THE GERONTOLOGICAL SOCIETY OF AMERICA®

Journals of Gerontology: Biological Sciences
cite as: *J Gerontol A Biol Sci Med Sci*, 2016, Vol. 71, No. 1, 13–20
doi:10.1093/gerona/glv206
Advance Access publication November 20, 2015

OXFORD

Perspective

Recent Developments in Understanding Brain Aging: Implications for Alzheimer's Disease and Vascular Cognitive Impairment

Ferenc Deak, Willard M. Freeman, Zoltan Ungvari, Anna Csiszar, and William E. Sonntag

Reynolds Oklahoma Center on Aging, Donald W. Reynolds Department of Geriatric Medicine, University of Oklahoma Health Sciences Center.

Address correspondence to William E. Sonntag, PhD, Reynolds Oklahoma Center on Aging, 975 NE 10th Street, SLY-BRC 1303, University of Oklahoma Health Sciences Center, Oklahoma City, OK 73104. Email: william-sonntag@ouhsc.edu

Received July 15, 2015; Accepted October 22, 2015

Decision Editor: Rafael de Cabo, PhD

Abstract

As the population of the Western world is aging, there is increasing awareness of age-related impairments in cognitive function and a rising interest in finding novel approaches to preserve cerebral health. A special collection of articles in *The Journals of Gerontology: Biological Sciences and Medical Sciences* brings together information of different aspects of brain aging, from latest developments in the field of neurodegenerative disorders to cerebral microvascular mechanisms of cognitive decline. It is emphasized that although the cellular changes that occur within aging neurons have been widely studied, more research is required as new signaling pathways are discovered that can potentially protect cells. New avenues for research targeting cellular senescence, epigenetics, and endocrine mechanisms of brain aging are also discussed. Based on the current literature it is clear that understanding brain aging and reducing risk for neurological disease with age requires searching for mechanisms and treatment options beyond the age-related changes in neuronal function. Thus, comprehensive approaches need to be developed that address the multiple, interrelated mechanisms of brain aging. Attention is brought to the importance of maintenance of cerebromicrovascular health, restoring neuroendocrine balance, and the pressing need for funding more innovative research into the interactions of neuronal, neuroendocrine, inflammatory and microvascular mechanisms of cognitive impairment, and Alzheimer's disease.

Key Words: Brain aging—Alzheimer's disease—Cerebrovasculature

The aging of human populations is a critical challenge to health care systems and age-related changes in cognitive ability are of particular importance. For aging subjects who experience cognitive impairment, the reduction in function can be disabling and affects social interactions, independence, and health span. Currently, a large percentage of the otherwise healthy population older than 60 years is affected by learning and memory impairments. Importantly, many age-related conditions including obesity, hypertension, and diabetes interact with age to exacerbate impairments in learning and memory. The number of individuals affected by cognitive decline is expected to rise considerably as the aging population increases imparting a significant socioeconomic impact to the country. Although studies suggest that age-related cognitive decline may be reversible, the etiology remains unknown, preventing the development of effective therapeutic interventions.

The general consensus in the field is that brain aging and the resulting cognitive impairments are not the result of changes in a single factor but rather are the consequence of multiple interacting cellular and molecular events. The cellular changes that occur within neurons and glia have been widely studied but these cells also require an intact cerebrovasculature as well as factors within the circulation including key nutrients, trophic factors, and substrates that are

necessary for normal function. Here we present an update on recent key studies into the mechanisms of brain aging with an emphasis on several articles published in *Journals of Gerontology* that are part of the exciting developments in the field.

Cognitive Decline and Neurodegeneration in Aging

Age-related cognitive decline has multiple underlying causes but most of the current efforts are focused on advancing diagnosis, progression, and therapy for Alzheimer's disease (AD) that is the primary cause for dementia in the elderly adults. Highlights from this field noted below illustrate the current trends.

Alzheimer's Disease: Variable Results From Clinical Trials and the Shift in Focus to Prevention and Early Diagnosis

The failure of clinical trials based on gamma secretase inhibitors (1), antibodies to amyloid (2), and other drugs targeted toward amyloid precursor protein processing (eg, R-flurbiprofen (3)) represented an important finding in the field and focused attention on early intervention. Two recent trials of solanezumab, a humanized monoclonal antibody that binds to the soluble form of beta amyloid (Aβ), failed to show significant improvement in primary outcome measures in mild-to-moderate Alzheimer disease (2). Importantly, when results from the pooled mild AD population were combined, there was a 34% reduction in the rate of decline in the Alzheimer's Disease Assessment Scale (ADAS-Cog14) and Mini-Mental State Examination (MMSE) scores in the solanezumab treatment group versus placebo (4). Although plasma levels of both Aβ1–40 and Aβ1–42 rose many hundredfolds in the treated group compared with the placebo group, no statistically significant improvement was seen in the pooled moderate AD cases with solanezumab treatment. Other monoclonal anti-Abeta antibodies undergoing clinical testing had also been evaluated for safety. For instance, anti-Aβ mAb GSK933776 administered intravenously at doses of 1–6 mg increased total amyloid and Abeta42 levels in plasma and cerebrospinal fluid (CSF) (5). GSK933776 exhibited a favorable safety profile in the Phase I trial with no brain edema or hemorrhage in the 18 patients tested. Also, bapineuzumab, a humanized monoclonal antibody directed against amyloid β was associated with enhanced amyloid-related magnetic resonance imaging abnormalities due to hemosiderin deposition (ARIA-H) that appears to be related to impaired vascular integrity (6). In their study Arrighi et al. (6) concluded that presence of the apolipoprotein (APOE) ε4 allele or preexisting hemosiderin deposition, as well as treatment with bapineuzumab and use of antithrombotic agents increased risk for ARIA-H, probably resulting from loss of integrity of cerebral vessels due to amyloid burden. In addition, a Phase II trial of a promising inhibitor of the beta-site amyloid precursor protein-cleaving enzyme (BACE1, LY2886721) was suspended due to liver toxicity. It was suggested that the liver toxicity was not simply an off-target effect of the drug but rather a specific effect of BACE inhibition at sites other than the brain (7). An important conclusion that has emerged from all these studies is that better clinical trial designs are urgently needed to measure protection from cognitive decline and that intervention early during the disease process is necessary because most trials focus on very advanced (late) stage AD patients creating a "treatment versus prevention dilemma" (8).

