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Adapting the reserve and resilience framework for motor and other aging phenotypes

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The conceptual framework presented by Stern and colleagues (Stern et al., 2022) defines *resilience* as the ability to maintain cognition and day-to-day functions despite aging and disease. Operational definitions and guidelines for studying three resilience mechanisms – *cognitive reserve, brain maintenance, and brain reserve* – are then presented to promote a better understanding of factors associated with successful cognitive aging. In this commentary, we discuss evidence for extending this framework to account for unexplained heterogeneous age-related differences observed in other phenotypes like *motor function*. We also review initial attempts to advance mechanistic studies of cognitive and motor resilience.

1. A reserve and resilience framework of motor function can inform cognition
   A reserve and resilience framework that incorporates motor function makes sense because cognitive and motor functions are strongly associated and share neural substrates in aging and dementia (Buchman et al., 2014; Clouston et al., 2013; Cohen et al., 2016; Leisman et al., 2016; Scherder et al., 2007). Gait decline, for example, is an early and reliable predictor of cognitive decline and dementia (Beauchet et al., 2016; Buracchio et al., 2010; Jayakody et al., 2021; Quan et al., 2017). Gait like cognition is also associated with various age-related changes and pathologies in brain regions particularly affected by aging, Alzheimer's disease and related dementia (ADRD) – including (but not limited to) the prefrontal cortex and hippocampus (Allali et al., 2015; Blumen et al., 2018; Buchman et al., 2019; Callisaya et al., 2013; Ezzati et al., 2015; Oveisgharan et al., 2023b; Rosso et al., 2017). Yet, while motor function is a volitional behavior regulated by the brain, cognition and motor function in aging are typically studied in isolation. Adopting reserve and resilience terminology could facilitate a better understanding of cognitive and motor aging and promote the identification of shared and distinct mechanisms of successful aging.
   Analogous to the concept of cognitive reserve, *motor reserve* could be defined as a property of the brain that allows for better-than-expected motor performance despite aging or disease. Likewise, brain maintenance could be defined as the relative absence of brain changes or disease as a cause for preserved motor function in aging. Factors that modify the relationship between brain changes and motor function could then be interpreted in terms of motor reserve and brain maintenance. Direct comparisons of how molecular mechanisms influence the relationship between brain changes and changes in <u>both</u> motor and cognitive functions will be particularly useful for identifying shared and distinct mechanisms. One initial step to facilitate this approach would be to include testing of common motor performances such as gait speed in studies of cognitive resilience. Gait speed can be assessed in most clinical and research settings without specialized equipment and personnel (e.g., timing participants walking a fixed distance down a hallway). Additional aspects of gait and other motor function can be assessed with low-cost, wearable, and unobtrusive sensors that can be employed to obtain remote multiday phenotyping of diverse behaviors during everyday living (Brand et al., 2022; Buchman et al., 2020).
2. Expanding the reserve and resilience framework beyond the brain and cognition
   The reserve and resilience framework developed by Stern and colleagues focuses exclusively on cognition and the brain. Resilience is a general feature of all physiologic systems. The exclusive focus on the brain can lead investigators to ignore other physiological systems that are critical for motor and cognitive function, including musculoskeletal, cardiopulmonary, and metabolic systems (Ferrucci et al., 2000; Rosso et al., 2013). While many essential cognitive resilience networks likely reside in the brain, the neural underpinning of motor control begins in the brain and extends through the entire central nervous system to reach musculoskeletal elements in the periphery that effect all movement (Rothwell, 2012). Accumulating evidence suggest that ADRD pathologies affect not only cognition but also non-cognitive phenotypes like motor function (Albers et al., 2015). While ADRD pathologies extend beyond the brain and accumulate in varied brainstem and spinal cord tissues, resilience mechanisms in tissues outside the brain are understudied (Buchman et al., 2018; Dugger et al., 2013; Oveisgharan et al., 2023a). Identifying tissue-specific and cross-tissue resilience mechanisms within and outside the brain of diverse phenotypes can lead to personalized resilience interventions.
3. Elucidating the molecular mechanisms of reserve and resilience
   The proposed framework focuses on several potential mechanisms that benefit some individuals to age successfully (i.e, manifest slower cognitive decline), but molecular resilience mechanisms like genes and proteins remain relatively unexplored. To fill this

gap, recent work has studied brain transcriptome or proteome to identify molecular mechanisms that may provide cognitive and/or motor resilience in aging. By regressing out the effects of ADRD pathologies, these studies have identified *resilience* genes and proteins associated with slower or faster cognitive and/or motor decline that cannot be attributed to ADRD pathologies (Buchman et al., 2023; Buchman et al., 2021; Yu et al., 2020; Zammit et al., 2022). These data suggest that resilience like other conventional risk factors exists on a continuum (Bennett, 2017; Buchman and Bennett, 2022; Rose et al., 2008). Hence, all living brains have some degree of resilience (i.e., the balance between many proteins, some that increase and some that decrease brain resilience). Given the same amount of brain pathology, some individuals manifest higher-than-average resilience and some lower-than-average resilience. Thus, elucidating the biology of resilience could inform both on efforts to promote successful aging, and provide new approaches for reversing vulnerability in older adults with lower-than-average resilience.

This expanded conceptualization of resilience can be employed to identify potential molecular mechanisms underlying diverse cognitive and non-cognitive aging phenotypes as well modifiable risk factors like physical activity – that may provide resilience via diverse mechanisms from tissues within and outside the brain. The resilience genes and proteins identified in these studies provide high-value therapeutic targets for mechanistic and drug discovery studies of novel "resilience" treatments. Despite decades of remarkable advances in aging research, there are no therapies for ADRD. It is time to move beyond the concept of resilience to catalyze the development of "resilience" treatments that can facilitate successful aging despite the accumulation of untreatable brain pathologies.

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