

PERSPECTIVE

# Mixed pathologies and neural reserve: Implications of complexity for Alzheimer disease drug discovery

David A. Bennett\*

Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, Illinois, United States of America

\* [David\\_A\\_Bennett@Rush.edu](mailto:David_A_Bennett@Rush.edu)



**OPEN ACCESS**

**Citation:** Bennett DA (2017) Mixed pathologies and neural reserve: Implications of complexity for Alzheimer disease drug discovery. *PLoS Med* 14 (3): e1002256. doi:10.1371/journal.pmed.1002256

**Published:** March 14, 2017

**Copyright:** © 2017 David A. Bennett. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

**Funding:** The work was supported by NIA grants P30AG10161, R01AG15819, R01AG17917, and U01AG46152.

**Competing interests:** I have read the journal's policy and have the following conflicts: DAB serves on the Adjudication Committee for AD4833/TOMM40\_301, Takeda Pharmaceuticals USA, Inc. and the Neuro Safety Data Monitoring Committee for ABBV-8E12, M15-566, AbbVie, Inc. DAB serves on the Scientific Advisory Board for Vigorous Minds, Inc.

**Abbreviations:** AD, Alzheimer disease; CSF, cerebrospinal fluid; MCI, mild cognitive impairment; NFT, neurofibrillary tangle; PET, positron emission tomography; TDP-43, tar DNA-binding protein 43.

**Provenance:** Commissioned; not externally peer reviewed

Alzheimer disease (AD) is among the most common causes of dementia worldwide. Approved medications for the symptoms of AD dementia have marginal benefit, and no new therapies have been approved in more than a dozen years. There are no approved treatments for the prevention of AD dementia. The lack of robust therapeutics comes despite intense efforts by the public and private research community to discover them. There have been about 450 failed clinical trials on [www.clinicaltrials.gov](http://www.clinicaltrials.gov) since the last drug approval by the Food and Drug Administration [1]. With changing demographics forecasting a marked increase in the number of persons with AD and other dementias worldwide, and with extraordinary attendant costs of care and toll on individuals and families, countries around the globe are investing substantial capital to stimulate basic and translational research in the hopes of developing new therapeutics for the treatment and prevention of AD and other dementia.

Clinical-pathologic findings, many from community-based studies that incorporate brain autopsy, are shedding light on the complexity of the AD dementia phenotype. This complexity, largely the result of mixed dementia and neural reserve, has important implications for clinical trial design and drug discovery.

## Mixed dementia

The pathologic hallmarks of AD are the extracellular deposits of the amyloid- $\beta$  peptide and the intracellular accumulation of abnormally phosphorylated tau neurofibrillary tangles (NFT). Much is known about the metabolism of these proteins, and amyloid- $\beta$  has been and remains the target of many therapeutic trials. The frequency of AD pathology increases markedly with age. Aging, however, is associated with the development of many common chronic diseases, including several brain diseases that affect cognition. Thus, the brains of older persons, many of whom have AD pathology, often exhibit macro- and/or microscopic infarctions, atherosclerosis, arteriolosclerosis, and white matter changes reflecting cerebrovascular disease, as well as tar DNA-binding protein 43 (TDP-43), hippocampal sclerosis, and neocortical Lewy bodies [2–5]. All of these pathologies can contribute to cognitive impairment and the AD dementia phenotype [6–8]. In fact, among older persons, who represent the greatest number of persons with the disease, mixed pathologies are the most common cause of AD dementia. Mixed pathologies are also very common in persons with mild cognitive impairment (MCI), including amnesic MCI, often thought to be relatively specific for MCI due to AD [9]. Some studies suggest that AD pathology accounts for the majority of dementia cases [10,11]. However, other studies suggest that the comorbid pathologies account for an equal amount of dementia and perhaps even more than AD, collectively [12].

Further, data suggest that the pathologies of these conditions account for less than half of the person-specific variance in change in cognition over multiple years prior to death [13]. It is highly likely that better methods to identify pathologies will be developed in the future—much like the relatively recent introduction of phospho-synuclein for visualizing Lewy bodies—and that new pathologies will be identified in the future, much like the relatively recent discovery of TDP-43. These future developments will reduce the unexplained variance. However, we also know that the brain, like other organs, has person-specific differences in its ability to protect itself from these pathologies—i.e., neural reserve.