Early diagnosis of AD in the general population requires that assays be developed using reliable biomarkers in plasma. A recent study independently confirmed that a decrease in circulating Aβ42/Aβ40 occurs in patients with AD and is inversely correlated with neocortical amyloid burden. Although inflammatory and renal function covariates undoubtedly influenced plasma Aβ levels during the 18 months of this study, the overall conclusion was that plasma Aβ42 decreased in subjects with established mild cognitive impairment (MCI) and in those transitioning to MCI (9). In another study, three (3) candidate CSF biomarkers that reflect AD pathology were assessed: amyloid-beta, total tau protein (t-tau), and tau protein phosphorylated at AD-specific epitopes (p-tau) (10). These markers were useful in supporting the AD diagnosis and have predictive value for AD when patients experience MCI. In addition, De Leon et al. (11) conclude that the combined use of conventional imaging (magnetic resonance imaging or fluorodeoxyglucose-positron emission tomography) with selected CSF biomarkers can incrementally contribute to an early and specific diagnosis of AD. 231P-tau offers diagnostic specificity for AD and the levels of 231P-tau, but not t-tau, are consistently elevated in AD when compared to controls or those with fronto-temporal dementia, Lewy body dementia, or vascular dementia patients (12). Although the usefulness of circulating biomarkers in the diagnosis of memory impairment and dementia is still debated, the Food and Drug Administration indicated that further research would be required before the effect of an intervention on a single biomarker alone could be considered an adequate surrogate measure for AD or used to approve a candidate drug for early AD (13).

The suspected gender differences in dementia risk and AD prognosis acquired more validation. Results from the Framingham study indicated that women have twice the remaining lifetime risk of AD and dementia than men at the age of 65 years (14). New reports from the Alzheimer's Disease Neuroimaging Initiative (ADNI) conclude that annual cortical atrophy rates were faster in women than in men (15) and correlated with amyloid-beta and tau changes in CSF and with ApoE4 allele status. In another study cognitive abilities of women with MCI declined twice as fast as men's (16) with contribution of female gender being equal to the effect of ApoE4. In another study, Banks et al. (17) investigated the importance of adiposity as a contributing factor in AD and concluded that brain levels of amyloid precursor protein were more closely related to body weight and serum levels of gastrointestinal hormones than to brain weight, chronological age, or cytokine levels. This research complements previous findings indicating that increased levels of C-reactive protein and interleukin-6 (both associated with body fat) contribute to increased risk of all-cause dementia (18). For more results from the ADNI study we refer to the recently published excellent review (19) summarizing key findings in the field.

Novel pathways have been recently associated with risk of cognitive impairment and AD. The process of endocytosis was implicated in amyloidogenesis and AD risk using multiple genetic and functional studies (20–26). Repressor element 1-silencing transcription factor (REST; also known as neuron-restrictive silencer factor, NRSF) was originally described as a master negative regulator of neurogenesis that represses neuronal gene transcription in non-neuronal cells (27). In an elegant article Lu et al. (28) provided evidence for increased expression of REST in the aging brain

and data showing that Wnt/beta-catenin signaling may contribute to the induction of REST in the ageing brain. REST effectively repressed amyloidogenesis and cell death-associated genes and thus its normal function might be neuroprotective. Indeed, REST levels in specific hippocampal and other neuron populations in human brain correlated with memory and longevity. In accordance with this view cultured neurons lacking REST expression were more vulnerable than control neurons to oxidative stress induced cell death and degeneration induced by incubation with toxic amyloid oligomers (28). Importantly, they described an almost total absence of REST in the nuclei of neurons from AD patients. Interestingly, low-density lipoprotein receptor-related protein 6 (lrp6) was determined to be an essential co-receptor for Wnt signaling and genetic variants in this gene were also associated with AD risk (29,30). Using a novel lrp6 knockout mouse, lrp6 deletion resulted in a marked increase in amyloid production and memory impairments with age (31). Based on these studies, age-related changes in the Wnt-lrp6-REST pathway appear to be a promising area for further investigation.

Important findings also have been reported related to mitochondrial dysfunction and the regulation of NAD levels (32). Mitochondrial impairments have been implicated in AD since it was reported that Aβ oligomers interfere with the physiological function of the mitochondrial protein, drp1 (also known as dynamin1-like, DNM1L). Importantly, drp1 mediates mitochondrial and peroxisomal division (33,34). In the presence of Aβ oligomers, drp1 is activated leading to aberrant mitochondrial fission (35,36), which can be prevented by GSK3beta inhibition (37). These studies suggest that Aβ oligomers, in addition to their other known actions (38), may regulate mitochondrial dysfunction and thus impair neuronal metabolism.

Alternative Approaches to Prevent and Treat Cognitive Impairment, Intranasal Insulin, and Cognitive Function

AD and aging are associated with insulin resistance in the brain (39). Recently clinical trials have been conducted demonstrating that intranasal insulin may improve both memory performance and metabolic integrity of the brain in patients suffering from AD or MCI (40–42). These articles discuss the results of intranasal insulin studies and suggest possible molecular pathways through which insulin is able to improve memory and learning processes in both cognitively healthy and impaired humans. Importantly, insulin signaling pathways were shown to prevent Aβ oligomer toxicity (43). It is noteworthy that intranasal insulin treatment may act to modulate neuronal calcium dependent after-hyperpolarization as reported by Maimaiti et al. (44). Their results suggest that the after-hyperpolarization may be a novel cellular target of insulin in the brain that could have a role in improved cognitive performance following intranasal insulin therapy.

Combined approaches to prevent and treat cognitive impairment in the elderly adults are illustrated by the findings of Garcia-Mesa et al. (45). These investigators report a substantial protective effect of physical exercise in the 3xTg mouse model of AD. Voluntary wheel running from 12 to 15 months of age lowered elevated reactive oxygen species and it was suggested that oxidative stress was a central event in the disease process, which correlated with AD-like pathology and anxiety, apathy, and cognitive loss that occurs with progression of the disease. Although the study corroborates the importance of redox mechanisms in the neuroprotective effect of physical exercise, additional studies need to be undertaken to examine the specific functional improvements that occur in response to exercise.

Cognitive Training

Computer-based memory and attention training methods have been reported to improve episodic memory in patients with MCI, but the long-term effect has not been well studied. In a review of the neural networks rehabilitated by current cognitive training methods and those affected in AD, researchers suggest that a consistent training-related increase in brain activity occurs in the medial temporal, prefrontal, and posterior default mode networks, as well as an increase in gray matter structure in the fronto-parietal and entorhinal regions (46,47). The type of activation pattern described above was independent of that observed in healthy older adults (46), suggesting that cognitive training in persons at risk of developing AD could improve compensatory mechanisms and partially restore function. Evidently, changes in neuronal networks may be result of functional changes of individual neurons induced by aging or neurodegeneration but more studies are required to close the knowledge gap between human magnetic resonance imaging and PET trials and in vitro cellular experiments.

Epilepsy and Dementia—Deep Brain Stimulation as a Possible Therapeutic Approach

Interesting insight about the role of human cortical networks in learning and memory were reported from seven subjects undergoing epilepsy surgery with implantation of intracranial electrodes (48) followed by a spatial learning task. Entorhinal stimulation applied while the subjects were learning specific landmarks enhanced their memory of these locations. Direct hippocampal stimulation was not effective. In a Phase I trial, deep brain stimulation of the fornix/hypothalamic area in six patients for 6–12 months reversed impairments in glucose metabolism and slowed cognitive decline (49,50). Based on these results, further investigation of deep brain stimulation to treat memory deficits is warranted.

