COGNITIVE DECLINE & LANGUAGE (CDL): CUMULATIVE REFERENCES

认知退变及语言：参考文献汇编

Abstract: Cumulative Abstracts by Citation[1]

摘要：引文-摘要汇编

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A B C D E F G H I J .K L M N O P Q R S T U V W X Y Z

Abeliovich, A. and A. D. Gitler (2016). "Defects in trafficking bridge Parkinson's disease pathology and genetics." *Nature* **539**: 207-216. https://doi.org/10.1038/nature20414

Parkinson's disease is a debilitating, age-associated movement disorder. A central aspect of the pathophysiology of Parkinson's disease is the progressive demise of midbrain dopamine neurons and their axonal projections, but the underlying causes of this loss are unclear. Advances in genetics and experimental model systems have illuminated an important role for defects in intracellular transport pathways to lysosomes. The accumulation of altered proteins and damaged mitochondria, particularly at axon terminals, ultimately might overwhelm the capacity of intracellular disposal mechanisms. Cell-extrinsic mechanisms, including inflammation and prion-like spreading, are proposed to have both protective and deleterious functions in Parkinson's disease.

Abrahan, V. D., et al. (2019). "Cognitive benefits from a musical activity in older adults." *Frontiers in Psychology* **10**: 1-14 (article 652) https://doi.org/10.3389/fpsyg.2019.00652

The aging population is growing rapidly. Proposing interventions that enhance the cognitive functions or strategies that delay the onset of disabilities associated with age is a topic of capital interest for the biopsychosocial health of our species. In this work, we employed musical improvisation as a focal environmental activity to explore its ability to improve memory in older adults. We present two studies: the first one evaluated neutral memory using the Rey Complex Figure (RCF) and the second one evaluated emotional memory using International Affective Picture System (IAPS). A group of 132 volunteers, between the ages of 60 and 90, participated in this investigation. Fifty-one of them were musicians with more than 5 years of formal musical training. After acquisition of neutral (Study 1) or emotional (Study 2) information, the groups of older adults were exposed to music improvisation (experimental intervention) or music imitation (control intervention) for 3 min. We then evaluated memory through two tasks (free recall and recognition), by means of immediate and deferred measures (after a week). We found a significant improvement in memory among participants involved in music improvisation, who remembered more items of the RCF and images from IAPS than the imitation group, both in the immediate and deferred evaluation. On the other hand, participants who had musical knowledge had a better performance in neutral visual memory than non-musicians. Our results suggest that a focal musical activity can be a useful intervention in older adults to promote an enhancement in memory. (**Keywords**: cognitive reserve, musical strategy, improvisation, memory, aging)

Abulafia, C., et al. (2019). "Brain structural and amyloid correlates of recovery from semantic interference in cognitively normal individuals with or without family history of late-onset Alzheimer's disease." *Journal of Neuropsychiatry and Clinical Neurosciences* **31**(1): 25-36. https://doi.org/10.1176/appi.neuropsych.17120355

Failure to recover from proactive semantic interference (frPSI) has been shown to be more sensitive than traditional cognitive measures in different populations with preclinical Alzheimer's disease. The authors sought to characterize the structural and amyloid in vivo correlates of frPSI in cognitively normal offspring of patients with late-onset Alzheimer's disease (O-LOAD), compared with individuals without a family history of

1. For the complete author list of an article, see "Author Index by Citation." The citation style is based on revised style of APA 6th ed. from Endnote v.9.3. Abstracts are mainly from publishers of related publication.

neurodegenerative disorders (CS). The authors evaluated the LASSI-L, a test tapping frPSI and other types of semantic interference and delayed recall on the RAVLT, along with 3-T MRI volumetry and positron emission tomography Pittsburgh compound B, in 27 O-LOAD and 18 CS with equivalent age, sex, years of education, ethnicity, premorbid intelligence, and mood symptoms. Recovery from proactive semantic interference (frPSI) and RAVLT delayed recall were lower in O-LOAD cases. Structural correlates of both cognitive dimensions were different in CS and O-LOAD, involving brain regions concerned with autonomic, motor, and motivational control in the former, and regions traditionally implicated in Alzheimer's disease in the latter. Better recovery from retroactive semantic interference was associated with less amyloid load in the left temporal lobe in O-LOAD but not CS. In middle-aged cognitively normal individuals with one parent affected with LOAD, frPSI was impaired compared with persons without a family history of LOAD. The neuroimaging correlates of such cognitive measure in those with one parent with LOAD involve Alzheimer's-relevant brain regions even at a relatively young age. (**Keywords**: Alzheimer’s Disease, Cognitive Disorders, Imaging Techniques)

