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Mechanisms underlying resilience in ageing

Yaakov Stern¹, Gaël Chételat², Christian Habeck³, Eider M. Arenaza-Urquijo⁴, Prashanthi Vemuri⁵, Ainara Estanga⁶, David Bartrés-Faz⁷, Marc Cantillon⁸, Sean A.P. Clouston⁹, Jeremy A. Elman¹⁰, Brian T. Gold¹¹, Richard Jones¹², Gerd Kempermann¹³, Yen Ying Lim¹⁴, Anita van Loenhoud¹⁵, Pablo Martínez-Lage¹⁶, Silvia Morbelli¹⁷, Ozioma Okonkwo¹⁸, Rik Ossenkoppele¹⁹, Corinne Pettigrew²⁰, Allyson C. Rosen²¹, Nikolaos Scarmeas²², Anja Soldan²³, Chinedu Udeh-Momoh²⁴, Michael Valenzuela²⁵ and Eero Vuoksima²⁶

The recent Opinion article by Cabeza and colleagues (Maintenance, reserve and compensation: the cognitive neuroscience of healthy ageing. *Nat. Rev. Neurosci.* **19**, 701–710 (2018))¹ provides definitions for reserve and maintenance along with a detailed description of compensatory mechanisms from a cognitive ageing perspective. The article represents a much-needed effort to refine the definitions for various forms of compensation. Nevertheless, the definitions presented by Cabeza et al. for reserve, maintenance and compensation diverge from the ‘white-paper’ consensus definitions developed by a workgroup of 31 researchers² in ways that we believe are not ideal in terms of their ability to capture the full extent of the mechanisms underlying individual differences in resilience.

Cabeza et al. argue that the differentiation between brain reserve and cognitive reserve should be eliminated, and that those concepts should be replaced by the single, generic term reserve. While it is undeniable that all cognition is brain-based, we disagree with the conclusion that the single term reserve can fully characterize the phenomena that we seek to investigate. All functional imaging observations, including compensation, must consider measures of the underlying brain status. The separation of the terms brain reserve and cognitive reserve therefore serves a critical purpose for empirical research: brain reserve is important for characterizing the physical status of the brain at any point in time (in terms of its volume, cortical thickness, white matter tract integrity and so on), whereas cognitive reserve moderates associations between brain morphology and clinical status (that is,

it explains why two people with the same amount of age or disease-related changes differ clinically).

We also advocate retaining the term brain maintenance as opposed to simply using the term maintenance. The specific concept of brain maintenance was proposed based on the observation that genetics and a set of life exposures are associated with reduced development of primary age-related brain changes and pathologies³. This clearly separates it from cognitive reserve, which describes resilience against these brain changes.

Finally, we feel that compensation should not be considered at the same level of abstraction as brain maintenance and cognitive reserve. Rather, we believe that compensation is one of many ways that cognitive reserve may be implemented. Thus, the manner and success of compensation is often modulated by lifestyle variables referred to as proxies of cognitive reserve. The authors themselves appear to recognize this issue, stating: “However, complicating the distinction, reserve and the capacity for compensation may interact”. In the context of investigating cognitive reserve, investigators might explore whether lifestyle exposures are associated with differential compensation. However, compensation without reference to individual differences and their sources, as well as to brain reserve, yields no insight into how to promote resilience against ageing and disease.

In summary, Cabeza and colleagues perform a valuable service by attempting to establish a common nomenclature for the study of a set of findings noted in functional activation studies, which they group under the overarching term compensation. However,

we believe that our recently published paper² presents consensus definitions for brain reserve, cognitive reserve and brain maintenance that will better enable us to pursue the understanding of individual differences and resilience, and generate approaches towards intervention.

There is a reply to this letter by Cabeza, R. et al. *Nat. Rev. Neurosci.* <https://doi.org/10.1038/s41583-019-0139-z> (2019).

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Competing interests

The authors declare no competing interests.