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Physiological and Self-Report Instruments to Measure Fatigue in Older Adults

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Fatigue is one of the most commonly reported clinical complaints in older adults and can severely affect the elderlies' mobility, quality of life and their ability to perform activities of everyday living (Vestergaard *et al.* 2009; Yu *et al.* 2010; Soyuer & Senol, 2011). For example, in a study of 754 nondisabled community-dwelling older adults ≥ 70 years of age (Gill *et al.* 2001), fatigue was reported as the most prevalent reason for restricted physical activity (~66% of participants). In fact, reports of fatigue in this study were nearly two-fold more prevalent than the second most frequently reported reason of 'pain or stiffness in joints' (~36%) and over four-fold more prevalent than reports of depression (~16%) or weakness of the extremities (~15%). Despite the widespread prevalence of fatigue in older adults, the etiologies of this phenomenon are unknown and treatments to help ameliorate its detrimental effects are lacking. Thus, studies aimed at elucidating the causes of fatigue in the elderly are imperative to inform therapeutic interventions to help restore or maintain physical function and autonomy in older adults ≥ 65 years of age, which is the fastest growing age demographic in the US (CDC, 2013).

The difficulty in identifying the causes of fatigue in the older adult population and our inability to effectively treat this condition are multifactorial. First, the term fatigue lacks a standard operational definition, and many investigators assume that the context of fatigue is known without providing an adequate definition. Second, as a direct consequence of the multiple definitions for fatigue, investigators have developed a wide array of both subjective and objective instruments to measure different aspects of this phenomenon (Dittner *et al.* 2004; Williams & Ratel, 2009). While the employment of multiple instruments has been useful to capture different features of fatigue, the lack of a common metric has made it inherently difficult to compare findings across studies. Third, biological aging—or senescence—is often accompanied by other diseases that have been documented to exacerbate fatigue. These diseases include but are not limited to cancer, neurological disorders such as multiple sclerosis, stroke or Parkinson disease, cardiovascular diseases, rheumatoid arthritis, osteoarthritis, respiratory dysfunction and psychiatric disorders such as depression, sleep disorders or chronic fatigue syndrome (NIA, 2007; Kluger *et al.* 2013). Given that the causes and manifestations of fatigue in these diseased states may fundamentally differ from the fatigue experienced as a result of the biological aging process per se, it is imperative that aging fatigue studies control for possible comorbidities. The multidimensionality of fatigue and the lack of a single definition in the clinical and research settings, therefore, requires the development of a conceptual framework with clearly operationalized concepts before specific instruments can be employed.

In this paper, the conceptual framework originally developed for studies of fatigue in neurological illnesses (Kluger *et al.* 2013) is adopted and simplified to systematically guide the selection of instruments to measure fatigue in older adults (Fig. 1). In this model, fatigue is treated as a construct with two operationalized concepts: *perception of fatigue* which refers to an individual's subjective sensations of fatigue, and *fatigability* which refers to the objective changes in mechanical performance that occur in response to prior activation of the neuromuscular system (Kluger *et al.* 2013). The fatigability concept is further divided into two sub concepts: *central fatigability* refers to the factors within the nervous system, and *peripheral fatigability* refers to the factors occurring within the skeletal muscle. The grey hatched double-sided arrow between perception of fatigue and fatigability indicates that the two concepts have the potential to influence each other but can also occur independently. A vast majority of studies on fatigue in older adults have focused on the age-related changes in one concept or the other.

However, to help develop a more thorough understanding of the causes of fatigue in the older adult population, future clinical research should test for associations between the two concepts rather than studying each in isolation.

