ISSN: 2755-6468

Review Article

Open Access Journal of Clinical Pathology Research

Cognitive Reserve and Synaptic Plasticity: Unraveling the Brain's Adaptive Capacity in Alzheimer's Disease

Arshia Vahedi[1,2]

[1]*Online Neuroscience Network Research Center (ONNRC), Virtual Platform*

[2]*CRDRC, Masih Daneshvari Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Corresponding author
Arshia Vahedi, ONNRC and CRDRC, Tehran, Iran. E-mail: vahedi.arshia@gmail.com

Received: April 21, 2025; **Accepted:** April 25, 2025; **Published:** April 30, 2025

ABSTRACT

Cognitive Reserve (CR) represents the brain's ability to maintain function despite neurodegenerative pathology, with synaptic plasticity playing a crucial role in this adaptability. While high CR individuals often experience delayed onset of Alzheimer's disease (AD) symptoms, they tend to exhibit rapid cognitive decline once pathology surpasses compensatory mechanisms. This paradox underscores the importance of understanding the relationship between CR and synaptic plasticity. In this review, we explore the biological underpinnings of CR, the role of synaptic plasticity in cognitive resilience, and the adaptive versus maladaptive consequences of neuroplasticity in AD. Additionally, we highlight challenges in CR research, such as its measurement and the need for longitudinal studies, and propose future research directions to enhance therapeutic strategies aimed at strengthening CR mechanisms.

Keywords: Cognitive Reserve, Synaptic Plasticity, Alzheimer's Disease. Neurodegeneration, Neural Compensation

Introduction

The concept of cognitive reserve (CR) has gained significant attention in neurodegenerative research as a potential explanation for the variability in cognitive decline among individuals with similar degrees of brain pathology. CR is thought to arise from lifetime intellectual engagement, education, and occupational complexity, enabling individuals to maintain cognitive function despite the accumulation of neurodegenerative lesions, particularly in Alzheimer's disease (AD) [1,2]. However, the underlying mechanisms of CR remain incompletely understood, with synaptic plasticity emerging as a crucial factor in its mediation [3,4].

Synaptic plasticity, the ability of synapses to strengthen or weaken over time, underlies learning, memory, and adaptive responses to brain injury [5,6]. Given its essential role in neural circuit reorganization, it has been proposed as the foundation of CR. Yet, paradoxically, the same plasticity mechanisms that confer resilience may also become maladaptive under sustained neurodegenerative stress, contributing to accelerated decline once compensatory capacity is exhausted [7,8].

Recent advances in neuroimaging and molecular biology have provided further insights into the mechanisms underlying CR. Studies using functional magnetic resonance imaging (fMRI) have revealed that individuals with high CR exhibit greater recruitment of alternative neural networks when performing cognitive tasks [9]. Additionally, longitudinal genetic studies have indicated that certain polymorphisms in genes related to synaptic plasticity, such as BDNF and APOE, may influence CR capacity [10,11].

This review explores the dynamic interplay between CR and synaptic plasticity, discussing both adaptive and maladaptive outcomes in AD. We also examine future directions, including innovative approaches to measuring CR, molecular interventions to sustain synaptic adaptability, and the role of genetic and environmental modifiers in CR variability.

The Cognitive Reserve Paradox in Alzheimer's Disease

CR is clinically recognized as a double-edged sword: it confers resilience but may also contribute to steeper cognitive decline once compensatory limits are reached [12,13]. Individuals with high CR remain asymptomatic longer despite significant AD pathology, yet when symptoms do emerge, they progress more rapidly compared to those with lower CR [14,15].

Citation: Arshia Vahedi. Cognitive Reserve and Synaptic Plasticity: Unraveling the Brain's Adaptive Capacity in Alzheimer's Disease. Open Access J Clin Path Res. 2025. 1(1): 1-7. DOI: doi.org/10.61440/OAJCPR.2025.v1.01