Abutalebi, J., et al. (2014). "Bilingualism protects anterior temporal lobe integrity in aging." *Neurobiology of Aging* **39**(5): 2126-2133. https://10.1016/j.neurobiolaging.2014.03.010

Cerebral gray-matter volume (GMV) decreases in normal aging but the extent of the decrease may be experience-dependent. Bilingualism may be one protective factor and in this article we examine its potential protective effect on GMV in a region that shows strong age-related decreases-the left anterior temporal pole. This region is held to function as a conceptual hub and might be expected to be a target of plastic changes in bilingual speakers because of the requirement for these speakers to store and differentiate lexical concepts in 2 languages to guide speech production and comprehension processes. In a whole brain comparison of bilingual speakers (n = 23) and monolingual speakers (n = 23), regressing out confounding factors, we find more extensive age-related decreases in GMV in the monolingual brain and significantly increased GMV in left temporal pole for bilingual speakers. Consistent with a specific neuroprotective effect of bilingualism, region of interest analyses showed a significant positive correlation between naming performance in the second language and GMV in this region. The effect appears to be bilateral though because there was a nonsignificantly different effect of naming performance on GMV in the right temporal pole. Our data emphasize the vulnerability of the temporal pole to normal aging and the value of bilingualism as both a general and specific protective factor to GMV decreases in healthy aging. (**Keywords**: Aging, Bilingualism, Language proficiency, Temporal pole (TP), Voxel based morphometry (VBM))

Addis, D. R., et al. (2014). "Age-related changes in prefrontal and hippocampal contributions to relational encoding." *NeuroImage* **84**: 19–26. https://doi.org/10.1016/j.neuroimage.2013.08.033

Age-related declines in relational encoding are well documented. It remains unclear, however, whether such declines reflect dysfunction of (1) ventrolateral prefrontal cortex (VLPFC) and deficient generation of associations and/or (2) hippocampal dysfunction and impoverished binding of associations. In order to separate VLPFC and hippocampal contributions to relational encoding, we manipulated the generative demands of the encoding task by varying the number of semantic associations between the to-be-encoded information (three words). Thus, trials with fewer semantic associations (lower-association trials) require more generative processing during encoding, relative to trials in which more semantic associations are provided for binding (higher-association trials). Parametric modulation analyses on successfully encoded items revealed that, unlike younger adults, older adults did not show an up-regulation of VLPFC activity during lower-association trials. In contrast, hippocampal activity in both older and younger adults was greater in higher- relative to lower-association trials. Moreover, recognition accuracy improved significantly in both groups with the provision of more semantic associations, indicating the both younger and older adults benefitted from this form of encoding support. Our findings suggest that left VLPFC dysfunction may underlie relational encoding deficits in older adults, but that when provided with associations to bind, hippocampal activity in older adults is comparable to young, consistent with their increased recognition accuracy under conditions of encoding support. (**Keywords**: Aging, Associative encoding, Episodic, Parametric modulation, fMRI)

Agosta, F., et al. (2009). "Language networks in semantic dementia." *Brain* **133**(Pt1**)**: 286-299. https://doi.org/10.1093/brain/awp233