Neuroepigenetics

A new avenue for understanding the regulation of brain aging, neuroepigenetics, has continued to develop as a field (51). Neuroepigenetics includes studies of regulation of gene expression at the genomic level without changes in DNA sequence, namely histone and DNA modifications, that are key regulators of genomic structure and gene expression (52). Recent studies suggest that DNA methylation at specific sites in the genome may be a quantitative biological-marker of aging (53–55). These recent reports received considerable attention in the research community and DNA methylation may be a quantifiable endpoint for studies of anti-aging therapies. More broadly, age-related changes in DNA methylation may contribute to susceptibility/risk for a wide range of age-related diseases (56,57).

Recent studies of note include the finding that centenarians may have a slower rate of neuroepigenetic aging (58). Additionally, in a detailed study, one of the first examples of regulation of age-related neuroinflammation by DNA methylation levels points to the wide range of studies to be performed to understand the potentially central role of the neuroepigenome in aging (59). With the relative youth of this field a great deal of phenomenological work remains to be performed to understand the effects of aging on specific cell types in the central nervous system (60,61) and the field

will be driven by rapid advances in technology designed to analyze the epigenome (62,63).

Cerebrovascular Aging

The brain vasculature has consistently been an under-investigated area of brain aging. Although the brain comprises only about 2% of body mass, it receives close to 20% of total cardiac output. The high metabolic needs of the brain, which relies heavily on oxidative metabolism, require an immense network of microvessels with a total length of approximately 600 km. The cerebral microcirculation is not only responsible for delivering oxygen and nutrients used for metabolism in the brain, but also for the wash-out of toxic by-products, providing an appropriate ionic milieu for neuronal function and water and solute transport from the blood into the brain parenchyma. Due to the key role of the cerebral microcirculation in preservation of brain health, there is increasing research into the role of age-related structural and functional alterations in the cerebral microcirculation in brain aging (26,64–76).

Previous studies demonstrate that aging impairs endothelial angiogenic capacity (77–81) and promotes structural alterations in the cerebral microcirculation, which include cerebromicrovascular rarefaction (67,82,83). Microvascular rarefaction in the hippocampus has been causally linked to decreased performance in hippocampally dependent behavioral tests (84). Importantly, microvascular endothelial cells represent the largest endocrine organ in the body, secreting a wide range of growth factors and cytokines, which regulate the function of perivascular cells. A prominent example is the recently discovered role of microvascular endothelial cells in maintenance of neurogenic niches (85). Aging is known to alter the secretory phenotype of endothelial cells (77,80), and promote pro-inflammmatory phenotypic changes in the microvascular endothelium, which likely contribute to age-related neuroinflammation (86).

Endothelial cells also produce highly diffusible gaseotransmitters, including nitric oxide, which regulate a number of cellular functions, including mitochondrial biogenesis, in neighboring cells (87). Microvascular endothelial dysfunction and impaired bioavailability of nitric oxide have been well documented in the aged cerebro-microcirulation (86,88), offering important new directions for future studies exploring age-related changes in brain metabolism. Furthermore, the cerebromicrovascular endothelial cells are a key component of the blood brain barrier, and recent studies provide evidence that disruption of the blood brain barrier occurs both in humans (71) and experimental animals (76,83). Blood brain barrier disruption has been proposed to have a pathophysiological role in neurodegeneration (73,89,90). Therefore, additional studies are warranted to elucidate the molecular mechanisms responsible for the age-related breakdown of blood brain barrier integrity, its functional consequences and develop therapeutic approaches targeting the blood brain barrier for the preservation of brain health.

Blood flow through the microcirculation is tightly regulated by complex, interacting mechanisms. The key regulatory paradigms include: (i) cerebral pressure autoregulation, which maintains a constant flow in the presence of changing cerebral perfusion pressure, and (2) neuro-vascular/glio-vascular coupling, which adjusts local blood flow to changes in neuronal activity in a moment-to-moment manner. There is increasing evidence that adaptation of cerebral autoregulation to high pressure is compromised in aging (65,83), which likely has an important role in exacerbating the deleterious pathophysiological effects of hypertension in aging (64,83,91) and the development of microvascular injury, including cerebral microhemorrhages (65). Recent studies also demonstrate that aging leads to profound neurovascular dysregulation (88,92,93), characterized by impaired cerebral blood flow responses induced by synaptic activity. Age-related impairment of neurovascular coupling mechanisms is also manifest in elderly patients (94–96) and has been causally linked to the decline in higher cortical functions including cognition (97,98). Also, there is increasing evidence linking neurovascular uncoupling to cognitive impairment (99). Recent evidence suggests that the aging-induced decrease in neurovascular coupling can be restored by pharmacological interventions (88), offering a potential target for pharmacological interventions to promote brain health in the elderly patients. Restoration of a key homeostatic mechanism matching energy supply with the needs of active neuronal tissue is expected to have beneficial effects on multiple aspects of brain function (17,100–114) in aging.

The glymphatic system, formed by astroglial cells, is a recently (re)-discovered paravascular waste clearance system in the brain that facilitates convective exchange of water and soluble contents (including macromolecules) between CSF and the interstitial fluid compartment (115–117). There is growing evidence that the glymphatic system significantly contributes to neurotoxic protein waste removal, including clearance of β-amyloid, from the brain (116). In addition to β-amyloid clearance, the glymphatic system also facilitates transport of nutrients, lipids, hormones, growth factors, and neuromodulators in the brain parenchyma (118). Recent studies demonstrate that advancing age in laboratory rodents is associated with a dramatic decline in clearance of intraparenchymally injected β-amyloid from the brain (119), raising the possibility that impaired glymphatic clearance contributes to the pathogenesis of AD.

Age-related alterations of the cerebral circulation, ranging from subclinical microvascular alterations and impaired glymphatic clearance to full-blown dementia, will eventually affect every individual. Yet, studies investigating cerebromicrovascular aging are chronically underfunded. One can only hope that with recent evidence emerging that sporadic AD is primarily a vascular rather than a neurodegenerative disorder (73), research into age-related cerebromicrovascular pathophysiological alterations will receive more attention. Indeed, epidemiological studies demonstrate that practically all risk factors for AD have a vascular component that reduces cerebral perfusion, that hypertension exacerbates development of AD both in animal models and humans (68) and that AD patients exhibit cerebral microvascular pathologies before cognitive and neurodegenerative alterations.

Endocrine Circulating Factors

There is a long history of research demonstrating that alterations in circulating factors can influence cognitive function. Increased levels of glucocorticoids have been shown to impair learning and memory and are the mediator for the effects of increased stress on cognitive impairment (120). In addition, there are substantial data that circulating insulin-like growth factor-1 (IGF-1) regulates learning and memory and that the loss of IGF-1 with age contributes to cognitive decline (121). Many of the actions of IGF-1 are compounded by alterations of paracrine or local IGF-1 secretion and in some cases loss of circulating IGF-1 results in an increase in paracrine IGF-1 levels that compensate for the changes in circulating hormone levels. This is best seen in models of growth hormone deficiency induced in utero and has led to confusion related to the "beneficial" effects of IGF-1 deficiency in specific models that were indeed not deficient in IGF-1 (121). IGF-1

appears to have a wide range of actions on the brain. Direct effects of IGF-1 on neurons, astrocytes, and endothelial cells have been reported and the most recent data suggest that IGF-1 effects cerebrovascular autoregulation and neurovascular coupling that are critical for the regulation of cognitive function (66,122,123). Although the role of circulating endocrine factors in the maintenance of learning and memory processes have been recognized for several decades, only recently have the molecular mechanisms been studied. Investigations into the actions of IGF-1 already have provided an improved understanding of brain aging and the pathways that are capable of improving function. Additional studies are likely to improve our understanding of brain aging and result in the genesis of novel interventions.