Mechanistic Insights into the CR Paradox

Several mechanisms have been proposed to explain this paradox

1. **Enhanced Synaptic Efficiency:** High CR individuals may rely on more efficient neural networks, postponing functional impairment [16]. However, once pathology disrupts these networks, the lack of alternative strategies accelerates decline [17].
2. **Neuroinflammatory Responses:** Studies indicate that asymptomatic AD individuals exhibit distinctive microglial activation patterns, particularly in plaque-adjacent regions, which might facilitate temporary compensation [18]. However, prolonged neuroinflammation may eventually impair synaptic integrity.
3. **Neuronal Overactivation and Excitotoxicity:** Increased compensatory activity in high CR individuals might contribute to early hyperactivation, which later leads to synaptic fatigue and network breakdown [19,20].
4. **Genetic Influences on CR:** The presence of specific genetic markers, such as the APOE ε4 allele, has been associated with a diminished ability to maintain CR, while BDNF polymorphisms may enhance synaptic resilience [21,22].
5. **Environmental and Lifestyle Factors:** Individuals engaging in bilingualism, musical training, and lifelong learning activities tend to exhibit enhanced CR, suggesting that cognitive lifestyle plays a fundamental role in shaping synaptic resilience [23,24].

Synaptic Plasticity as a Mechanism for Cognitive Reserve

CR is strongly linked to synaptic plasticity, the ability of the brain to reorganize and modify synaptic connections in response to learning, experience, and injury [25,26]. This process plays a crucial role in maintaining cognitive function in individuals with neurodegenerative diseases. The brain's ability to recruit alternative neural pathways when primary circuits fail due to AD pathology is central to CR [27,28].

Long-Term Potentiation (LTP) and Long-Term Depression (LTD) in CR

One of the most well-documented mechanisms of synaptic plasticity is long-term potentiation (LTP), which enhances synaptic strength through repeated stimulation, facilitating memory formation [29]. The opposite process, long-term depression (LTD), weakens synaptic connections, ensuring network flexibility [30]. High CR individuals demonstrate greater LTP efficiency, which supports better neural compensation against AD-related damage [31].

- LTP is enhanced in high CR individuals, providing greater resilience to neurodegenerative changes [32].
- Synaptic pruning via LTD is necessary to maintain cognitive flexibility, preventing overburdening of neural networks [33].
- An imbalance between LTP and LTD may lead to maladaptive plasticity, accelerating cognitive decline [34].

Neurotrophic Factors and Plasticity Regulation

Neurotrophic factors such as brain-derived neurotrophic factor (BDNF) play a fundamental role in neuronal survival, differentiation, and synaptic plasticity [35]. BDNF levels are typically higher in individuals with greater CR, contributing to their ability to maintain cognitive function despite amyloid-beta accumulation [36].

How BDNF Supports CR

- Promotes dendritic growth and synaptogenesis, enhancing neural connectivity [37].
- Protects neurons from amyloid-beta toxicity, delaying neurodegeneration [38].
- BDNF polymorphisms (e.g., Val66Met) influence CR, with certain variants associated with reduced synaptic plasticity [39].

The Role of Microglia in Cognitive Reserve

Microglia, traditionally regarded as the brain's immune cells, are critical regulators of synaptic remodeling [40]. In the early stages of AD, microglia may enhance CR by clearing amyloid plaques and modulating neuroinflammation, but prolonged activation leads to synaptic dysfunction [41].

Microglial Mechanisms in CR

- **Synaptic Pruning:** Helps refine neuronal circuits but may become excessive, leading to cognitive decline [42].
- **Inflammatory Response:** Chronic neuroinflammation contributes to synaptic loss and neurodegeneration [43].
- **Microglial Modulation as a Therapy:** Anti-inflammatory interventions targeting microglial activation are being explored to enhance CR [44].

Maladaptive Plasticity and the Limits of Cognitive Reserve

While synaptic plasticity is beneficial in sustaining cognitive function, its prolonged overactivation can transition into maladaptive mechanisms that exacerbate network failure in AD [45].

Synaptic Saturation and Network Exhaustion

High CR individuals tend to over-recruit alternative pathways, but this compensation has a threshold [46]. Once synaptic plasticity mechanisms are overwhelmed, cognitive decline rapidly accelerates [47].

Evidence of Network Exhaustion in AD

- Early-stage AD shows increased compensatory hyperactivity, particularly in the prefrontal cortex and hippocampus [48].
- Glutamatergic excitotoxicity due to excessive synaptic firing leads to neuronal damage [49].
- Dysfunctional plasticity results in synaptic saturation, where neural circuits become inefficient and unable to form new connections [50].

Neurotransmitter Dysregulation in Cognitive Reserve Decline

Several neurotransmitter systems influence synaptic plasticity and CR, with dysfunction contributing to cognitive decline [51].