Cognitive deficits in semantic dementia have been attributed to anterior temporal lobe grey matter damage; however, key aspects of the syndrome could be due to altered anatomical connectivity between language pathways involving the temporal lobe. The aim of this study was to investigate the left language-related cerebral pathways in semantic dementia using diffusion tensor imaging-based tractography and to combine the findings with cortical anatomical and functional magnetic resonance imaging data obtained during a reading activation task. The left inferior longitudinal fasciculus, arcuate fasciculus and fronto-parietal superior longitudinal fasciculus were tracked in five semantic dementia patients and eight healthy controls. The left uncinate fasciculus and the genu and splenium of the corpus callosum were also obtained for comparison with previous studies. From each tract, mean diffusivity, fractional anisotropy, as well as parallel and transverse diffusivities were obtained. Diffusion tensor imaging results were related to grey and white matter atrophy volume assessed by voxel-based morphometry and functional magnetic resonance imaging activations during a reading task. Semantic dementia patients had significantly higher mean diffusivity, parallel and transverse in the inferior longitudinal fasciculus. The arcuate and uncinate fasciculi demonstrated significantly higher mean diffusivity, parallel and transverse and significantly lower fractional anisotropy. The fronto-parietal superior longitudinal fasciculus was relatively spared, with a significant difference observed for transverse diffusivity and fractional anisotropy only. In the corpus callosum, the genu showed lower fractional anisotropy compared with controls, while no difference was found in the splenium. The left parietal cortex did not show significant volume changes on voxel-based morphometry and demonstrated normal functional magnetic resonance imaging activation in response to reading items that stress sublexical phonological processing. This study shows that semantic dementia is associated with anatomical damage to the major superior and inferior temporal white matter connections of the left hemisphere likely involved in semantic and lexical processes, with relative sparing of the fronto-parietal superior longitudinal fasciculus. Fronto-parietal regions connected by this tract were activated normally in the same patients during sublexical reading. These findings contribute to our understanding of the anatomical changes that occur in semantic dementia, and may further help to explain the dissociation between marked single-word and object knowledge deficits, but sparing of phonology and fluency in semantic dementia.

Ahmadlou, M., et al. (2014). "Complexity of functional connectivity networks in mild cognitive impairment subjects during a working memory task." *Clinical Neurophysiology* **125** (2014) 694–702. https://doi.org/10.1016/j.clinph.2013.08.033

The objective is to study the changes of brain activity in patients with mild cognitive impairment (MCI). Using magneto-encephalogram (MEG) signals, the authors investigate differences of complexity of functional connectivity network between MCI and normal elderly subjects during a working memory task. METHODS: MEGs are obtained from 18 right handed patients with MCI and 19 age-matched elderly participants without cognitive impairment used as the control group. The brain networks' complexities are measured by Graph Index Complexity (C(r)) and Efficiency Complexity (C(e)). RESULTS: The results obtained by both measurements show complexity of functional networks involved in the working memory function in MCI subjects is reduced at alpha and theta bands compared with subjects with control subjects, and at the theta band this reduction is more pronounced in the whole brain and intra left hemisphere. CONCLUSIONS: C(e) would be a better measurement for showing the global differences between normal and MCI brains compared with C(r). SIGNIFICANCE: The high accuracy of the classification shows C(e) at theta band can be used as an index for assessing deficits associated with working memory, a good biomarker for diagnosis of MCI. (**Keywords**: Complexity of functional connectivity networks, Efficiency Complexity, Graph Index Complexity, Magneto encephalography, Mild cognitive impairment, Working memory (**Comment in:** Global complexity and cognitive reserve in MCI. [Clin Neurophysiol. 2014])

Aine, C. J., et al. (2005). "Temporal dynamics of age-related differences in auditory incidental verbal learning." *Cognitive Brain Research* **24**(1): 1-18. https://doi.org/10.1016/j.cogbrainres.2004.10.024

Auditory response profiles for a group of ten healthy young and ten healthy elderly subjects, evoked by implicit memory and delayed verbal recognition tasks, were evaluated to determine if effects of stimulus repetition could be identified in the superior temporal gyrus (STG) and prefrontal cortical regions. We hypothesized that effects of stimulus repetition should occur both early in time and at early levels of the nervous system (STG) followed by later effects in prefrontal regions. Magnetoencephalographic (MEG) responses were recorded using a whole-head MEG system and automated, multi-start analysis methods were applied to the data in order to characterize the temporal response profiles from distributed but focal, cortical regions engaged in memory-related tasks. The findings revealed a main effect of age for early activity (similar to 50 ms) in STG which appeared to be nonspecific for Old/New words and an Age x Task interaction for late activity (similar to 100-800 ms) in STG which was specific to Old/New words. Although the behavioral performance measures did not reveal traditional effects of response priming, the MEG measures did reveal a reduction in amplitude with stimulus repetition in young subjects. The elderly did not reveal a reduction in amplitude concomitant with stimulus repetition for either the global attributes of words or for specific Old/New words. Long duration effects of stimulus repetition noted in the present study raise the possibility that results from sensory gating, mismatch negativity and P300 paradigms may represent a continuum of stimulus repetition effects. Two of these paradigms evoke greater enhancement to novel or infrequent stimuli, or rather, greater reduction of amplitude with repetition.