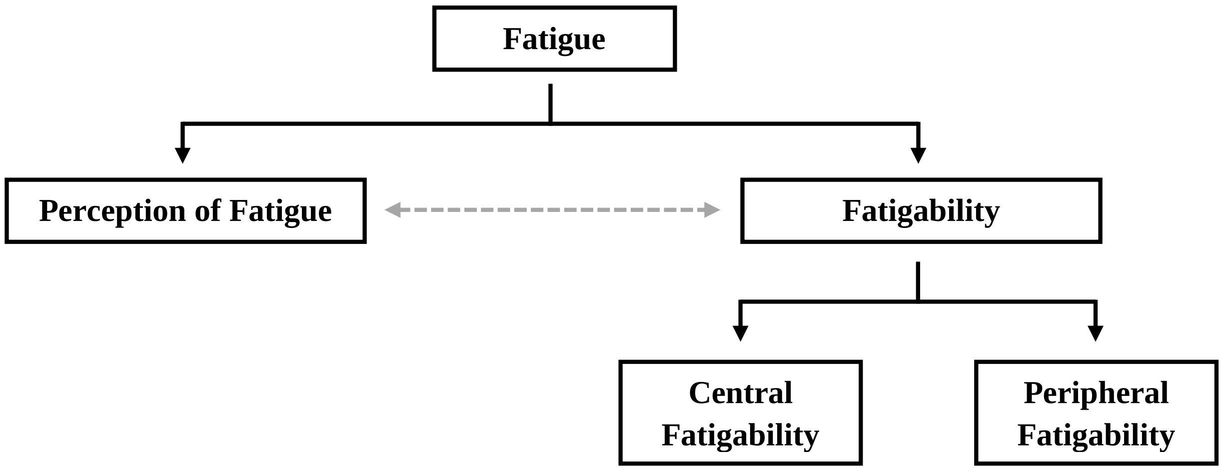

Fig. 1. Schematic diagram of the conceptual framework for fatigue in older adults. This figure was modified from Kluger *et al.* (2013).

Self-Report Instrument to Measure Perception of Fatigue in Older Adults

Perception of fatigue in this article is defined as the "subjective sensations of weariness, increasing sense of effort, mismatch between effort expended and actual performance, or exhaustion" (Kluger *et al.* 2013). This concept is measured exclusively by self-report instruments, typically through a series of written questions answered on either a Likert scale or visual analogue scale. Over 30 self-report instruments have been validated and used to assess an individual's perception of fatigue; however, most of these instruments were conceptualized for specific disease populations and few have been validated in the elderly population (Tralongo *et al.* 2003; Dittner *et al.* 2004). The consequence of the wide array of instruments designed for distinct disease populations has been an inability to use these instruments in other patient populations and difficulty in comparing findings across studies. Although no 'gold standard' currently exists to measure perception of fatigue generally, or in the elderly population specifically, the National Institutes of Health launched the Patient-Reported Outcomes Measurement Information System (PROMIS) initiative in 2004 to help remedy these issues in a variety of self-report outcome measurements including perception of fatigue (Cella *et al.* 2010; Riley *et al.* 2010).

The PROMIS instrument to measure perception of fatigue consists of a bank of 95 items selected and calibrated based on multiple advanced psychometric testing procedures including, identification of extant items in the literature, expert panel reviews, focus groups, item piloting, item response theory modelling, among others (DeWalt *et al.* 2007; Cella *et al.* 2010; Lai *et al.* 2011). In addition to the rigorous psychometric testing, a primary advantage of using the PROMIS instrument in the elderly population is the items were specifically designed to provide a valid and reliable measure of the perception of fatigue in a wide range of populations irrespective of the age, gender, ethnicity or disease state (Cella *et al.* 2010; Cook *et al.* 2011; Junghaenel *et al.* 2011). Because all 95 items are statistically linked through the item response theory model, the scores generated by any item from the calibrated bank can be directly compared across populations regardless of the question asked. The adult form of the instrument quantifies the experience (frequency, duration and intensity) and the impact of the perception of fatigue on participation in daily activities over a recall period of seven days using a five-point scale. Although seven day recalls typically suffer from bias due to the most intense or most recent experience of the concept being measured, perceptions of fatigue appear to be unaffected by these concerns (Schneider *et al.* 2011).

The PROMIS instrument can be administered using the full 95 item test, a computerized adaptive test or one of the four developed short forms. While the computerized adaptive test score is more highly correlated with the score from the entire item bank, more simplified paper administered instruments are desired for the older adult population to maximize their ability to successfully complete the questionnaire (Tralongo *et al.* 2003). The short forms can be administered using the 4, 6, 7 or 8 item versions. All of the short forms are highly correlated with both the computerized adaptive test and the full 95 item PROMIS bank and have high degree of reliability based on internal consistency calculations. For example, the 7-item short form was correlated with the full item bank with an r = 0.76, and the internal consistency reliability for over 95% of the participants was greater than 0.91 (Cella *et al.* 2010). The longer item short forms offer the best correlation with the full item bank and a higher degree of precision, reliability and sensitivity in measuring perceptions of fatigue compared to the shorter forms (NIH-PROMIS, 2014). The only disadvantage of the longer item short forms is the potential increased burden on the participants based on the increased number of questions; however, it seems unlikely that increasing the number of items from 4 to 8 would be a major concern in the healthy older adult population. Thus, the 8-item PROMIS short form appears to be the most suitable instrument for measuring the perception of fatigue in older adults (Table 1).

