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SI: RESILIENCE/RESERVE IN AD

Stemming the Alzheimer tsunami: introduction to the special issue on reserve and resilience in Alzheimer's disease

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As the world's population ages at an accelerated rate, there is projected to be a dramatic increase in the number of persons diagnosed with Alzheimer's disease dementia (AD) (Alzheimer's Association 2016). AD is primarily characterized by the misfolding of two proteins – amyloid and tau – leading to the aggregation of senile plaques and neurofibrillary tangles, respectively (Braak and Braak 1991). While an effective therapeutic for AD and its associated pathophysiology are yet to emerge, the concepts of reserve and resilience are increasingly considered important for delaying the onset of cognitive impairment and dementia. Broadly speaking, "reserve" and "resilience" in AD refer to the disconnect between the presence of AD pathologies and cognitive impairment (Stern 2012). Individuals with high levels of reserve and resilience remain cognitively normal even at high levels of AD pathology whereas those with lower levels of reserve and resilience are cognitively impaired at the same level of AD pathology. Reserve and resilience could also refer to the ability of some individuals to remain relatively spared from both cognitive decline and AD pathophysiological changes (Stern 2012), despite harboring the primary risk factors for the disease: advanced age and carriage of one or more ε4 alleles of the apolipoprotein E (*APOE*) gene. Although these concepts are gaining wide traction, there is still considerable ground that needs to be covered in order to extend the frontiers of this growing line of inquiry. Two questions that are particularly salient include: How can we most effectively measure reserve and resilience? What are the mechanisms through which reserve and resilience aid in delaying the onset of cognitive impairment? Answering these questions would be critical to the successful translation of emerging findings in this field into treatment strategies.

In this Special Issue on *Reserve and Resilience in Alzheimer's disease*, our goal was to bring together key aspects of research in this area. The common thread among the assembled cadre of investigators is the use of state-of-the art brain imaging methodologies to further our understanding of reserve and resilience.

Education and occupation are among the most commonly-used proxies of reserve, since early and midlife intellectual enrichment significantly influence brain health as a person ages (Kramer et al. 2004). Three papers in this Special Issue investigated the impact of these proxies on brain structure and function. Boller et al. (2016) found a positive association between years of education and gray matter volume in AD-relevant regions such as the posterior cingulate. In addition, they found that education modified age-related volumetric declines in frontal and medial cingulate gyri. The authors also investigated education-based differences in brain activation during an n-back working memory task. They observed augmented network activation with age in those with higher educational attainment, suggesting a compensatory arrest

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of the deleterious impact of aging on brain function. Vaque-Alcazar et al. (2016) investigated whether education associates with better cognition via neuroprotective (i.e., higher education correlating with better brain health and, thus, better cognition) versus compensatory (i.e., higher education correlating with better cognition despite maladaptive brain aging) mechanisms. They found evidence for both neuroprotection and compensation. Specifically, compared to their less educated peers, highly educated adults exhibited greater cortical thickness particularly in frontal and cingulate regions. In contrast, highly educated adults presented with diminished fractional anisotropy in several associative and commissural white matter tracts. Even so, the highly educated group performed better than the less educated group on cognitive domains of Memory and Speed of Processing. Furthermore, the adverse effect of aging on fractional anisotropy was attenuated among the highly educated. With respect to occupation, Suo et al. (2016) examined whether managerial experience was related to brain indices and cognition among individuals diagnosed with non-amnestic mild cognitive impairment (MCI). Participants were classified into high and low managerial experience groups based on the number of people they supervised during each five-year epoch from age 30 to retirement. They found that high managerial experience was related to better memory performance, which was mediated by greater hippocampal volume. Interestingly, they also found that the management of large groups of employees was associated with more pessimistic appraisal of one's own memory function, which correlated with diminished hippocampal-prefrontal network connectivity. Such studies are important for understanding the complex impact of reserve on brain aging.

Cognitive and physical activities in midlife and late adulthood have both been suggested to increase cognitive reserve and resilience (Okonkwo et al. 2014; Vemuri et al. 2016). Arenaza-Urquijo et al. (2016) used structural magnetic resonance imaging to investigate the associations between cognitive and physical activities in late-adulthood and regional gray matter volume. They found evidence for independent salutary effects of each of these exposures on gray matter volume in brain regions implicated in aging and AD. This study offers the intriguing promise that cognitive- and physical activity-based interventions may aid in building reserve and resilience to counter brain changes due to aging and AD in the elderly.