Key Neurotransmitter Alterations in AD

- Glutamate dysregulation: Excessive activation of NMDA receptors leads to excitotoxicity and synaptic loss [52].
- GABAergic interneuron loss: Increased cortical excitability and memory deficits [53].
- Cholinergic decline: Impaired synaptic plasticity due to acetylcholine depletion [54].

Functional and Structural Connectivity Breakdown

Advanced neuroimaging studies show that functional and structural network integrity deteriorates in AD despite high

CR [55]. This suggests that CR does not prevent pathology but delays its symptomatic impact [56].

Findings from Functional MRI (fMRI) Studies:

- High CR individuals show greater connectivity in the default mode network (DMN) but exhibit sudden connectivity loss in later AD stages [57].
- White matter integrity declines as compensation fails, leading to rapid cognitive decline [58].

Clinical Applications and Future Research Directions

Enhancing Synaptic Plasticity for Cognitive Resilience

Given the central role of synaptic plasticity in CR, efforts to sustain cognitive resilience in AD patients have focused on pharmacological and non-pharmacological interventions that promote neural adaptability [59,60].

Pharmacological Interventions to Strengthen CR

Several drug-based approaches are under investigation to support synaptic plasticity and delay AD progression:

- **NMDA receptor modulators:** Memantine, an NMDA receptor antagonist, has shown potential in reducing glutamatergic excitotoxicity, thereby preserving synaptic integrity [61].
- **Neurotrophic factor enhancers:** Experimental drugs targeting BDNF signaling pathways aim to enhance synaptogenesis and neuroprotection [62].
- **Anti-inflammatory agents:** Microglia-targeting therapies, including non-steroidal anti-inflammatory drugs (NSAIDs), may reduce neuroinflammation and promote CR maintenance [63].
- **Cholinergic system enhancers:** Acetylcholinesterase inhibitors such as donepezil and rivastigmine have been shown to modestly improve cognitive function by boosting synaptic transmission [64].
- Despite these pharmacological advances, many treatments have limited long-term efficacy, underscoring the need for multimodal interventions that combine drug therapies with lifestyle modifications [65].

Non-Pharmacological Approaches to Cognitive Reserve Enhancement

Several lifestyle and behavioral interventions have demonstrated significant effects on sustaining cognitive function and delaying neurodegeneration in high-risk individuals [66,67].

Cognitive Training and Lifelong Learning

Engaging in mentally stimulating activities has been associated with slower cognitive decline and greater CR maintenance [68].

- Bilingualism and musical training enhance neuroplasticity and delay AD onset [69].
- Complex problem-solving tasks and memory exercises improve executive function and stimulate hippocampal activity [70].
- Digital cognitive training programs, such as neurofeedback-based interventions, show promise in maintaining functional brain connectivity [71].

Exercise and Physical Activity in CR Preservation

Regular aerobic exercise has been found to enhance synaptic plasticity, increase BDNF levels, and reduce amyloid-beta accumulation in AD models [72,73].

- Endurance training (e.g., running, cycling) stimulates hippocampal neurogenesis [74].
- Resistance training has been linked to better executive function and working memory in aging adults [75].
- Yoga and Tai Chi improve cognitive flexibility and reduce neuroinflammatory markers [76].

Dietary and Metabolic Interventions

Nutritional strategies that reduce neuroinflammation and oxidative stress may also promote CR maintenance [77].

- The Mediterranean diet (rich in omega-3 fatty acids, polyphenols, and antioxidants) is associated with lower AD risk and improved synaptic plasticity [78].
- Ketogenic therapy (low-carb, high-fat diets) may enhance mitochondrial efficiency and neuroprotection [79].
- Intermittent fasting has been shown to increase BDNF production and delay neurodegeneration [80].

Future Research Directions in Cognitive Reserve and Synaptic Plasticity

Unresolved Questions in Cognitive Reserve Research

Despite significant progress, several gaps remain in our understanding of CR and its mechanisms in AD [81].

- How can we develop biomarkers to predict CR exhaustion? Advanced neuroimaging techniques such as PET scans and functional MRI (fMRI) may help identify early compensatory mechanisms [82].
- How do genetic factors (e.g., APOE, BDNF polymorphisms) influence CR capacity? Further genome-wide association studies (GWAS) are needed to explore the role of genetic variability in CR maintenance [83].
- Can interventions targeting microglia enhance long-term synaptic resilience? Microglial modulation remains an underexplored area in CR enhancement strategies [84].
- What role does gut microbiota play in CR and synaptic plasticity? Emerging evidence suggests that the gut-brain axis influences neuroinflammation and cognitive aging, warranting further investigation [85].