Table 1: 8-item PROMIS short form to measure perception of fatigue.

Item Number	During the past 7 days…	Not at all	A little bit	Somewhat	Quite a bit	Very much
1	I feel fatigued	1	2	3	4	5
2	I have trouble starting things because I am tired	1	2	3	4	5
	In the past 7 days…					
3	How run-down did you feel on average?	1	2	3	4	5
4	How fatigued were you on average?	1	2	3	4	5
5	How much were you bothered by your fatigue on average?	1	2	3	4	5
6	To what degree did your fatigue interfere with your physical functioning?	1	2	3	4	5
	In the past 7 days…	**Never**	**Rarely**	**Sometimes**	**Often**	**Always**
7	How often did you have to push yourself to get things done because of your fatigue?	1	2	3	4	5
8	How often did you have trouble finishing things because of your fatigue?	1	2	3	4	5

Although the validity and reliability of the 8-item short form to measure perception of fatigue has been extensively tested through the PROMIS initiative, a few simple procedures during administration of the instrument can be used to minimize error and improve the reliability of this measure. First, since visits to the lab will be required to obtain measurements of fatigability, the questionnaire should be administered in the temperature controlled, quiet lab environment, and the test should be administered by the same research personnel at the beginning of the first testing session (Walsh *et al.* 2010). Second, the data from the questionnaires should be analyzed by multiple personnel and compared using the item-level calibration scoring system (NIH-PROMIS, 2014). And third, activity levels should be evaluated to normalize the perception of fatigue measures to account for older adults that may attempt to minimize their ‘fatigue’ experiences by restricting their activity levels (Eldadah, 2010).

Physiological Instrument to Measure Fatigability in Older Adults

In contrast to perception of fatigue, fatigability is an objectively measured phenomenon typically defined as the transient reduction in force or power occurring in response to prior contractile activity that is reversible by periods of rest (Kent-Braun *et al.* 2012). Acknowledging that fatigability is reversible by rest is important to highlight, especially in studies on older adults, because it distinguishes fatigability from neuromuscular injury or diseased states that result in muscle weakness. Fatigability is most commonly quantified as 1) the relative reduction in force or power during and following a specific contraction protocol and/or 2) the duration a sustained or sequence of repeated contractions can be maintained at a specified contraction intensity (Kent-Braun *et al.* 2012; Hunter, 2014). Greater relative reductions in force or power and/or contractions that are sustained for shorter durations are considered to be more fatigable. The measurements of fatigability are typically obtained from either custom designed or prefabricated ergometers instrumented with transducers that measure force (e.g., strain gauges, piezoelectric crystals) and velocity (e.g., potentiometers, encoders). These devices should be calibrated regularly to help ensure that the measurements of force and velocity are both accurate and reliable. However, although measurements of force, velocity and power provide valuable information about whether older adults are more fatigable compared to younger adults, these measures alone are unable to determine the causes of fatigability so are often coupled with more mechanistic physiological measurements.

Fatigability is a complex phenomenon that has multiple physiological mechanisms which may or may not be directly related to the perception of fatigue. These mechanisms range from 1) pain or discomfort leading to the unwillingness or lack of motivation to perform the activity, 2) an inability of the nervous system to adequately drive the muscle (Gandevia, 2001) and/or 3) impairments in excitation-contraction coupling or disruptions in the crossbridge cycle within the muscle cells (Fitts, 1994, 2008; Allen *et al.* 2008). The recognition that fatigability can arise from changes occurring anywhere along the motor pathway has caused two sub concepts to emerge that are differentiated based on anatomy (Fig. 1). Central fatigability refers to all of the processes proximal to the neuromuscular junction and within the nervous system, whereas peripheral fatigability refers to everything distal to the neuromuscular junction and within the contracting muscle (Allen *et al.* 2008). An instrument that provides the opportunity to identify the sites responsible for the changes of fatigability in older adults is ideal, because it may help develop more specific treatments and therapeutic interventions to ameliorate the detrimental effects of increased fatigability.