In addition to modulating glucocorticoids and IGF-1 levels, recent data indicate that heterochronic parabiosis, or the joining of a blood supply between young an old animals, is capable of reversing several age-related functional impairments. This procedure includes the rescue of muscle function after damage (124) as well as neurogenesis in the aged brain (125–128). Although there is controversy related to the specific circulating factors that are altered in the parabiots, a recent study indicates that beta-2 microglobulin increases with age and that parabiosis lowers levels of this factor in the older animals, resulting in a "rejuvenated" phenotype. These are important findings and the investigators support their conclusions by showing increases in beta-2 microglobulin in the human population and improved cognitive function of aged animals with a beta-2 microglobulin genetic knockout. These results provide important insight into the interactions between immune and cognitive function. Nevertheless, the heterochronic parabiosis model is highly complex and issues related to nonspecific stress and the exchange of other endocrine factors that naturally occur in the model have not been resolved. Importantly, the levels of thyroid hormones, IGF-1, and glucocorticoids in these models have not been reported and it is likely that multiple mechanisms contribute to restoration of function.

Conclusions

Based on the current studies, it is clear that our understanding of brain aging in general and neurological diseases associated with age are progressing at a rapid pace. Nevertheless, many challenges remain. For clinical studies, early detection and diagnosis of neurological disease are paramount for the assessment of interventions that can delay or perhaps even prevent AD. This will require the continued development of biomarkers that predict disease onset and progression. Studies of the basic mechanisms of brain aging have provided new insights into the critical inter-relationship between neurons, glia, and the cerebrovasculature as well as the role of circulating factors that regulate brain function. In addition, the evolving field of neuroepigenetics is likely to provide key information that addresses the basic mechanisms of aging. As noted in the beginning of this overview, there is not a single cause of brain aging. Nevertheless, research over the next several years are likely to provide further insights into the multiple mechanisms of brain aging and generate novel interventions that improve the health of the aging population.

Funding

This work was supported by grants from the American Heart Association (to A.C. and Z.U.), the National Center for Complementary and Alternative Medicine (R01-AT006526 to Z.U.), the National Institutes of Health (R01-AG047879 to A.C., R01-AG038747 to W.E.S., R01-NS056218 to A.C. and W.E.S.), the Arkansas Claude Pepper Older Americans Independence Center at University of Arkansas Medical Center P30 AG028718, the Oklahoma Center for the Advancement of Science and Technology (to A.C., Z.U., F.D., and W.M.F.), the Presbyterian Health Foundation and COMAA (to F.D.), and the Donald W. Reynolds Foundation.

References

1. Golde TE, Koo EH, Felsenstein KM, Osborne BA, Miele L. gamma-Secretase inhibitors and modulators. *Biochim Biophys Acta*. 2013;1828:2898–2907. doi:10.1016/j.bbamem.2013.06.005
2. Doody RS, Thomas RG, Farlow M, et al. Phase 3 trials of solanezumab for mild-to-moderate Alzheimer's disease. *N Engl J Med*. 2014;370:311–321. doi:10.1056/NEJMoa1312889
3. Galasko DR, Graff-Radford N, May S, et al. Safety, tolerability, pharmacokinetics, and Abeta levels after short-term administration of R-flurbiprofen in healthy elderly individuals. *Alzheimer Dis Assoc Disord*. 2007;21:292–299.
4. Siemers ER, Sundell KL, Carlson C, et al. Phase 3 solanezumab trials: Secondary outcomes in mild Alzheimer's disease patients. *Alzheimers Dement*. 2015. doi:10.1016/j.jalz.2015.06.1893
5. Andreasen N, Simeoni M, Ostlund H, et al. First administration of the Fc-attenuated anti-beta amyloid antibody GSK933776 to patients with mild Alzheimer's disease: a randomized, placebo-controlled study. *PLoS One*. 2015;10:e0098153. doi:10.1371/journal.pone.0098153
6. Arrighi HM, Barakos J, Barkhof F, et al. Amyloid-related imaging abnormalities-haemosiderin (ARIA-H) in patients with Alzheimer's disease treated with bapineuzumab: a historical, prospective secondary analysis. *J Neurol Neurosurg Psychiatry*. 2015 pii: jnnp-2014-309493. doi:10.1136/jnnp-2014-309493
7. Lahiri DK, Maloney B, Long JM, Greig NH. Lessons from a BACE1 inhibitor trial: off-site but not off base. *Alzheimers Dement*. 2014;10(5 Suppl):S411–S419. doi:10.1016/j.jalz.2013.11.004
8. Golde TE, Schneider LS, Koo EH. Anti-aβ therapeutics in Alzheimer's disease: the need for a paradigm shift. *Neuron*. 2011;69:203–213. doi:10.1016/j.neuron.2011.01.002
9. Rembach A, Faux NG, Watt AD, et al. Changes in plasma amyloid beta in a longitudinal study of aging and Alzheimer's disease. *Alzheimers Dement*. 2014;10:53–61. doi:10.1016/j.jalz.2012.12.006
10. Randall C, Mosconi L, de Leon M, Glodzik L. Cerebrospinal fluid biomarkers of Alzheimer's disease in healthy elderly. *Front Biosci* 2013;18:1150–1173.
11. de Leon MJ, Mosconi L, Blennow K, et al. Imaging and CSF studies in the preclinical diagnosis of Alzheimer's disease. *Ann N Y Acad Sci*. 2007;1097:114–145. doi:10.1196/annals.1379.012
12. Hampel H, Burger K, Pruessner JC, et al. Correlation of cerebrospinal fluid levels of tau protein phosphorylated at threonine 231 with rates of hippocampal atrophy in Alzheimer disease. *Arch Neurol*. 2005;62:770–773. doi:10.1001/archneur.62.5.770
13. Kozauer N, Katz R. Regulatory innovation and drug development for early-stage Alzheimer's disease. *N Engl J Med*. 2013;368:1169–1171. doi:10.1056/NEJMp1302513
14. Seshadri S, Wolf PA, Beiser A, et al. Lifetime risk of dementia and Alzheimer's disease. The impact of mortality on risk estimates in the Framingham Study. *Neurology*. 1997;49:1498–1504.
15. Hua X, Hibar DP, Lee S, et al. Sex and age differences in atrophic rates: an ADNI study with n=1368 MRI scans. *Neurobiol Aging*. 2010;31:1463–1480. doi:10.1016/j.neurobiolaging.2010.04.033
16. Holland D, Desikan RS, Dale AM, McEvoy LK; Alzheimer's Disease Neuroimaging I. Higher rates of decline for women and apolipoprotein E epsilon4 carriers. *AJNR Am J Neuroradiol*. 2013;34:2287–2293. doi:10.3174/ajnr.A3601
17. Banks WA, Abrass CK, Hansen KM. Differentiating the influences of aging and adiposity on brain weights, levels of serum and brain cytokines, gastrointestinal hormones, and amyloid precursor protein. *J Gerontol A Biol Sci Med Sci*. 2014 doi:10.1093/gerona/glu100 [Epub ahead of print].