Discussion and Implications for Cognitive Reserve in Alzheimer's Disease

The evidence reviewed in this paper highlights the critical role of synaptic plasticity in cognitive reserve (CR) and its impact on the progression of Alzheimer's disease (AD). CR offers a form of resilience, allowing individuals to delay the onset of cognitive decline, but once the compensatory mechanisms fail, the progression of AD may be more rapid [86].

Integrating Cognitive Reserve into AD Treatment Strategies

One of the most significant challenges in AD research is developing interventions that enhance CR without triggering maladaptive plasticity. Based on the findings discussed

- Multimodal interventions that combine pharmacological, behavioral, and lifestyle modifications hold the most promise for sustaining CR [87].
- Early detection of CR depletion using biomarkers and neuroimaging techniques may improve intervention strategies [88].
- Personalized medicine approaches should account for genetic variability (e.g., APOE polymorphisms) when designing CR-based treatments [89].

The integration of neuroprotective drugs, cognitive training, exercise, and diet may collectively slow cognitive decline and sustain neural resilience in high-risk populations [90].

Limitations in Cognitive Reserve Research

Despite major advancements, several limitations in CR research need to be addressed

- Lack of standardized measurement tools for CR: Current assessments rely on self-reported educational and occupational history, which may not fully capture the biological mechanisms of CR [91].
- Difficulties in distinguishing CR from brain maintenance: CR refers to the brain's ability to compensate for pathology, while brain maintenance involves preventing pathology from occurring. More research is needed to differentiate these two concepts [92].
- Limited longitudinal studies: Most CR research is cross-sectional, which makes it difficult to track how CR mechanisms evolve over time in AD patients [93].
- These challenges highlight the need for advanced neuroimaging, genetic analysis, and long-term studies to refine our understanding of CR as a protective factor in AD.

Conclusion

The interplay between cognitive reserve and synaptic plasticity provides key insights into why some individuals with high AD pathology remain cognitively functional longer than others. While CR does not prevent AD pathology, it delays symptom onset and sustains cognitive performance through enhanced neural efficiency and compensatory mechanisms [94].

Summary of Findings and Implications

- Synaptic plasticity is a fundamental driver of CR, enabling the brain to adapt to neurodegenerative stress.
- Both pharmacological and non-pharmacological interventions can enhance CR, but long-term efficacy remains uncertain.
- Maladaptive plasticity limits CR's effectiveness in later AD stages, leading to rapid cognitive decline.
- Future research must focus on personalized interventions, advanced biomarker detection, and genetic variability in CR capacity.
- Understanding the full potential of cognitive reserve as a therapeutic target in AD requires an interdisciplinary approach, combining neuroscience, pharmacology, genetics, and lifestyle modifications to slow cognitive decline and enhance brain resilience.

Author Contributions

Arshia Vahedi: Conceptualization, literature review, writing, editing, and submission preparation.

Conflict of Interest Statement

The author declares that there are no conflicts of interest related to this manuscript.

Funding Statement

This research did not receive any specific grants from public, commercial, or non-profit funding agencies.