At present, the most widely used and validated instrument to measure the amount of central and peripheral fatigability is the interpolated twitch technique (Gandevia, 2001). This instrument was first developed by Merton in 1954 and has more recently been applied to fatigability studies in the older adult population (e.g., Yoon *et al.* 2008). The technique uses a single supramaximal transcutaneous electrical pulse delivered over the motor nerves innervating the muscle group of interest while the subject performs a maximal voluntary isometric contraction (MVC). Any increased force generated by the superimposed stimulus indicates that either not all of the motor units were recruited or the discharge frequencies were not high enough to maximize force summation. Thus, any increment in force produced by the stimulus is interpreted as submaximal voluntary activation (Fig. 2). To quantify the amount of voluntary activation, the amplitude of the superimposed twitch is expressed relative to the amplitude of the potentiated control twitch from the electrical stimulus delivered immediately after the MVC [voluntary activation (%) = {1-(superimposed twitch/potentiated resting twitch)}*100] (Bellemare & Bigland-Ritchie, 1984; Bigland-Ritchie *et al.* 1986). The amplitude of the

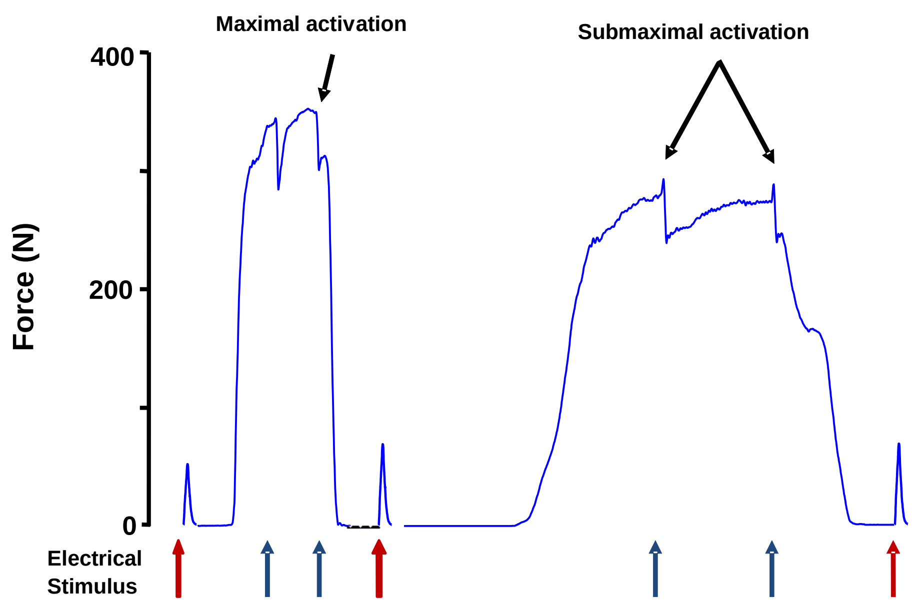

Fig. 2. Force traces demonstrating the interpolated twitch technique. Vertical blue arrows are single electrical pulses superimposed on the MVC, whereas the vertical red arrows are single electrical pulses to the relaxed muscle. Notice the amplitude of the twitch before the MVC is smaller than after the MVC. The trace on the left represents a voluntary effort reaching maximum voluntary activation, and the trace on the right represents submaximal voluntary activation.

potentiated twitch is larger than the twitch delivered prior to the MVC and is used to quantify voluntary activation, because it more closely resembles the state of potentiation of the superimposed twitch (Hamada *et al.* 2003; Folland & Williams, 2007; MacIntosh *et al.* 2012). To reduce variability in the calculation of voluntary activation, the delivery of the potentiated resting stimulus should be standardized to occur immediately following the MVC (i.e., < 5 s) due to the rapid loss in potentiation that occurs following the contraction. Based on the calculations of voluntary activation, central fatigability can be quantified by measuring the change in the voluntary activation obtained before and after the fatiguing contraction protocol. Peripheral fatigability can then be quantified either based on the amount of force that is lost and cannot be attributed to central fatigability or based on the changes in the amplitude of the resting potentiated control twitch obtained before and after the fatiguing protocol.