## Neural reserve

The concept of reserve refers to the ability of a physiologic system to maintain function despite damage from injury or disease. All human physiologic systems exhibit reserve. In the context of the AD dementia syndrome, neural (or cognitive) reserve refers to the ability to maintain cognitive function despite the accumulation of the various pathologies that contribute to cognitive impairment. Nearly three decades ago, the first report of a series of persons without dementia who met pathologic criteria for AD was published [14]. It is now known that about a third of older persons without dementia or MCI meet pathologic criteria for AD, suggesting that many people are able to maintain excellent cognition despite the accumulation of brain pathology [15,16]. Amyloid- $\beta$  cerebrospinal fluid (CSF) and positron emission tomography (PET) studies now suggest that AD pathology begins to accumulate years if not decades prior to the onset of clinical symptoms [17].

Among the most interesting things about neural reserve is that it may be amenable to lifestyle interventions. For example, there are many experiential and psychological risk factors for cognitive decline and AD dementia that do not appear to be related to any known brain pathology [18]. In other words, many factors can increase or decrease neural reserve agnostic to the underlying brain pathologies. Some studies have estimated that the number of AD dementia cases can be reduced by about a third through lifestyle interventions [19]. The interventions identified would likely reduce the burden of vascular disease, but others would operate through other, as yet unidentified mechanisms. Whether any would have a major effect on AD pathology itself seems unlikely [20–23]. Finally, we are now beginning to elucidate the cellular and molecular machinery underlying neural reserve [24–26].

## Implications of complexity for drug discovery

The data paint a picture of cognitive decline, MCI, and AD dementia resulting from a complex interaction between the accumulation of one or more brain pathologies in the context of a brain that is more or less resilient to these pathologies. This complexity has important implications for both clinical trial design and drug discovery.

Consider a drug that targets amyloid- $\beta$ . Studies suggest that AD pathology accounts for about a third of the variance of cognitive decline if one includes the effects of both amyloid- $\beta$  and NFT [7]. One can enrich a study for amyloid- $\beta$  with PET scans or CSF amyloid- $\beta$ , but the study still needs to be powered to affect only that portion of the cognitive trajectory associated with this pathology. It is not clear that most studies have explicitly powered their trials in this fashion.

Further, consider the sheer number of pathologies that contribute to AD dementia. Is it scalable to use a cocktail to target each one and to give these cocktails to older persons with aging kidneys and livers? Can health care systems absorb these costs, particularly in lower- and middle-income countries or even high-income countries with challenged economies and health systems? Currently, trials targeting a single molecular marker (i.e., amyloid- $\beta$ ) are expensive, requiring many costly PET scans.

By contrast, consider neural reserve as a therapeutic endpoint. There is no evolutionary pressure to create systems that protect the brain from any brain pathology of old age, let alone different systems that offer protection from different pathologies. Thus, finding that myriad factors alter the trajectory of cognitive decline agnostic to underlying brain pathologies is expected. A hypothetical therapeutic agent that targets neural reserve could be used to offset any and likely all common brain pathologies that alter cognition. How one would design such a clinical trial is a challenge that would need to be vetted with regulatory agencies. The simplest approach, assuming a relatively safe agent, would be a large longitudinal study of cognitive decline among people at slightly elevated risk of cognitive decline (e.g., over age 74 with cognitive complaints). Depending on the anticipated effect size, such a study would likely need a minimum of a few thousand subjects followed for at least four years. In such a design, one would let the randomization distribute the common brain pathologies relatively equally between the study arms and simply use the rate of cognitive decline as the endpoint. However, should regulatory agencies require proof that the mechanism of action is reserve and/or require that the trial demonstrate target engagement, study designs could become very complex and expensive. Although many issues remain to be addressed, neural reserve offers a new paradigm for approaching the treatment and prevention of AD and indeed all dementia syndromes.