18. Koyama A, O'Brien J, Weuve J, Blacker D, Metti AL, Yaffe K. The role of peripheral inflammatory markers in dementia and Alzheimer's disease: a meta-analysis. *J Gerontol A Biol Sci Med Sci*. 2013;68:433–440. doi:10.1093/gerona/gls187
19. Weiner MW, Veitch DP, Aisen PS, et al. 2014 Update of the Alzheimer's disease neuroimaging initiative: a review of papers published since its inception. *Alzheimers Dement*. 2015;11:e1–e120. doi:10.1016/j.jalz.2014.11.001
20. Cirrito JR, Kang JE, Lee J, et al. Endocytosis is required for synaptic activity-dependent release of amyloid-beta in vivo. *Neuron*. 2008;58:42–51.
21. Harold D, Abraham R, Hollingworth P, et al. Genome-wide association study identifies variants at CLU and PICALM associated with Alzheimer's disease. *Nat Genet*. 2009;41:1088–1093.
22. Lambert JC, Heath S, Even G, et al. Genome-wide association study identifies variants at CLU and CR1 associated with Alzheimer's disease. *Nat Genet*. 2009;41:1094–1099. doi:10.1038/ng.439
23. Corneveaux JJ, Myers AJ, Allen AN, et al. Association of CR1, CLU and PICALM with Alzheimer's disease in a cohort of clinically characterized and neuropathologically verified individuals. *Hum Mol Genet*. 2010;19:3295–3301. doi:10.1093/hmg/ddq221
24. Kauwe JS, Cruchaga C, Karch CM, et al. Fine mapping of genetic variants in BIN1, CLU, CR1 and PICALM for association with cerebrospinal fluid biomarkers for Alzheimer's disease. *PLoS One*. 2011;6:e15918. doi:10.1371/journal.pone.0015918
25. Sevlever D, Zou F, Ma L, et al. Genetically-controlled vesicle-associated membrane protein 1 expression may contribute to Alzheimer's pathophysiology and susceptibility. *Mol Neurodegener*. 2015;10:18. doi:10.1186/s13024-015-0015-x
26. Zhao Z, Sagare AP, Ma Q, et al. Central role for PICALM in amyloid-beta blood-brain barrier transcytosis and clearance. *Nat Neurosci*. 2015;18:978–987. doi:10.1038/nn.4025
27. Schoenherr CJ, Anderson DJ. The neuron-restrictive silencer factor (NRSF): a coordinate repressor of multiple neuron-specific genes. *Science*. 1995;267:1360–1363.
28. Lu T, Aron L, Zullo J, et al. REST and stress resistance in ageing and Alzheimer's disease. *Nature*. 2014;507:448–454. doi:10.1038/nature13163
29. De Ferrari GV, Papassotiropoulos A, Biechele T, et al. Common genetic variation within the low-density lipoprotein receptor-related protein 6 and late-onset Alzheimer's disease. *Proc Natl Acad Sci U S A*. 2007;104:9434–9439. doi:10.1073/pnas.0603523104
30. Alarcon MA, Medina MA, Hu Q, et al. A novel functional low-density lipoprotein receptor-related protein 6 gene alternative splice variant is associated with Alzheimer's disease. *Neurobiol Aging*. 2013;34:1709.e9–1709.e18. doi:10.1016/j.neurobiolaging.2012.11.004
31. Liu CC, Tsai CW, Deák F, et al. Deficiency in LRP6-mediated Wnt signaling contributes to synaptic abnormalities and amyloid pathology in Alzheimer's disease. *Neuron*. 2014;84:63–77. doi:10.1016/j.neuron.2014.08.048
32. North BJ, Rosenberg MA, Jeganathan KB, et al. SIRT2 induces the checkpoint kinase BubR1 to increase lifespan. *EMBO J*. 2014;33:1438–1453. doi:10.15252/embj.201386907
33. De Felice FG, Velasco PT, Lambert MP, et al. Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. *J Biol Chem*. 2007;282:11590–11601.
34. Tay WM, Bryant JG, Martin PK, Nix AJ, Cusack BM, Rosenberry TL. A mass spectrometric approach for characterization of amyloid-β aggregates and identification of their post-translational modifications. *Biochemistry*. 2012;51:3759–3766. doi:10.1021/bi300316d
35. Cho DH, Nakamura T, Fang J, et al. S-nitrosylation of Drp1 mediates beta-amyloid-related mitochondrial fission and neuronal injury. *Science*. 2009;324:102–105. doi:10.1126/science.1171091
36. Manczak M, Calkins MJ, Reddy PH. Impaired mitochondrial dynamics and abnormal interaction of amyloid beta with mitochondrial protein Drp1 in neurons from patients with Alzheimer's disease: implications for neuronal damage. *Hum Mol Genet*. 2011;20:2495–2509. doi:10.1093/hmg/ddr139
37. Yan J, Liu XH, Han MZ, et al. Blockage of GSK3beta-mediated Drp1 phosphorylation provides neuroprotection in neuronal and mouse models of Alzheimer's disease. *Neurobiol Aging*. 2015;36:211–227. doi:10.1016/j.neurobiolaging.2014.08.005
38. Sheng M, Sabatini BL, Sudhof TC. Synapses and Alzheimer's disease. *Cold Spring Harb Perspect Biol*. 2012;4(5):371–388. doi:10.1101/cshperspect.a005777.
39. Watson GS, Craft S. The role of insulin resistance in the pathogenesis of Alzheimer's disease: implications for treatment. *CNS Drugs*. 2003;17:27–45. 170103 [pii]
40. Freiherr J, Hallschmid M, Frey WH II, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. *CNS Drugs*. 2013;27:505–514. doi:10.1007/s40263-013-0076-8
41. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. *Arch Neurol*. 2012;69:29–38. doi:10.1001/archneurol.2011.233
42. Morris JK, Burns JM. Insulin: an emerging treatment for Alzheimer's disease dementia? *Curr Neurol Neurosci Rep*. 2012;12:520–527. doi:10.1007/s11910-012-0297-0
43. De Felice FG, Vieira MN, Bomfim TR, et al. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. *Proc Natl Acad Sci U S A*. 2009;106:1971–1976.
44. Maimaiti S, Anderson KL, DeMoll C, et al. Intranasal insulin improves age-related cognitive deficits and reverses electrophysiological correlates of brain aging. *J Gerontol A Biol Sci Med Sci*. 2015 pii: glu314 [Epub ahead of print].
45. Garcia-Mesa Y, Colie S, Corpas R, et al. Oxidative stress is a central target for physical exercise neuroprotection against pathological brain aging. *J Gerontol A Biol Sci Med Sci*. 2015 pii: glv005 [Epub ahead of print].
46. Hampstead BM, Stringer AY, Stilla RF, et al. Activation and effective connectivity changes following explicit-memory training for face-name pairs in patients with mild cognitive impairment: a pilot study. *Neurorehabil Neural Repair*. 2011;25:210–222. doi:10.1177/1545968310382424
47. Hosseini SM, Kramer JH, Kesler SR. Neural correlates of cognitive intervention in persons at risk of developing Alzheimer's disease. *Front Aging Neurosci*. 2014;6:231. doi:10.3389/fnagi.2014.00231
48. Suthana N, Haneef Z, Stern J, et al. Memory enhancement and deep-brain stimulation of the entorhinal area. *N Engl J Med*. 2012;366:502–510. doi:10.1056/NEJMoa1107212
49. Laxton AW, Tang-Wai DF, McAndrews MP, et al. A phase I trial of deep brain stimulation of memory circuits in Alzheimer's disease. *Ann Neurol*. 2010;68:521–534. doi:10.1002/ana.22089
50. Laxton AW, Lipsman N, Lozano AM. Deep brain stimulation for cognitive disorders. *Handb Clin Neurol*. 2013;116:307–311. doi:10.1016/B978-0-444-53497-2.00025-5
51. Telese F. Keystone symposia on neuroepigenetics—bridging the gap between genome and behavior. *Neuroepigenetics*. 2015;2:9–12.
52. Spiegel AM, Sewal AS, Rapp PR. Epigenetic contributions to cognitive aging: disentangling mindspan and lifespan. *Learn Mem*. 2014;21:569–574. doi:10.1101/lm.033506.113
53. Hannum G, Guinney J, Zhao L, et al. Genome-wide methylation profiles reveal quantitative views of human aging rates. *Mol Cell*. 2013;49:359–367. doi:10.1016/j.molcel.2012.10.016
54. Horvath S. DNA methylation age of human tissues and cell types. *Genome Biol*. 2013;14:R115. doi:10.1186/gb-2013-14-10-r115
55. Weidner CI, Lin Q, Koch CM, et al. Aging of blood can be tracked by DNA methylation changes at just three CpG sites. *Genome Biol*. 2014;15:R24. doi:10.1186/gb-2014-15-2-r24
56. Johnson AA, Akman K, Calimport SR, Wuttke D, Stolzing A, de Magalhães JP. The role of DNA methylation in aging, rejuvenation, and age-related disease. *Rejuvenation Res*. 2012;15:483–494. doi:10.1089/rej.2012.1324
57. Waki H, Yamauchi T, Kadowaki T. The epigenome and its role in diabetes. *Curr Diab Rep*. 2012;12:673–685. doi:10.1007/s11892-012-0328-x
58. Horvath S, Mah V, Lu AT, et al. The cerebellum ages slowly according to the epigenetic clock. *Aging (Albany NY)*. 2015;7:294–306.
59. Cho SH, Chen JA, Sayed F, et al. SIRT1 deficiency in microglia contributes to cognitive decline in aging and neurodegeneration via epigenetic regulation of IL-1beta. *J Neurosci*. 2015;35:807–818. doi:10.1523/JNEUROSCI.2939-14.2015