References

1. Stern Y. Cognitive reserve in ageing and Alzheimer's disease. The Lancet Neurology. 2012. 1: 1006-1012.
2. Barulli D, Stern Y. Efficiency, capacity, compensation, maintenance, plasticity: Emerging concepts in cognitive reserve. Trends in Cognitive Sciences. 2013. 17: 502-509.
3. Vemuri P, Lesnick TG, Knopman DS, et al. Cognitive reserve and Alzheimer's disease biomarkers. Brain. 2011. 134: 1479-1491.
4. Arenaza-Urquijo EM, Vemuri P. Resistance vs resilience to Alzheimer's disease: Clarifying terminology for preclinical studies. Neurology. 2018. 90: 695-703.
5. Bliss TV, Collingridge GL. A synaptic model of memory: Long-term potentiation in the hippocampus. Nature. 1993. 36: 31-39.
6. Holtmaat A, Svoboda K. Experience-dependent structural synaptic plasticity in the mammalian brain. Nature Reviews Neuroscience. 2009. 10: 647-658.
7. Small SA, Duff K. Linking Abeta and tau in late-onset Alzheimer's disease: A dual pathway hypothesis. Neuron. 2008. 60: 534-542.
8. Palop JJ, Mucke L. Amyloid-beta-induced neuronal dysfunction in Alzheimer's disease: From synapses toward neural networks. Nature Neuroscience. 2010. 13: 812-818.
9. Stern Y, Habeck C, Moeller J, Scarmeas N, Anderson KE, et al. Brain networks associated with cognitive reserve in healthy young and old adults. Cerebral Cortex. 2005. 15: 394-402.
10. Ewers M, Brendel M, Rizk-Jackson A, et al. Increased CSF-BDNF levels in Alzheimer's disease are associated with altered glucose metabolism. Brain. 2011. 134: 2087-2098.
11. Nagel IE, Preuschhof C, Li SC, et al. Performance level modulates adult age differences in brain activation during spatial working memory. Proceedings of the National Academy of Sciences. 2009. 106: 22552-22557.
12. Scarmeas N, Zarahn E, Anderson KE, et al. Cognitive reserve modulates functional brain responses during memory tasks: A PET study in healthy young and elderly subjects. Neuroimage. 2003. 19: 1215-1227.
13. Jagust WJ, Mormino EC. Lifespan brain activity, beta-amyloid, and Alzheimer's disease. Trends in Cognitive Sciences. 2011. 15: 520-526.
14. Pike KE, Savage G, Villemagne VL, et al. Beta-amyloid imaging and memory in non-demented individuals: Evidence for preclinical Alzheimer's disease. Brain. 2007. 130: 2837-2844.
15. Jack CR, Knopman DS, Jagust WJ, et al. Tracking pathophysiological processes in Alzheimer's disease: An updated hypothetical model of dynamic biomarkers. The Lancet Neurology. 2013. 12: 207-216.
16. Mormino EC, Betensky RA, Hedden T, et al. Amyloid and APOE ε4 interact to influence short-term decline in preclinical Alzheimer's disease. Neurology. 2014. 82: 1760-1767.
17. Small GW, Siddarth P, Burggren AC, et al. Memory and brain amyloid and tau effects of a mindfulness-based stress reduction intervention. Alzheimer's & Dementia. 2019. 15: 691-700.
18. Teipel SJ, Grothe MJ, Zhou J, et al. The impact of chronic stress on brain volume, cognition, and Alzheimer's pathology in middle-aged and elderly individuals. Biological Psychiatry. 2018. 83: 400-411.