Although the interpolated twitch technique is considered the best instrument available to measure central and peripheral fatigability, many factors should be considered regarding the sensitivity, validity and reliability of this technique to avoid over interpretation of the results. First, the calculation of voluntary activation used to measure central fatigability assumes that the relationship between the amplitude of the superimposed twitch and the level of voluntary force output is linear. This relationship, however, is more accurately described using a curvilinear function, and as a result, calculations of voluntary activation are typically overestimated as the force output approaches the MVC (Allen *et al.* 1995, 1998; Behm *et al.* 1996; Oskouei *et al.* 2003). The loss of accuracy and sensitivity in contractions performed at intensities between ~80 and 100% of the MVC (Fig. 3) calls into question the validity of using this instrument to quantify both voluntary activation and central fatigability and remains a topic of considerable debate (Place *et al.* 2008; de Haan *et al.* 2009; Horstman *et al.* 2009; Taylor *et al.* 2009; Gandevia *et al.* 2013). Second, test-retest reliability experiments have revealed that random error causes a wide range of variability in voluntary activation measures between MVCs performed prior to a fatiguing contraction protocol (Place *et al.* 2007). This variability is exacerbated in older adults, and therefore, requires additional familiarization sessions and practice to obtain more consistent

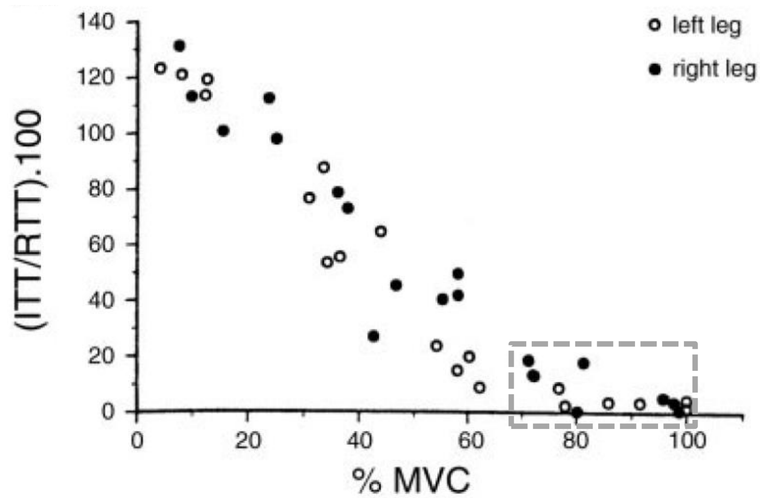

Fig. 3. Interpolated twitch torque (ITT) expressed relative to the resting potentiated twitch torque (RTT) for the knee extensors of the right and left leg for a single young subject. Notice that it becomes difficult to differentiate the ITT/RTT ratio at intensities greater than ~80% of the MVC. This figure is redrawn from Oskouei *et al.* (2003).

voluntary activation measures (Jakobi & Rice, 2002). Third, the rapid recovery in force following the fatiguing contraction protocol considerably limits the number of voluntary activation measurements that can be obtained. No study has investigated the impact of this limitation in quantifying central fatigability; however, the convention is to compare the highest voluntary activation measurement—obtained from a sequence of ~5-10 MVCs performed prior to the fatiguing contraction protocol—to a single voluntary activation after the fatiguing protocol. Fourth, the interpolated twitch technique is limited to isolated muscle groups and cannot be applied to dynamic whole-body movements that are more representative of daily activities. Despite these limitations, incorporating the interpolated twitch technique with measures of force, velocity and power following a fatiguing contraction protocol may provide a more robust opportunity to advance our understanding of the causes of fatigability in older adults.

Concluding Remarks

The goal of fatigue research in older adults is to identify the causal factors responsible for the increased complaint of fatigue that is hindering the elderlies' mobility, ability to perform activities of daily living and quality of life. The lack of a standard operational definition for fatigue, however, has resulted in the employment of a vast array of subjective and objective measures making it difficult to compare findings across studies. Adopting a model that clearly defines the concepts and subconcepts underlying fatigue may help remedy this issue and is necessary for the selection of the most valid and reliable instruments. Aging fatigue studies that incorporate the use of both physiological and self-report instruments and control for comoborbidities are long overdue. Regardless of whether or not perceptions of fatigue and performance fatigability are directly associated, these studies will provide a valuable opportunity to not only advance our understanding of fatigue, but to guide and test the efficacy of new therapeutic interventions to help ameliorate the detrimental effects of fatigue in older adults.