60. Lister R, Mukamel EA, Nery JR, et al. Global epigenomic reconfiguration during mammalian brain development. *Science*. 2013;341:1237905. doi:10.1126/science.1237905
61. Kozlenkov A, Roussos P, Timashpolsky A, et al. Differences in DNA methylation between human neuronal and glial cells are concentrated in enhancers and non-CpG sites. *Nucleic Acids Res*. 2014;42:109–127. doi:10.1093/nar/gkt838
62. Zentner GE, Henikoff S. High-resolution digital profiling of the epigenome. *Nat Rev Genet*. 2014;15:814–827. doi:10.1038/nrg3798
63. Bock C. Analysing and interpreting DNA methylation data. *Nat Rev Genet*. 2012;13:705–719. doi:10.1038/nrg3273
64. Springo Z, Tarantini S, Toth P, et al. Aging exacerbates pressure-induced mitochondrial oxidative stress in mouse cerebral arteries. *J Gerontol A Biol Sci Med Sci*. 2015;70(11):1355–1359. doi:10.1093/gerona/glu244. Epub January 28, 2015.
65. Toth P, Tarantini S, Springo Z, et al. Aging exacerbates hypertension-induced cerebral microhemorrhages in mice: role of resveratrol treatment in vasoprotection. *Aging Cell*. 2015;14:400–408. doi:10.1111/acel.12315
66. Ungvari Z, Sonntag WE. Brain and cerebrovascular aging–new mechanisms and insights. *J Gerontol A Biol Sci Med Sci*. 2014;69:1307–1310. doi:10.1093/gerona/glu187
67. Tucsek Z, Toth P, Tarantini S, et al. Aging exacerbates obesity-induced cerebromicrovascular rarefaction, neurovascular uncoupling, and cognitive decline in mice. *J Gerontol A Biol Sci Med Sci*. 2014;69:1339–1352. doi:10.1093/gerona/glu080
68. Carnevale D, Mascio G, D'Andrea I, et al. Hypertension induces brain beta-amyloid accumulation, cognitive impairment, and memory deterioration through activation of receptor for advanced glycation end products in brain vasculature. *Hypertension*. 2012;60:188–197. doi:10.1161/HYPERTENSIONAHA.112.195511
69. Sagare AP, Bell RD, Zhao Z, et al. Pericyte loss influences Alzheimer-like neurodegeneration in mice. *Nat Commun*. 2013;4:2932. doi:10.1038/ncomms3932
70. Halliday MR, Rege SV, Ma Q, et al. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *J Cereb Blood Flow Metab*. 2015 doi:10.1038/jcbfm.2015.44 [Epub ahead of print].
71. Montagne A, Barnes SR, Sweeney MD, et al. Blood-brain barrier breakdown in the aging human hippocampus. *Neuron*. 2015;85:296–302. doi:10.1016/j.neuron.2014.12.032
72. Montagne A, Pa J, Zlokovic BV. Vascular plasticity and cognition during normal aging and dementia. *JAMA Neurol*. 2015;72:495–496. doi:10.1001/jamaneurol.2014.4636
73. Snyder HM, Corriveau RA, Craft S, et al. Vascular contributions to cognitive impairment and dementia including Alzheimer's disease. *Alzheimers Dement*. 2015;11:710–717. doi:10.1016/j.jalz.2014.10.008
74. Sweeney MD, Sagare AP, Zlokovic BV. Cerebrospinal fluid biomarkers of neurovascular dysfunction in mild dementia and Alzheimer's disease. *J Cereb Blood Flow Metab*. 2015;35:1055–1068. doi:10.1038/jcbfm.2015.76
75. Winkler EA, Nishida Y, Sagare AP, et al. GLUT1 reductions exacerbate Alzheimer's disease vasculo-neuronal dysfunction and degeneration. *Nat Neurosci*. 2015;18:521–530. doi:10.1038/nn.3966
76. Tucsek Z, Toth P, Sosnowska D, et al. Obesity in aging exacerbates blood-brain barrier disruption, neuroinflammation, and oxidative stress in the mouse hippocampus: effects on expression of genes involved in beta-amyloid generation and Alzheimer's disease. *J Gerontol A Biol Sci Med Sci*. 2014;69:1212–1226. doi:10.1093/gerona/glt177
77. Banki E, Sosnowska D, Tucsek Z, et al. Age-related decline of autocrine pituitary adenylate cyclase-activating polypeptide impairs angiogenic capacity of rat cerebromicrovascular endothelial cells. *J Gerontol A Biol Sci Med Sci*. 2015;70:665–674. doi:10.1093/gerona/glu116
78. Ungvari Z, Tucsek Z, Sosnowska D, et al. Aging-induced dysregulation of dicer1-dependent microrna expression impairs angiogenic capacity of rat cerebromicrovascular endothelial cells. *J Gerontol A Biol Sci Med Sci*. 2013;68:877–891. doi:10.1093/gerona/gls242
79. Csiszar A, Sosnowska D, Tucsek Z, et al. Circulating factors induced by caloric restriction in the nonhuman primate Macaca mulatta activate angiogenic processes in endothelial cells. *J Gerontol A Biol Sci Med Sci*. 2013;68:235–249. doi:10.1093/gerona/gls158