In a longitudinal study of cognitively-normal adults enrolled in the BIOCARD cohort, Pettigrew et al. (2016) investigated the relationships between brain morphometry, cognitive reserve, and risk of progression to MCI. Their measure of cognitive reserve was a composite derived from years of education, reading, and vocabulary. An interesting observation from this study was the differential existence of an interaction between cortical thickness and cognitive reserve depending on the timing of symptom onset. Specifically, both cognitive reserve and thickness were additively, but not interactively, associated with symptom onset within 7 years (median follow-up time) of baseline assessment. However, for symptom onset beyond 7 years of baseline, there was a significant interaction between reserve and thickness such that the effect of cortical thinning on symptom onset was attenuated among those with high reserve, suggesting a compensatory process.

Franzmeier et al. (2016) developed an imaging-based metric for capturing inter-individual differences in cognitive reserve in persons at risk for AD. For this, they focused on resting-state global functional connectivity (GFC) within the cognitive control network, because of this network's key role in higher cognitive function and its link to other reserve proxies. In a training sample of cognitively-healthy adults and those with MCI, they found that MCI patients with high education harbored greater GFC compared to those with low education. This finding was further cross-validated in an independent test sample of MCI patients, suggesting that GFC-based measures may be good candidate biomarkers for reserve. The importance of this work is that an imaging-derived measure of reserve might be better tuned to capturing the underlying construct of "reserve" relative to proxies such as education and occupation, which are inherently prone to measurement error and bias.

Positron emission tomography with tracers for aggregated amyloid and tau proteins have drastically improved our understanding of the AD disease process (Okonkwo 2014). Rentz et al. (2016) employed this technology to investigate the associations among reading ability (their proxy for reserve), amyloid, tau, and cognition. As expected, higher amyloid and tau deposition were associated with worse cognitive performance whereas higher reading ability was associated with better cognitive performance. Importantly, the authors also found that the deleterious impact of amyloid and tau deposition on cognition was abated in individuals with higher reserve.

Genetics plays an important role in aging and the development of AD. While certain genetic variants, such as *APOE4*, are now known to increase the risk of AD (Lambert et al. 2013), the study of genes that provide resilience against AD is just emerging. Two papers in this Special Issue investigated concepts related to such "genetic resilience." The first one, by Yokoyama et al. (2016) focused on the longevity promoter *KLOTHO* (*KL*-VS) and its systemic levels, building off prior studies that showed that *KL*-VS heterozygosity was associated with better cognition and resilience against AD pathologies (Dubal et al. 2015). The authors reported that klotho levels are increased with *KL*-VS heterozygosity but paradoxically decreased with *KL*-VS homozygosity. Furthermore, the authors presented novel data showing that higher serum klotho is associated with enhanced connectivity in functional hubs, such as the default mode network, that are compromised in aging and AD; suggesting that klotho confers resilience by perhaps promoting intrinsic connectivity of critical brain regions. In the second paper on genetic resilience, Hohman et al. (2016) set out to identify novel genes that modify the association between amyloid deposition and longitudinal cognitive change using PrediXcan, a recently-developed predicted gene expression technique (Gamazon et al. 2015). The analyses

uncovered three genes (*CNTLN*, *PROK1*, and *PRRS50*) that modified the association between amyloid burden and memory decline and two genes (*TMC4* and *HMBS*) that exerted similar modification of amyloid-related decline in executive function. Although the results of the PrediXcan study need to be validated using independent samples, development and application of such novel analytic methods are important for identifying genes that might provide resilience against AD.

In the concluding article, Yaakov Stern (2016) put forward a framework for evaluating the concepts of cognitive reserve, brain reserve, and brain maintenance. As seen in the articles included in this Special Issue, the methods used to evaluate reserve and its putatively underlying mechanisms are diverse. Drawing from the extensive work he and his colleagues have done in this area, Stern proposed conceptual frameworks that seek to both parse and harmonize these divergent perspectives, with a view to igniting conversations that would, ultimately, lead to commonalities in definitions, methodologies, and approaches.

While the articles compiled in this Special Issue only represent a slice of the research enterprise in this bourgeoning field, we hope that it provides a sense of the enormous scientific effort being devoted to understanding the mechanics of resilience to AD. We are optimistic that the investigations described in this Special Issue, as well as those being pursued by several other laboratories across the world, will aid in the translation of the concepts of "reserve" and "resilience" into successful prevention strategies for AD in the years to come, thereby averting the forecast AD tsunami (Selkoe 2013). We hope that you enjoy reading this Special Issue as much as we enjoyed putting it together.

Compliance with ethical standards

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References

Alzheimer's Association. (2016). 2016 Alzheimer's disease facts and figures. *Alzheimer's & Dementia, 12*(4), 459–509.

Arenaza-Urquijo, E. M., de Flores, R., Gonneaud, J., Wirth, M., Ourry, V., Callewaert, W., et al. (2016). Distinct effects of late adulthood cognitive and physical activities on gray matter volume. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9617-3.