References

1. Allen DG, Lamb GD, Westerblad H. Skeletal muscle fatigue: cellular mechanisms. *Physiol Rev* 81: 287-332, 2008.
2. Allen GM, Gandevia SC, McKenzie DK. Reliability of measurements of muscle strength and voluntary activation using twitch interpolation. *Muscle Nerve* 18: 593-600, 1995.
3. Allen GM, McKenzie DK, Gandevia SC. Twitch interpolation of the elbow flexor muscles at high forces. *Muscle Nerve* 21: 318-328, 1998.
4. Behm DG, St-Pierre DMM, Perez D. Muscle inactivation: assessment of interpolated twitch technique. *J Appl Physiol* 81: 2267-2273, 1996.
5. Bellemare F, Bigland-Ritchie B. Assessment of human diaphragm strength and activation using phrenic nerve stimulation. *Respir Physiol* 58: 263-277, 1984.
6. Bigland-Ritchie B, Furbush F, Woods JJ. Fatigue of intermittent submaximal voluntary contractions: central and peripheral factors. *J Appl Physiol* 61(2): 421-429, 1986.
7. Cella D, Riley W, Stone A, Rothrock N, Reeve B, Yount S, Amtmann D *et al.* The Patient-Reported Outcomes Measurement Information System (PROMIS) developed and tested its first wave of adult self-reported health outcome item banks: 2005-2008. *J Clin Epidemiol* 63(11): 1179-1194, 2010.
8. Centers for Disease Control and Prevention. *The State of Aging and Health in America 2013*. Atlanta, GA: Centers for Disease Control and Prevention, US Dept of Health and Human Services; 2013.
9. Cook KF, Molton IR, Jensen MP. Fatigue and aging with a disability. *Arch Phys Med Rehabil* 92: 1126-1133, 2011.
10. de Haan A, Gerrits KHL, de Ruiter CJ. Counterpoint: the interpolated twitch does not provide a valid measure of the voluntary activation of muscle. *J Appl Physiol* 107: 355-357, 2009.
11. DeWalt DA, Rothrock N, Yount S, Stone AA. Evaluation of item candidates: the PROMIS qualitative item review. *Med Care* 45(5s1): S12-21, 2007.
12. Dittner AJ, Wessely SC, Brown RG. The assessment of fatigue a practical guide for clinicians and researchers. *J Psychosom Res* 56(2): 157-170, 2004.
13. Eldadah BA. Fatigue and fatigability in older adults. *PM R* 2: 406-413, 2010.
14. Fitts RH. The cross-bridge cycle and skeletal muscle fatigue. *J Appl Physiol* 104: 551-558, 2008.
15. Fitts RH. Cellular mechanisms of muscle fatigue. *Physiol Rev* 74: 49-94, 1994.
16. Folland JP, Williams AG. Methodological issues with the interpolated twitch technique. *J Electromyogr Kines* 17: 317-327, 2007.
17. Gandevia SC. Spinal and supraspinal factors in human muscle fatigue. *Physiol Rev* 81: 1725-1789, 2001.
18. Gandevia SC, McNeil CJ, Carroll TJ, Taylor JL. Twitch interpolation: superimposed twitches decline progressively during a tetanic contraction of human adductor pollicis. *J Physiol* 591.5: 1373-1383, 2013.
19. Gill TM, Desai MM, Gahbauer EA, Holford TR, Williams CS. Restricted activity among community-living older persons: incidence, precipitants, and health care utilization. *Ann Intern Med* 135(5): 313-321, 2001.