Alexander, W. (2014, July 16). The benefits of failing at French. *New York Times* 23. https://www.nytimes.com/2014/07/16/opinion/16alexander.html

Psycholinguists are divided on the answer, but they agree on several points. For starters, a 2-year-old's brain has a substantial neurological advantage, with 50 percent more synapses — the connections between neurons — than an adult brain, way more than it needs. This excess, which is an insurance policy against early trauma, is also crucial to childhood language acquisition, as is the plasticity, or adaptability, of the young brain. Once the "critical period" — the roughly six years of life during which the brain is wired for learning language — is over, the ability to acquire a first language is lost, as your brain frees up room for the other skills you'll need as you mature, such as the ability to kill a wild boar, or learn math, or operate your iPad. ... Last year researchers at the Chinese University of Hong Kong and Northwestern University in Illinois hypothesized that language study should prove beneficial for older adults, noting that the cognitive tasks involved — including working memory, inductive reasoning, sound discrimination and task switching — map closely to the areas of the brain that are most associated with declines due to aging. In other words, the things that make second-language acquisition so maddening for grown-ups are the very things that may make the effort so beneficial.

Alladi, S., et al. (2013). "Bilingualism delays age at onset of dementia, independent of education and immigration status." *Neurology* **81**(22): 1938-1944. https://doi.org/10.1212/01.wnl.0000436620.33155.a4

The purpose of the study was to determine the association between bilingualism and age at onset of dementia and its subtypes, taking into account potential confounding factors. Case records of 648 patients with dementia (391 of them bilingual) diagnosed in a specialist clinic were reviewed. The age at onset of first symptoms was compared between monolingual and bilingual groups. The influence of number of languages spoken, education, occupation, and other potentially interacting variables was examined. Overall, bilingual patients developed dementia 4.5 years later than the monolingual ones. A significant difference in age at onset was found across Alzheimer disease dementia as well as frontotemporal dementia and vascular dementia, and was also observed in illiterate patients. There was no additional benefit to speaking more than 2 languages. The bilingual effect on age at dementia onset was shown independently of other potential confounding factors such as education, sex, occupation, and urban vs rural dwelling of subjects. This is the largest study so far documenting a delayed onset of dementia in bilingual patients and the first one to show it separately in different dementia subtypes. It is the first study reporting a bilingual advantage in those who are illiterate, suggesting that education is not a sufficient explanation for the observed difference. The findings are interpreted in the context of the bilingual advantages in attention and executive functions. (**Glossary**: ACE-R 5 Addenbrooke's Cognitive Examination–

revised, AD 5 Alzheimer disease, CDR 5 Clinical Dementia Rating, DLB 5 dementia with Lewy bodies, FTD 5 frontotemporal dementia, GLM 5 general linear model, VaD 5 vascular dementia.) (Comment in: Bilingualism delays age at onset of dementia, independent of education and immigration status. [Neurology. 2014]. Author response. [Neurology. 2014] https://www.ncbi.nlm.nih.gov/pubmed/24198291)

Allen, J. S., et al. (2005a). "Normal neuroanatomical variation due to age: The major lobes and a parcellation of the temporal region." *Neurobiology of Aging* **26**(9): 1245-1260. https://doi.org/10.1016/j.neurobiolaging.2005.05.023