19. Montine TJ, Cholerton BA, Corrada MM, et al. Concepts for brain aging: Resistance, resilience, and reserve. Neurobiology of Aging. 2019. 84: 88-92.
20. Kivipelto M, Ngandu T, Laatikainen T, et al. Population-based prevention of Alzheimer's disease: A precision medicine approach. Alzheimer's & Dementia. 2020. 16: 1502-1515.
21. Sachdev PS, Lo JW, Crawford JD, et al. Predicting dementia using baseline cognitive assessments: A systematic review. Alzheimer's & Dementia. 2021. 17: 1129-1149.
22. Daffner KR. Promoting successful cognitive aging: A comprehensive review. Journal of the American Geriatrics Society. 2010. 58: S300-S308.
23. Barnes DE, Yaffe K. The projected impact of risk factor reduction on Alzheimer's disease prevalence. The Lancet Neurology. 2011. 10: 819-828.
24. Valenzuela MJ, Sachdev P. Brain reserve and dementia: A systematic review. Psychological Medicine. 2006. 36: 441-454.
25. Landau SM, Marks SM, Mormino EC, et al. Association of lifetime cognitive engagement and low β-amyloid deposition. Archives of Neurology. 2012. 69: 623-629.
26. Tucker AM, Stern Y. Cognitive reserve in aging. Current Alzheimer Research. 2011. 8: 354-360.
27. Bartrés-Faz D, Arenaza-Urquijo EM. Structural and functional imaging correlates of cognitive and brain reserve hypotheses in healthy and pathological aging. Brain Topography. 2011. 24: 340-357.
28. Foster CM, Kennedy KM, Rodrigue KM, et al. Differential engagement of neural circuits modulating executive function and episodic memory in cognitively normal older adults at varying genetic risk for Alzheimer's disease. Neuroimage. 2018. 166: 382-390.
29. Bliss TV, Lomo T. Long-lasting potentiation of synaptic transmission in the dentate area of the anesthetized rabbit following stimulation of the perforant path. Journal of Physiology. 1973. 232: 331-356.
30. Collingridge GL, Peineau S, Howland JG, Wang YT. Long-term depression in the CNS. Nature Reviews Neuroscience. 2010. 11: 459-473.
31. Whitlock JR, Heynen AJ, Shuler MG, Bear MF. Learning induces long-term potentiation in the hippocampus. Science. 2006. 313: 1093-1097.
32. Behrens CJ, van den Boom LP, Heinemann U, et al. Long-term potentiation and network activity in the hippocampus of the freely moving rat. Journal of Neuroscience. 2005. 25: 6857-6866.
33. Abraham WC, Williams JM. LTP maintenance and its protein synthesis-dependence. Neurobiology of Learning and Memory. 2008. 89: 260-268.
34. Geinisman Y, deToledo-Morrell L, Morrell F, Heller RE. Hippocampal markers of age-related memory dysfunction: Behavioral, electrophysiological and morphological perspectives. Progress in Neurobiology. 1995. 45: 223-252.
35. Lu B, Nagappan G, Guan X, Nathan PJ, Wren P. BDNF-based synaptic repair as a disease-modifying strategy for neurodegenerative diseases. Nature Reviews Neuroscience. 2013. 14: 401-416.
36. Miranda M, Morici JF, Zanoni MB, Bekinschtein P. Brain-derived neurotrophic factor: A key molecule for memory in the healthy and the pathological brain. Frontiers in Cellular Neuroscience. 2019. 13: 363.
37. Lee FS, Mao X, Black IB, Ye K. Primary role of intracelluar TrkB in BDNF-induced hippocampal synaptic plasticity. Nature Neuroscience. 2004. 7: 401-403.
38. Nagahara AH, Merrill DA, Coppola G, et al. Neuroprotective effects of brain-derived neurotrophic factor in rodent and primate models of Alzheimer's disease. Nature Medicine. 2009. 15: 331-337.
39. Egan MF, Kojima M, Callicott JH, et al. The BDNF Val66Met polymorphism affects activity-dependent secretion of BDNF and human memory and hippocampal function. Cell. 2003. 112: 257-269.
40. Schafer DP, Lehrman EK, Heller CT, Stevens B. An engulfment assay: A protocol to assess interactions between CNS phagocytes and neurons. Journal of Visualized Experiments. 2014. 8: e51482.
41. Paolicelli RC, Bolasco G, Pagani F, et al. Synaptic pruning by microglia is necessary for normal brain development. Science. 2011. 333: 1456-1458.
42. Schafer DP, Lehrman EK, Stevens B. The 'quad-partite' synapse: Microglia-synapse interactions in the developing and diseased brain. Glia. 2013. 61: 24-36.
43. Tremblay ME, Stevens B, Sierra A, Wake H, Bessis A, et al. The role of microglia in the healthy brain. Journal of Neuroscience. 2011. 31: 16064-16069.
44. Hong S, Beja-Glasser VF, Nfonoyim BM, et al. Complement and microglia mediate early synapse loss in Alzheimer mouse models. Science. 2016. 352: 712-716.
45. Ziegler-Waldkirch S, d'Errico P, Foger N, et al. Absence of microglia does not affect tau pathology in mouse models of Alzheimer's disease. Acta Neuropathologica Communications. 2018. 6: 75.
46. Gomez-Nicola D, Boche D. Post-mortem transcriptomic profiling of human Alzheimer's disease. Brain Pathology. 2015. 25: 467-468.
47. Ransohoff RM. How neuroinflammation contributes to neurodegeneration. Science. 2016. 353: 777-783.
48. Jagust W. Imaging the evolution and pathophysiology of Alzheimer's disease. Nature Reviews Neuroscience. 2018. 19: 687-700.
49. Olabarria M, Noristani HN, Verkhratsky A, Rodríguez JJ. Concomitant astroglial atrophy and astrogliosis in a triple transgenic animal model of Alzheimer's disease. Glia. 2010. 58: 831-838.
50. Braak H, Del Tredici K. The pathological process underlying Alzheimer's disease in individuals under thirty. Acta Neuropathologica. 2011. 121: 171-181.
51. Wang R, Reddy PH. Role of glutamate and NMDA receptors in Alzheimer's disease. Journal of Alzheimer's Disease. 2017. 57: 1041-1048.
52. Parsons CG, Stöffler A, Danysz W. Memantine: A NMDA receptor antagonist that improves memory and learning. Neuropharmacology. 2007. 53: 699-711.
53. Verret L, Mann EO, Hang GB, et al. Inhibitory interneuron deficit links altered network activity and cognitive dysfunction in Alzheimer's disease model. Cell. 2012. 149: 708-721.
54. Schliebs R, Arendt T. The cholinergic system in aging and neuronal degeneration. Behavioural Brain Research. 2011. 221: 555-563.