20. Hamada T, Sale DG, MacDougall JD, Tarnopolsky MA. Interaction of fibre type, potentiation and fatigue in human knee extensor muscles. *Acta Physiol Scand* 178: 165-173, 2003.
21. Horstman AM *et al.* Comments on point:counterpoint: the interpolated twitch does/does not provide a valid measure of the voluntary activation of muscle. *J Appl Physiol* 107: 359-366, 2009.
22. Hunter SK. Sex differences in human fatigability: mechanisms and insight to physiological responses. *Acta Physiol* 210(4): 768-789, 2014.
23. Jakobi JM, Rice CL. Voluntary muscle activation varies with age and muscle group. *J Appl Physiol* 93: 457-462, 2002.
24. Junghaenel DU, Christodoulou C, Lai JS, Stone AA. Demographic correlates of fatigue in the US general population: results from the patient-reported outcomes measurement information system (PROMIS) initiative. *J Psychosom Res* 71: 117-123, 2011.
25. Kent-Braun JA, Fitts RH, Christie A. Skeletal muscle fatigue. *Compr Physiol* 2: 997-1044, 2012.
26. Kluger BM, Krupp LB, Enoka RM. Fatigue and fatigability in neurologic illnesses. *Neurology* 80: 409-416, 2013.
27. Lai JS, Cella D, Choi S, Junghaenel DU, Christodoulou C, Gershon R, Stone A. How item banks and their application can influence measurement practice in rehabilitation medicine: a PROMIS fatigue item bank example. *Arch Phys Med Rehabil* 29(10s1): S20-27, 2011.
28. MacIntosh BR, Holash RJ, Renaud JM. Skeletal muscle fatigue – regulation of excitation-contraction coupling to avoid metabolic catastrophe. *J Cell Sci* 125: 1-10, 2012.
29. Merton PA. Voluntary strength and fatigue. *J Physiol* 123: 553-564, 1954.
30. National Institutes of Health Patient-Reported Outcomes Measurement Information System. *Fatigue: A brief guide to the PROMIS fatigue instruments*. Silver Spring, MD: PROMIS Network Center; 2014. Retrieved from https://www.assessmentcenter.net/documents/PROMIS%20Fatigue%20Scoring%20Manual.pdf.
31. National Institute on Aging. *Unexplained Fatigue in the Elderly*. Bethesda, MD: National Institutes of Health US Dept of Health and Human Services; 2007. Retrieved from http://www.nia.nih.gov/about/events/2011/unexplained-fatigue-elderly.
32. Oskouei MAE, van Mazijk BCF, Schuiling MHC, Herzog W. Variability in the interpolated twitch torque for maximal and submaximal voluntary contractions. *J Appl Physiol* 95: 1648-1655, 2003.
33. Place N, Maffiuletti NA, Martin A, Lepers R. Assessment of the reliability of central and peripheral fatigue after sustained maximal voluntary contraction of the quadriceps muscle. *Muscle Nerve* 35: 486-495, 2007.
34. Place N, Yamada T, Bruton JD, Westerblad H. Interpolated twitches in fatiguing single mouse muscle fibres: implications for the assessment of central fatigue. *J Physiol* 586.11: 2799-2805, 2008.
35. Riley WT, Rothrock N, Bruce B, Christodolou C, Cook K, Hahn EA, Cell D. Patient-reported outcomes measurement information system (PROMIS) domain names and definitions revisions: further evaluation of content validity in IRT-derived item banks. *Qual Life Res* 19: 1311-1321, 2010.
36. Soyuer F, Senol V. Fatigue and physical activity levels of 65 and over older people living in rest home. *Int J Gerontol* 5: 13-16, 2011.

37. Taylor JL. Point: the interpolated twitch does provide a valid measure of the voluntary activation of muscle. *J Appl Physiol* 107: 354-355, 2009.
38. Tralongo P, Respini D, Ferrau F. Fatigue and aging. *Crit Rev Oncol Hematol* 48s: S57-65, 2003.
39. Vestergaard S, Nayfield SG, Patel KV, Eldadah B, Cesari M, Ferruci L, Ceresini G, Guralnik JM. Fatigue in a representative population of older persons and its association with functional impairment, functional limitation, and disability. *J Gerontol A Biol Sci Med Sci* 64(1): 76-82, 2009.
40. Walsh CF, Strickland OL, Lenz ER. *Measurement in nursing and health research* (fourth edition). New York: Springer Publishing Company, 2010.
41. Williams C, Ratel S. (Eds.). *Human Muscle Fatigue*. New York, NY: Routledge, 2009.
42. Yoon T, Schlinder-DeLap B, Griffith EE, Hunter SK. Age-related muscle fatigue after a low-force fatiguing contraction is explained by central fatigue. *Muscle Nerve* 37: 457-466, 2008.
43. Yu DSF, Lee DTF, Man NW. Fatigue among older people: a review of the research literature. *Int J Nurs Stud* 47: 216-228, 2010.