitudinal study of the relationship between walking speed and cognitive function in community-dwelling elderly people. J Gerontol A Biol Sci Med Sci. 2009; 64(10):1058–1065. [PubMed: 19561146]
31. Abellan Van KG, Rolland Y, Andrieu S, Bauer J, Beauchet O, et al. Gait speed at usual pace as a predictor of adverse outcomes in community-dwelling older people an International Academy on Nutrition and Aging (IANA) Task Force. J Nutr Health Aging. 2009; 13(10):881–889. [PubMed: 19924348]
32. Wang L, Larson EB, Bowen JD, van BG. Performance-based physical function and future dementia in older people. Arch Intern Med. 2006; 166(10):1115–1120. [PubMed: 16717174]
33. Hajjar I, Yang F, Sorond F, Jones RN, Milberg W, Cupples LA, Lipsitz LA. A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: relationship to blood pressure and other cardiovascular risks. J Gerontol A Biol Sci Med Sci. 2009; 64(9):994–1001. [PubMed: 19535785]

34. Zimmermann LJ, Ferrucci L, Kiang L, Lu T, Guralnik JM, Criqui MH, Yihua L, McDermott MM. Poorer clock draw test scores are associated with greater functional impairment in peripheral artery disease: the Walking and Leg Circulation Study II. Vasc Med. 2011; 16(3):173–181. [PubMed: 21636676]

35. Verghese J, Robbins M, Holtzer R, Zimmerman M, Wang C, Xue X, Lipton RB. Gait dysfunction in mild cognitive impairment syndromes. J Am Geriatr Soc. 2008; 56(7):1244–1251. [PubMed: 18482293]

36. Verghese J, Wang C, Lipton RB, Holtzer R, Xue X. Quantitative gait dysfunction and risk of cognitive decline and dementia. J Neurol Neurosurg Psychiatry. 2007; 78(9):929–935. [PubMed: 17237140]

37. Buchman AS, Boyle PA, Wilson RS, Tang Y, Bennett DA. Frailty is associated with incident Alzheimer's disease and cognitive decline in the elderly. Psychosom Med. 2007; 69(5):483–489. [PubMed: 17556640]

38. Brinkley TE, Leng X, Miller ME, Kitzman DW, Pahor M, Berry MJ, Marsh AP, Kritchevsky SB, Nicklas BJ. Chronic inflammation is associated with low physical function in older adults across multiple comorbidities. J Gerontol A Biol Sci Med Sci. 2009; 64(4):455–461. [PubMed: 19196644]

39. Hsu FC, Kritchevsky SB, Liu Y, Kanaya A, Newman AB, Perry SE, Visser M, Pahor M, Harris TB, Nicklas BJ. Association Between Inflammatory Components and Physical Function in the Health, Aging, and Body Composition Study: A Principal Component Analysis Approach. J Gerontol A Biol Sci Med Sci. 2009; 64(5):581–589. [PubMed: 19228783]

40. Scalzo P, Kummer A, Bretas TL, Cardoso F, Teixeira AL. Serum levels of brain-derived neurotrophic factor correlate with motor impairment in Parkinson's disease. J Neurol. 2010; 257(4):540–545. [PubMed: 19847468]

41. Erickson KI, Prakash RS, Voss MW, Chaddock L, Heo S, McLaren M, Pence BD, Martin SA, Vieira VJ, Woods JA, McAuley E, Kramer AF. Brain-derived neurotrophic factor is associated with age-related decline in hippocampal volume. J Neurosci. 2010; 30(15):5368–5375. [PubMed: 20392958]

42. Yaffe K, Lindquist K, Penninx BW, Simonsick EM, Pahor M, Kritchevsky S, Launer L, Kuller L, Rubin S, Harris T. Inflammatory markers and cognition in well-functioning African-American and white elders. Neurology. 2003; 61(1):76–80. [PubMed: 12847160]