Boller, B., Mellah, S., Ducharme-Laliberte, G., & Belleville, S. (2016). Relationships between years of education, regional grey matter volumes, and working memory-related brain activity in healthy older adults. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9621-7.

Braak, H., & Braak, E. (1991). Neuropathological stageing of Alzheimer-related changes. *Acta Neuropathologica, 82*, 239–259.

Dubal, D. B., Zhu, L., Sanchez, P. E., Worden, X., Broestl, L., Johnson, E., et al. (2015). Life extension factor klotho prevents mortality and enhances cognition in hAPP transgenic mice. *Journal of Neuroscience, 35*(6), 2358–2371.

Franzmeier, N., Caballero, M. A., Taylor, A. N., Simon-Vermot, L., Buerger, K., Ertl-Wagner, B., et al. (2016). Resting-state global functional connectivity as a biomarker of cognitive reserve in mild cognitive impairment. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9599-1.

Gamazon, E. R., Wheeler, H. E., Shah, K. P., Mozaffari, S. V., Aquino-Michaels, K., Carroll, R. J., et al. (2015). A gene-based association method for mapping traits using reference transcriptome data. *Nature Genetics, 47*(9), 1091–1098. doi:10.1038/ng.3367.

Hohman, T. J., Dumitrescu, L., Cox, N. J., Jefferson, A. L., & Alzheimer's Neuroimaging, I. (2016). Genetic resilience to amyloid related cognitive decline. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9615-5.

Kramer, A. F., Bherer, L., Colcombe, S. J., Dong, W., & Greenough, W. T. (2004). Environmental influences on cognitive and brain plasticity during aging. *Journals of Gerontology. Series A, Biological Sciences and Medical Sciences, 59*(9), M940–M957.

Lambert, J. C., Ibrahim-Verbaas, C. A., Harold, D., Naj, A. C., Sims, R., Bellenguez, C., et al. (2013). Meta-analysis of 74,046 individuals identifies 11 new susceptibility loci for Alzheimer's disease. *Nature Genetics, 45*(12), 1452–1458. doi:10.1038/ng.2802.

Okonkwo, O. C. (2014). At the crossroads of preclinical AD and normal brain ageing. *Lancet Neurology, 13*(10), 965–966. doi:10.1016/S1474-4422(14)70207-8.

Okonkwo, O. C., Schultz, S. A., Oh, J. M., Larson, J., Edwards, D., Cook, D., et al. (2014). Physical activity attenuates age-related biomarker alterations in preclinical AD. *Neurology, 83*(19), 1753–1760. doi:10.1212/WNL.0000000000000964.

Pettigrew, C., Soldan, A., Zhu, Y., Wang, M. C., Brown, T., Miller, M., et al. (2016). Cognitive reserve and cortical thickness in preclinical Alzheimer's disease. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9581-y.

Rentz, D. M., Mormino, E. C., Papp, K. V., Betensky, R. A., Sperling, R. A., & Johnson, K. A. (2016). Cognitive resilience in clinical and preclinical Alzheimer's disease: the Association of Amyloid and Tau Burden on cognitive performance. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9640-4.

Selkoe, D. J. (2013). The therapeutics of Alzheimer's disease: where we stand and where we are heading. *Annals of Neurology, 74*(3), 328–336. doi:10.1002/Ana.24001.

Stern, Y. (2012). Cognitive reserve in ageing and Alzheimer's disease. *Lancet Neurology, 11*(11), 1006–1012. doi:10.1016/S1474-4422(12)70191-6.

Stern, Y. (2016). An approach to studying the neural correlates of reserve. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9566-x.

Suo, C., Gates, N., Fiatarone Singh, M., Saigal, N., Wilson, G. C., Meiklejohn, J., et al. (2016). Midlife managerial experience is linked to late life hippocampal morphology and function. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9649-8.

Vaque-Alcazar, L., Sala-Llonch, R., Valls-Pedret, C., Vidal-Pineiro, D., Fernandez-Cabello, S., Bargallo, N., et al. (2016). Differential age-related gray and white matter impact mediates educational influence on elders' cognition. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9584-8.

Vemuri, P., Lesnick, T. G., Przybelski, S. A., Knopman, D. S., Machulda, M., Lowe, V. J., et al. (2016). Effect of intellectual enrichment on AD biomarker trajectories: longitudinal imaging study. *Neurology, 86*(12), 1128–1135. doi:10.1212/WNL.0000000000002490.

Yokoyama, J. S., Marx, G., Brown, J. A., Bonham, L. W., Wang, D., Coppola, G., et al. (2016). Systemic klotho is associated with KLOTHO variation and predicts intrinsic cortical connectivity in healthy human aging. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9598-2.