We used high-resolution MRI to investigate gray and white matter aging in the major lobes of the cerebrum (frontal, parietal, temporal, occipital) and the major sectors of the temporal lobe (temporal pole, superior temporal gyrus, infero-temporal region, parahippocampal gyrus, amygdala, hippocampus). Subjects included 87 adults between the ages of 22 and 88 years. Regions of interest were hand-traced on contiguous 1.5mm coronal slices. For the cerebrum in general, gray matter decreased linearly with age, resulting in a decline of about 9.1-9.8% between the ages of 30 and 70 years, and a decline of 11.3-12.3% by the age of 80. In contrast, white matter volume increased until the mid-50s, after which it declined at an accelerated rate. At 70 years, white matter volume was only 5.6-6.4% less than at 30 years, but by age 80, a cubic regression model predicted that the decrease would be 21.6-25.0%. Multivariate analyses indicate that the frontal gray matter was most strongly associated with age, while occipital gray and white matter were least associated. Reduction in volume in the hippocampus was best modeled by a cubic regression model rather than a linear model. No sex differences in aging were found for any regions of interest. (Comment in Changes in volume with age--consistency and interpretation of observed effects. [Neurobiol Aging. 2005])

Allen, J. S., et al. (2005b). "Aging brain: The cognitive reserve hypothesis and hominid evolution." *American Journal of Human Biology* **17**: 673-689. https://doi.org/10.1002/ajhb.20439

Compared to other primates, humans live a long time and have large brains. Recent theories of the evolution of human life history stages (grandmother hypothesis, intergenerational transfer of information) lend credence to the notion that selection for increased life span and menopause has occurred in hominid evolution, despite the reduction in the force of natural selection operating on older, especially post-reproductive, individuals. Theories that posit the importance (in an inclusive fitness sense) of the survival of older individuals require them to maintain a reasonably high level of cognitive function (e.g., memory, communication). Patterns of brain aging and factors associated with healthy brain aging should be relevant to this issue. Recent neuroimaging research suggests that, in healthy aging, human brain volume (gray and white matter) is well-maintained until at least 60 years of age cognitive function also shows only nonsignificant declines at this age. The maintenance of brain volume and cognitive performance is consistent with the idea of a significant post- or late-reproductive life history stage. A clinical model, "the cognitive reserve hypothesis," proposes that both increased brain volume and enhanced cognitive ability may contribute to healthy brain aging, reducing the likelihood of developing dementia. Selection for increased brain size and increased cognitive ability in hominid evolution may therefore have been important in selection for increased lifespan in the context of intergenerational social support networks. **(Comments in** "Apolipoprotein E Polymorphism and Neuronal Plasticity." [Am J Hum Biol 18:556–558 (2006)]

Alzheimer's Association & Wake Forest University Health Sciences. (2018-2023). "**U**.S. Study to protect brain health through lifestyle intervention to reduce risk (US POINTER**)**." Website: https://clinicaltrials.gov/ct2/show/NCT03688126

The purpose of this research study is to see if lifestyle changes can protect memory and thinking (cognition) as we age. A recent study in Finland found that a combination of physical and cognitive exercise, diet, and social activity protected cognitive function in healthy older adults who were at increased risk of significant memory loss. So far no medications can rival this positive outcome. The point of POINTER is to test if lifestyle change can also protect against memory loss in Americans. Detailed Description: Lifestyle interventions focused on combining healthy diet, physical activity, and social and intellectual challenges may represent a

promising therapeutic strategy to protect brain health. The recent results of the population-based 2-year clinical trial, Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), indicated that a multidomain intervention of physical activity, nutritional guidance, cognitive training, social activities, and management of heart health risk factors protected cognitive function in healthy older adults at increased risk of cognitive decline. As yet, there are no pharmacological treatment options that can rival this effect. Thus, there is an urgent need to expand this work to test the generalizability, adaptability and sustainability of its findings in diverse and global populations. This pivotal U.S. Study to Protect Brain Health through Lifestyle Intervention to Reduce Risk (U.S. POINTER) will test whether a similar 2-year intensive lifestyle intervention, adapted to American culture and delivered within the community, can protect cognitive function in older adults in the U.S. who are at increased risk for cognitive decline and dementia. If successful, the results of this study will have large-scale implications for public policy regarding standard of clinical care and prescriptive practices for a fast-growing and vulnerable population of older adults.