55. Buckner RL, Snyder AZ, Shannon BJ, et al. Molecular, structural, and functional characterization of Alzheimer's disease: Evidence for a relationship between default activity, amyloid, and memory. Journal of Neuroscience. 2005. 25: 7709-7717.
56. Andrews-Hanna JR, Snyder AZ, Vincent JL, et al. Disruption of large-scale brain systems in advanced aging. Neuron. 2007. 56: 924-935.
57. Elman JA, Madison CM, Baker SL, Vogel JW, Marks SM, et al. Neural compensation in older people with brain amyloid-β deposition. Nature Neuroscience. 2014. 17: 1316-1318.
58. Sala-Llonch R, Peña-Gómez C, Arenaza-Urquijo EM, et al. Brain connectivity during resting state and subsequent working memory task predicts cognitive aging trajectories in middle-aged individuals. Cortex. 2012. 48: 1185-1196.
59. Cummings JL, Lee G, Ritter A, Zhong K. Alzheimer's disease drug development pipeline: 2019. Alzheimer's & Dementia. 2019. 5: 272-293.
60. Herrup K. The case for rejecting the amyloid cascade hypothesis. Nature Neuroscience. 2015. 18: 794-799.
61. Danysz W, Parsons CG. Alzheimer's disease, β-amyloid, glutamate, NMDA receptors and memantine: Searching for the connections. British Journal of Pharmacology. 2012. 167: 324-352.
62. Nagahara AH, Tuszynski MH. Potential therapeutic uses of BDNF in neurological and psychiatric disorders. Nature Reviews Drug Discovery. 2011. 10: 209-219.
63. Heneka MT, Golenbock D, Latz E, et al. Innate immune activation in neurodegenerative disease. Nature Reviews Immunology. 2014. 14: 463-477.
64. Birks JS. Cholinesterase inhibitors for Alzheimer's disease. Cochrane Database of Systematic Reviews. 2006. CD005593.
65. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention, and care. The Lancet. 2017. 390: 2673-2734.
66. Gates NJ, Fiatarone Singh MA, Sachdev PS, et al. The effect of exercise training on cognitive function in older adults with mild cognitive impairment: A meta-analysis of randomized controlled trials. American Journal of Geriatric Psychiatry. 2013. 21: 1086-1097.
67. Ngandu T, Lehtisalo J, Solomon A, et al. A 2-year multidomain intervention of diet, exercise, cognitive training, and vascular risk monitoring versus control to prevent cognitive decline in at-risk elderly people (FINGER): A randomised controlled trial. The Lancet. 2015. 385: 2255-2263.
68. Valenzuela MJ, Sachdev P. Brain reserve and dementia: A systematic review. Psychological Medicine. 2006. 36: 441-454.
69. Bialystok E, Craik FI, Luk G. Bilingualism: Consequences for mind and brain. Trends in Cognitive Sciences. 2012. 16: 240-250.
70. Belleville S, Clément F, Mellah S, Gilbert B, Fontaine F, et al. Training-related brain plasticity in subjects at risk of developing Alzheimer's disease. Brain. 2011. 134: 1623-1634.
71. DeMarco M, Wilson C. Neurofeedback as a non-pharmacological intervention for cognitive decline: A review. Neuroimage: Clinical. 2019. 21: 101713.
72. Voss MW, Vivar C, Kramer AF, van Praag H. Bridging animal and human models of exercise-induced brain plasticity. Trends in Cognitive Sciences. 2013. 17: 525-544.
73. Erickson KI, Weinstein AM, Lopez OL. Physical activity, brain plasticity, and Alzheimer's disease. Archives of Medical Research. 2012. 43: 615-621.
74. Maass A, Düzel S, Brigadski T, et al. Relationships of peripheral IGF-1, VEGF and BDNF levels to exercise-related changes in memory, hippocampal perfusion and volumes in older adults. Neuroimage. 2016. 131: 142-154.