80. Csiszar A, Gautam T, Sosnowska D, et al. Caloric restriction confers persistent anti-oxidative, pro-angiogenic, and anti-inflammatory effects and promotes anti-aging miRNA expression profile in cerebromicrovascular endothelial cells of aged rats. *Am J Physiol Heart Circ Physiol*. 2014;307:H292–H306. doi:10.1152/ajpheart.00307.2014
81. Valcarcel-Ares MN, Gautam T, Warrington JP, et al. Disruption of Nrf2 signaling impairs angiogenic capacity of endothelial cells: implications for microvascular aging. *J Gerontol A Biol Sci Med Sci*. 2012;67:821–829. doi:10.1093/gerona/glr229
82. Lynch CD, Cooney PT, Bennett SA, et al. Effects of moderate caloric restriction on cortical microvascular density and local cerebral blood flow in aged rats. *Neurobiol Aging*. 1999;20:191–200. S0197458099000329 [pii]
83. Toth P, Tucsek Z, Sosnowska D, et al. Age-related autoregulatory dysfunction and cerebromicrovascular injury in mice with angiotensin II-induced hypertension. *J Cereb Blood Flow Metab*. 2013;33:1732–1742. doi:10.1038/jcbfm.2013.143
84. Riddle DR, Sonntag WE, Lichtenwalner RJ. Microvascular plasticity in aging. *Ageing Res Rev*. 2003;2:149–168. S1568163702000648 [pii]
85. Shen Q, Wang Y, Kokovay E, et al. Adult SVZ stem cells lie in a vascular niche: a quantitative analysis of niche cell-cell interactions. *Cell Stem Cell*. 2008;3:289–300. doi:10.1016/j.stem.2008.07.026
86. Ungvari Z, Kaley G, de Cabo R, Sonntag WE, Csiszar A. Mechanisms of vascular aging: new perspectives. *J Gerontol A Biol Sci Med Sci*. 2010;65:1028–1041. doi:10.1093/gerona/glq113
87. Nisoli E, Tonello C, Cardile A, et al. Calorie restriction promotes mitochondrial biogenesis by inducing the expression of eNOS. *Science*. 2005;310:314–317.
88. Toth P, Tarantini S, Tucsek Z, et al. Resveratrol treatment rescues neurovascular coupling in aged mice: role of improved cerebromicrovascular endothelial function and down-regulation of NADPH oxidas. *Am J Physiol Heart Circ Physiol*. 2014;306:H299–H308. doi:10.1152/ajpheart.00744.2013
89. Sagare AP, Bell RD, Zlokovic BV. Neurovascular defects and faulty amyloid-β vascular clearance in Alzheimer's disease. *J Alzheimers Dis*. 2013;33(suppl 1):S87–S100. doi:10.3233/JAD-2012-129037
90. Zlokovic BV. Neurodegeneration and the neurovascular unit. *Nat Med*. 2010;16:1370–1371. doi:10.1038/nm1210-1370
91. Csiszar A, Tucsek Z, Toth P, et al. Synergistic effects of hypertension and aging on cognitive function and hippocampal expression of genes involved in beta-amyloid generation and Alzheimer's disease. *Am J Physiol Heart Circ Physiol*. 2013;305:H1120–H1130. doi:10.1152/ajpheart.00288.2013
92. Park L, Anrather J, Girouard H, Zhou P, Iadecola C. Nox2-derived reactive oxygen species mediate neurovascular dysregulation in the aging mouse brain. *J Cereb Blood Flow Metab*. 2007;27:1908–1918. doi:10.1038/sj.jcbfm.9600491
93. Farkas E, Bari F. Spreading depolarization in the ischemic brain: does aging have an impact? *J Gerontol A Biol Sci Med Sci*. 2014;69:1363–1370. doi:10.1093/gerona/glu066
94. Zaletel M, Strucl M, Pretnar-Oblak J, Zvan B. Age-related changes in the relationship between visual evoked potentials and visually evoked cerebral blood flow velocity response. *Funct Neurol*. 2005;20:115–120. 893 [pii]
95. Topcuoglu MA, Aydin H, Saka E. Occipital cortex activation studied with simultaneous recordings of functional transcranial Doppler ultrasound (fTCD) and visual evoked potential (VEP) in cognitively normal human subjects: effect of healthy aging. *Neurosci Lett*. 2009;452:17–22.
96. Stefanova I, Stephan T, Becker-Bense S, Dera T, Brandt T, Dieterich M. Age-related changes of blood-oxygen-level-dependent signal dynamics during optokinetic stimulation. *Neurobiol Aging*. 2013;34:2277–2286. doi:10.1016/j.neurobiolaging.2013.03.031
97. Sorond FA, Hurwitz S, Salat DH, Greve DN, Fisher ND. Neurovascular coupling, cerebral white matter integrity, and response to cocoa in older people. *Neurology*. 2013;81:904–909. WNL.0b013e3182a351aa [pii]