## References

1. Cummings JL, Morstorf T, Zhong K. Alzheimer's disease drug-development pipeline: few candidates, frequent failures. *Alzheimers Res Ther.* 2014; 3;6:37.
2. White LR, Edland SD, Hemmy LS, Montine KS, Zarow C, Sonnen JA, et al. Neuropathologic comorbidity and cognitive impairment in the Nun and Honolulu-Asia Aging Studies. *Neurology.* 2016; 86:1000–8. doi: [10.1212/WNL.0000000000002480](https://doi.org/10.1212/WNL.0000000000002480) PMID: [26888993](https://pubmed.ncbi.nlm.nih.gov/26888993/)
3. Montine TJ, Sonnen JA, Montine KS, Crane PK, Larson EB. Adult Changes in Thought study: dementia is an individually varying convergent syndrome with prevalent clinically silent diseases that may be modified by some commonly used therapeutics. *Curr Alzheimer Res.* 2012; 9:718–23. PMID: [22471861](https://pubmed.ncbi.nlm.nih.gov/22471861/)
4. Grinberg LT, Nitrini R, Suemoto CK, et al. Prevalence of dementia subtypes in a developing country: a clinicopathological study. *Clinics (Sao Paulo).* 2013; 68:1140–5.
5. Honda H, Sasaki K, Hamasaki H, et al. Trends in autopsy-verified dementia prevalence over 29 years of the Hisayama study. *Neuropathology.* 2016; 36:383–7. doi: [10.1111/neup.12298](https://doi.org/10.1111/neup.12298) PMID: [26989005](https://pubmed.ncbi.nlm.nih.gov/26989005/)
6. Savva GM, Wharton SB, Ince PG, Forster G, Matthews FE, Brayne C; Medical Research Council Cognitive Function and Ageing Study. Age, neuropathology, and dementia. *N Engl J Med.* 2009; 360:2302–9. doi: [10.1056/NEJMoa0806142](https://doi.org/10.1056/NEJMoa0806142) PMID: [19474427](https://pubmed.ncbi.nlm.nih.gov/19474427/)
7. Arvanitakis Z, Capuano AW, Leurgans SE, Bennett DA, Schneider JA. Relation of cerebral vessel disease to Alzheimer's disease dementia and cognitive function in elderly people: a cross-sectional study. *Lancet Neurol.* 2016; 15:934–43. doi: [10.1016/S1474-4422\(16\)30029-1](https://doi.org/10.1016/S1474-4422(16)30029-1) PMID: [27312738](https://pubmed.ncbi.nlm.nih.gov/27312738/)
8. James BD, Wilson RS, Boyle PA, Trojanowski JQ, Bennett DA, Schneider JA. TDP-43 stage, mixed pathologies, and clinical Alzheimer's-type dementia. *Brain.* 2016; 139:2983–2993.
9. Schneider JA, Arvanitakis Z, Leurgans SE, Bennett DA. The neuropathology of probable Alzheimer disease and mild cognitive impairment. *Ann Neurol.* 2009; 66:200–8. doi: [10.1002/ana.21706](https://doi.org/10.1002/ana.21706) PMID: [19743450](https://pubmed.ncbi.nlm.nih.gov/19743450/)
10. Dodge HH, Zhu J, Woltjer R, et al; SMART data consortium. Risk of incident clinical diagnosis of Alzheimer's disease-type dementia attributable to pathology-confirmed vascular disease. *Alzheimers Dement.* 2016. E-pub ahead of print.
11. Brookmeyer R, Kawas CH, Abdallah N, Paganini-Hill A, Kim RC, Corrada MM. Impact of interventions to reduce Alzheimer's disease pathology on the prevalence of dementia in the oldest-old. *Alzheimers Dement.* 2016; 12:225–32. doi: [10.1016/j.jalz.2016.01.004](https://doi.org/10.1016/j.jalz.2016.01.004) PMID: [26900132](https://pubmed.ncbi.nlm.nih.gov/26900132/)
12. Matthews FE, Brayne C, Lowe J, McKeith I, Wharton SB, Ince P. Epidemiological pathology of dementia: attributable-risks at death in the Medical Research Council Cognitive Function and Ageing Study. *PLoS Med.* 2009; 6:e1000180. doi: [10.1371/journal.pmed.1000180](https://doi.org/10.1371/journal.pmed.1000180) PMID: [19901977](https://pubmed.ncbi.nlm.nih.gov/19901977/)
13. Boyle PA, Wilson RS, Yu L, Barr AM, Honer WG, Schneider JA, Bennett DA. Much of late life cognitive decline is not due to common neurodegenerative pathologies. *Ann Neurol.* 2013; 74:478–89. doi: [10.1002/ana.23964](https://doi.org/10.1002/ana.23964) PMID: [23798485](https://pubmed.ncbi.nlm.nih.gov/23798485/)

14. Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, et al. Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol*. 1988; 23:138–44. doi: [10.1002/ana.410230206](https://doi.org/10.1002/ana.410230206) PMID: [2897823](https://pubmed.ncbi.nlm.nih.gov/2897823/)
15. Sonnen JA, Santa Cruz K, Hemmy LS, Woltjer R, Leverenz JB, Montine KS, et al. Ecology of the aging human brain. *Arch Neurol*. 2011; 68:1049–56. doi: [10.1001/archneurol.2011.157](https://doi.org/10.1001/archneurol.2011.157) PMID: [21825242](https://pubmed.ncbi.nlm.nih.gov/21825242/)
16. Stephan BC, Matthews FE, et al. Alzheimer and vascular neuropathological changes associated with different cognitive States in a non-demented sample. *J Alzheimers Dis*. 2012; 29(2):309–18. doi: [10.3233/JAD-2011-110518](https://doi.org/10.3233/JAD-2011-110518) PMID: [22233761](https://pubmed.ncbi.nlm.nih.gov/22233761/)
17. Jack CR Jr, Wiste HJ, Weigand SD, Knopman DS, Vemuri P, Mielke MM, et al. Age, Sex, and APOE  $\epsilon$ 4 Effects on Memory, Brain Structure, and  $\beta$ -Amyloid Across the Adult Life Span. *JAMA Neurol*. 2015; 72:511–9. doi: [10.1001/jamaneurol.2014.4821](https://doi.org/10.1001/jamaneurol.2014.4821) PMID: [25775353](https://pubmed.ncbi.nlm.nih.gov/25775353/)
18. Yu L, Boyle PA, Segawa E, Leurgans S, Schneider JA, Wilson RS, Bennett DA. Residual decline in cognition after adjustment for common neuropathologic conditions. *Neuropsychology*. 2015; 29:335–43. doi: [10.1037/neu0000159](https://doi.org/10.1037/neu0000159) PMID: [25495832](https://pubmed.ncbi.nlm.nih.gov/25495832/)
19. Norton S, Matthews FE, Barnes DE, Yaffe K, Brayne C. Potential for primary prevention of Alzheimer's disease: an analysis of population-based data. *Lancet Neurol*. 2014; 13:788–94. doi: [10.1016/S1474-4422\(14\)70136-X](https://doi.org/10.1016/S1474-4422(14)70136-X) PMID: [25030513](https://pubmed.ncbi.nlm.nih.gov/25030513/)
20. Del Ser T, Hachinski V, Merskey H, Munoz DG. An autopsy-verified study of the effect of education on degenerative dementia. *Brain* 1999; 122:2309–2319 PMID: [10581224](https://pubmed.ncbi.nlm.nih.gov/10581224/)
21. EClipSE Collaborative Members., Brayne C, Ince PG, Keage HA, McKeith IG, Matthews FE, Polvikoski T, Sulkava R. Education, the brain and dementia: neuroprotection or compensation? *Brain*. 2010; 133:2210–6. doi: [10.1093/brain/awq185](https://doi.org/10.1093/brain/awq185) PMID: [20826429](https://pubmed.ncbi.nlm.nih.gov/20826429/)
22. Farfel JM, Nitrini R, Suemoto CK, et al. Very low levels of education and cognitive reserve: a clinicopathologic study. *Neurology*. 2013; 81:650–7 doi: [10.1212/WNL.0b013e3182a08f1b](https://doi.org/10.1212/WNL.0b013e3182a08f1b) PMID: [23873971](https://pubmed.ncbi.nlm.nih.gov/23873971/)
23. Valenzuela MJ, Matthews FE, Brayne C, et al. Multiple biological pathways link cognitive lifestyle to protection from dementia. *Biol Psychiatry*. 2012; 71:783–91. doi: [10.1016/j.biopsych.2011.07.036](https://doi.org/10.1016/j.biopsych.2011.07.036) PMID: [22055015](https://pubmed.ncbi.nlm.nih.gov/22055015/)
24. Iacono D, Marksbery WR, Gross M, Pletnikova O, Rudow G, Zandi P, Troncoso JC. The Nun study: clinically silent AD, neuronal hypertrophy, and linguistic skills in early life. *Neurology*. 2009 1; 73:665–73. doi: [10.1212/WNL.0b013e3181b01077](https://doi.org/10.1212/WNL.0b013e3181b01077) PMID: [19587326](https://pubmed.ncbi.nlm.nih.gov/19587326/)
25. Wilson RS, Nag S, Boyle PA, Hizez LP, Yu L, Buchman AS, Schneider JA, Bennett DA. Neural reserve, neuronal density in the locus ceruleus, and cognitive decline. *Neurology*. 2013; 80:1202–8. doi: [10.1212/WNL.0b013e3182897103](https://doi.org/10.1212/WNL.0b013e3182897103) PMID: [23486878](https://pubmed.ncbi.nlm.nih.gov/23486878/)
26. Buchman AS, Yu L, Boyle PA, Schneider JA, De Jager PL, Bennett DA. Higher brain BDNF gene expression is associated with slower cognitive decline in older adults. *Neurology*. 2016; 86:735–41. doi: [10.1212/WNL.0000000000002387](https://doi.org/10.1212/WNL.0000000000002387) PMID: [26819457](https://pubmed.ncbi.nlm.nih.gov/26819457/)