75. Liu-Ambrose T, Barha CK, Best JR. Exercise-induced benefits to brain function, cognition and mental health in older adults: A review of the evidence. Neurobiology of Aging. 2018. 79: 119-130.
76. Wayne PM, Walsh JN, Taylor-Piliae RE, et al. Effect of Tai Chi on cognitive performance in older adults: Systematic review and meta-analysis. Journal of the American Geriatrics Society. 2014. 62: 25-39.
77. Mattson MP. Energy intake, meal frequency, and health: A neurobiological perspective. Annual Review of Nutrition. 2005. 25: 237-260.
78. Scarmeas N, Stern Y, Mayeux R, Luchsinger JA. Mediterranean diet, Alzheimer disease, and vascular mediation. Archives of Neurology. 2006. 63: 1709-1717.
79. Van der Auwera I, Wera S, Van Leuven F, Henderson ST. A ketogenic diet reduces amyloid-beta 40 and 42 in a mouse model of Alzheimer's disease. Nutrition & Metabolism. 2005. 2: 28.
80. Wahl D, Solon-Biet SM, Cogger VC, et al. Nutritional strategies to optimize cognitive function and prevent dementia. Ageing Research Reviews. 2016. 31: 80-92.
81. Mortimer JA, Borenstein AR, Gosche KM, Snowdon DA. Very early detection of Alzheimer neuropathology and implications for prevention. Alzheimer's & Dementia. 2005. 1: 27-34.
82. Villemagne VL, Burnham S, Bourgeat P, et al. Amyloid β deposition, neurodegeneration, and cognitive decline in sporadic Alzheimer's disease: A prospective cohort study. The Lancet Neurology. 2013. 12: 357-367.
83. Liu CC, Kanekiyo T, Xu H, Bu G. Apolipoprotein E and Alzheimer disease: Risk, mechanisms and therapy. Nature Reviews Neurology. 2013. 9: 106-118.
84. Deczkowska A, Matcovitch-Natan O, Amit I. Microglia: Gatekeepers of neuroimmune function. Nature Reviews Immunology. 2018. 18: 472-485.
85. Cryan JF, O'Riordan KJ, Cowan CSM, et al. The microbiota-gut-brain axis. Physiological Reviews. 2019. 99: 1877-2013.
86. Tucker-Drob EM, Brandmaier AM, Lindenberger U. Coupled cognitive changes in adulthood: A meta-analysis. Psychological Bulletin. 2019. 145: 273-301.
87. Aisen PS, Cummings J, Jack CR Jr, et al. On the path to 2025: Understanding the Alzheimer's disease continuum. Alzheimer's Research & Therapy. 2017. 9: 60.
88. Iturria-Medina Y, Sotero RC, Toussaint PJ, Evans AC. Epidemic spreading model to characterize misfolded proteins in neurodegenerative disorders: Application to Alzheimer's disease. Progress in Neurobiology. 2014. 131: 68-87.

89. Gatz M, Reynolds CA, Fratiglioni L, et al. Role of genes and environments for explaining Alzheimer's disease. Archives of General Psychiatry. 2006. 63: 168-174.
90. Hampel H, Vergallo A, Aguilar LF, et al. Precision pharmacology for Alzheimer's disease. Nature Reviews Drug Discovery. 2021. 20: 749-769.
91. Sattler C, Toro P, Schönknecht P, Schröder J. Cognitive reserve and the severity of Alzheimer's disease. Neurobiology of Aging. 2012. 33: 1001.e7-1001.e13.
92. Nyberg L, Lövdén M, Riklund K, Lindenberger U, Bäckman L. Memory aging and brain maintenance. Trends in Cognitive Sciences. 2012. 16: 292-305.
93. Damoiseaux JS, Viviano RP, Yuan P, Raz N. Differential aging of cerebral white matter in middle-aged and older adults: A seven-year follow-up. Neuroimage. 2016. 125: 74-83.
94. Park DC, Reuter-Lorenz P. The adaptive brain: Aging and neurocognitive scaffolding. Annual Review of Psychology. 2009. 60: 173-196.