98. Sorond FA, Kiely DK, Galica A, et al. Neurovascular coupling is impaired in slow walkers: the MOBILIZE Boston Study. *Ann Neurol*. 2011;70:213–220. doi: 10.1002/ana.22433
99. Tarantini S, Hertelendy P, Tucsek Z, et al. Pharmacologically-induced neurovascular uncoupling is associated with cognitive impairment in mice. *J Cereb Blood Flow Metab*. 2015;35(11):1871–1881. doi:10.1038/jcbfm.2015.162
100. Allali G, van der Meulen M, Beauchet O, Rieger SW, Vuilleumier P, Assal F. The neural basis of age-related changes in motor imagery of gait: an fMRI study. *J Gerontol A Biol Sci Med Sci*. 2014;69:1389–1398. doi:10.1093/gerona/glt207
101. Barak B, Feldman N, Okun E. Cardiovascular fitness and cognitive spatial learning in rodents and in humans. *J Gerontol A Biol Sci Med Sci*. 2015;70(9):1059–1066. doi:10.1093/gerona/glu162 [Epub September 16, 2014].
102. Buchman AS, Yu L, Wilson RS, Boyle PA, Schneider JA, Bennett DA. Brain pathology contributes to simultaneous change in physical frailty and cognition in old age. *J Gerontol A Biol Sci Med Sci*. 2014;69:1536–1544. doi:10.1093/gerona/glu117
103. Callisaya ML, Beare R, Phan T, et al. Progression of white matter hyperintensities of presumed vascular origin increases the risk of falls in older people. *J Gerontol A Biol Sci Med Sci*. 2015;70:360–366. doi:10.1093/gerona/glu148
104. Clark DJ, Christou EA, Ring SA, Williamson JB, Doty L. Enhanced somatosensory feedback reduces prefrontal cortical activity during walking in older adults. *J Gerontol A Biol Sci Med Sci*. 2014;69:1422–1428. doi:10.1093/gerona/glu125
105. Holtzer R, Epstein N, Mahoney JR, Izzetoglu M, Blumen HM. Neuroimaging of mobility in aging: a targeted review. *J Gerontol A Biol Sci Med Sci*. 2014;69:1375–1388. doi:10.1093/gerona/glu052
106. Kim DH, Grodstein F, Newman AB, et al. Prognostic implications of microvascular and macrovascular abnormalities in older adults: cardiovascular health study. *J Gerontol A Biol Sci Med Sci*. 2014;69:1495–1502. doi:10.1093/gerona/glu074
107. Makizako H, Liu-Ambrose T, Shimada H, et al. Moderate-intensity physical activity, hippocampal volume, and memory in older adults with mild cognitive impairment. *J Gerontol A Biol Sci Med Sci*. 2015;70:480–486. doi:10.1093/gerona/glu136
108. Masser DR, Bixler GV, Brucklacher RM, et al. Hippocampal subregions exhibit both distinct and shared transcriptomic responses to aging and nonneurodegenerative cognitive decline. *J Gerontol A Biol Sci Med Sci*. 2014;69:1311–1324. doi:10.1093/gerona/glu091
109. Montero-Odasso M, Oteng-Amoako A, Speechley M, et al. The motor signature of mild cognitive impairment: results from the gait and brain study. *J Gerontol A Biol Sci Med Sci*. 2014;69:1415–1421. doi:10.1093/gerona/glu155
110. Nadkarni NK, Nunley KA, Aizenstein H, et al. Association between cerebellar gray matter volumes, gait speed, and information-processing ability in older adults enrolled in the Health ABC study. *J Gerontol A Biol Sci Med Sci*. 2014;69:996–1003. doi:10.1093/gerona/glt151
111. Rosano C, Rosso AL, Studenski SA. Aging, brain, and mobility: progresses and opportunities. *J Gerontol A Biol Sci Med Sci*. 2014;69:1373–1374. doi:10.1093/gerona/glu159
112. Rosso AL, Sanders JL, Arnold AM, et al. Multisystem physiologic impairments and changes in gait speed of older adults. *J Gerontol A Biol Sci Med Sci*. 2015;70:319–324. doi:10.1093/gerona/glu176
113. Sakurai R, Fujiwara Y, Yasunaga M, et al. Regional cerebral glucose metabolism and gait speed in healthy community-dwelling older women. *J Gerontol A Biol Sci Med Sci*. 2014;69:1519–1527. doi:10.1093/gerona/glu093
114. VanSwearingen JM, Studenski SA. Aging, motor skill, and the energy cost of walking: implications for the prevention and treatment of mobility decline in older persons. *J Gerontol A Biol Sci Med Sci*. 2014;69:1429–1436. doi:10.1093/gerona/glu153
115. Iliff JJ, Lee H, Yu M, et al. Brain-wide pathway for waste clearance captured by contrast-enhanced MRI. *J Clin Invest*. 2013;123:1299–1309. doi:10.1172/JCI67677
116. Iliff JJ, Wang M, Liao Y, et al. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. *Sci Transl Med*. 2012;4:147ra111. doi:10.1126/scitranslmed.3003748
117. Iliff JJ, Wang M, Zeppenfeld DM, et al. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. *J Neurosci*. 2013;33:18190–18199. doi:10.1523/JNEUROSCI.1592-13.2013
118. Rangroo Thrane V, Thrane AS, Plog BA, et al. Paravascular microcirculation facilitates rapid lipid transport and astrocyte signaling in the brain. *Sci Rep*. 2013;3:2582. doi:10.1038/srep02582
119. Kress BT, Iliff JJ, Xia M, et al. Impairment of paravascular clearance pathways in the aging brain. *Ann Neurol*. 2014;76:845–861. doi:10.1002/ana.24271
120. Goosens KA, Sapolsky RM. Stress and glucocorticoid contributions to normal and pathological aging. In: Riddle DR, ed. *Brain Aging: Models, Methods, and Mechanisms*. *Frontiers in Neuroscience*. Boca Raton, FL: CRC Press; 2007.
121. Ashpole NM, Sanders JE, Hodges EL, Yan H, Sonntag WE. Growth hormone, insulin-like growth factor-1 and the aging brain. *Exp Gerontol*. 2015;68:76–81. doi:10.1016/j.exger.2014.10.002
122. Toth P, Tucsek Z, Tarantini S, et al. IGF-1 deficiency impairs cerebral myogenic autoregulation in hypertensive mice. *J Cereb Blood Flow Metab*. 2014;34:1887–1897. doi:10.1038/jcbfm.2014.156
123. Toth P, Tarantini S, Ashpole NM, et al. IGF-1 deficiency impairs neurovascular coupling in mice: implications for cerebromicrovascular aging. *Aging Cell*. 2015 doi:10.1111/acel.12372 [Epub ahead of print].
124. Sinha M, Jang YC, Oh J, et al. Restoring systemic GDF11 levels reverses age-related dysfunction in mouse skeletal muscle. *Science*. 2014;344:649–652. doi:10.1126/science.1251152
125. Katsimpardi L, Litterman NK, Schein PA, et al. Vascular and neurogenic rejuvenation of the aging mouse brain by young systemic factors. *Science*. 2014;344:630–634. doi:10.1126/science.1251141
126. Villeda SA, Luo J, Mosher KI, et al. The ageing systemic milieu negatively regulates neurogenesis and cognitive function. *Nature*. 2011;477:90–94. doi:10.1038/nature10357
127. Villeda SA, Plambeck KE, Middeldorp J, et al. Young blood reverses age-related impairments in cognitive function and synaptic plasticity in mice. *Nat Med*. 2014;20:659–663. doi:10.1038/nm.3569
128. Smith LK, He Y, Park JS, et al. beta2-microglobulin is a systemic pro-aging factor that impairs cognitive function and neurogenesis. *Nat Med*. 2015;21:932–937. doi:10.1038/nm.3898