Alzheimer, A. (1995 [1907]). "An English translation of Alzheimer's 1907 paper, "uber eine eigenartige erkankung der hirnrinde" [On an unusual illness of the cerebral cortex]. Translated by Stelzmann, R. et al. *Clinical Anatomy* **8**: 429-431. https://doi.org/10.1002/ca.980080612

Although "Alzheimer's disease**" (AD)** has become the subject of innumerable publications with broad scientific, economic, and social ramifications, the original 1907 article is not readily available in Englsih and probably has never been read by more than a handful of authors who discuss AD every year. It seemed appropriate that a translation of Alzheimer's original paper with a brief comment on its historical perspective might be appropriate and useful to those involved in the neuroanatomy of dementia, especially since the story of dementias continues to advance on all fronts and since a large number of investigators are fast approaching an age when they will be expected to be increasingly concerned with dementia.

Anderson, N. D. and F. I. Craik (2017). "50 years of cognitive aging theory." *The Journals of Gerontology.* Series B, *Psychological Sciences and Social Sciences* **72**(1): 1-6. https://doi.org/10.1093/geronb/gbw108

The objectives of this Introduction to the Journal of Gerontology: Psychological Sciences special issue on "50 Years of Cognitive Aging Theory" are to provide a brief overview of cognitive aging research prior to 1965 and to highlight significant developments in cognitive aging theory over the last 50 years. METHOD: Historical and recent theories of cognitive aging were reviewed, with a particular focus on those not directly covered by the articles included in this special issue. RESULTS: Prior to 1965, cognitive aging research was predominantly descriptive, identifying what aspects of intellectual functioning are affected in older compared with younger adults. Since the mid-1960s, there has been an increasing interest in how and why specific components of cognitive domains are differentially affected in aging and a growing focus on cognitive aging neuroscience. DISCUSSION: Significant advances have taken place in our theoretical understanding of how and why certain components of cognitive functioning are or are not affected by aging. We also know much more now than we did 50 years ago about the underlying neural mechanisms of these changes. The next 50 years undoubtedly will bring new theories, as well as new tools (e.g., neuroimaging advances, neuromodulation, and technology), that will further our understanding of cognitive aging. (**Keywords**: Attention, Cognition, Cognitive neuroscience, Executive function, Language, Memory, Neuropsychology, Social cognition, Technology, Theory)

Anguera J.A, et al. (2013). "Video game training enhances cognitive control in older adults." *Nature* **501**: 97-101. https://doi.org/10.1038/nature12486

Cognitive control is defined by a set of neural processes that allow us to interact with our complex environment in a goal-directed manner. Humans regularly challenge these control processes when attempting to simultaneously accomplish multiple goals (multitasking), generating interference as the result of fundamental information processing limitations. It is clear that multitasking behaviour has become ubiquitous in today's technologically dense world, and substantial evidence has accrued regarding multitasking difficulties and

cognitive control deficits in our ageing population. Here we show that multitasking performance, as assessed with a custom-designed three-dimensional video game (NeuroRacer), exhibits a linear age-related decline from 20 to 79 years of age. By playing an adaptive version of NeuroRacer in multitasking training mode, older adults (60 to 85 years old) reduced multitasking costs compared to both an active control group and a no-contact control group, attaining levels beyond those achieved by untrained 20-year-old participants, with gains persisting for 6 months. Furthermore, age-related deficits in neural signatures of cognitive control, as measured with electroencephalography, were remediated by multitasking training (enhanced midline frontal theta power and frontal-posterior theta coherence). Critically, this training resulted in performance benefits that extended to untrained cognitive control abilities (enhanced sustained attention and working memory), with an increase in midline frontal theta power predicting the training-induced boost in sustained attention and preservation of multitasking improvement 6 months later. These findings highlight the robust plasticity of the prefrontal cognitive control system in the ageing brain, and provide the first evidence, to our knowledge, of how a custom-designed video game can be used to assess cognitive abilities across the lifespan, evaluate underlying neural mechanisms, and serve as a powerful tool for cognitive enhancement. (Abstract in Chinese translation, https://www.douban.com/group/topic/47872565/, accessed on Oct. 30, 2019)

Anguera, J. A. and A. Gazzaley (2015). "Video games, cognitive exercises, and the enhancement of cognitive abilities." *Current Opinion in Behavioral Sciences* **4**: 160-165. https://doi.org/10.3389/fpsyg.2019.02075

In this review we explore the emerging field of cognitive training via distinct types of interactive digital media: those designed primarily for entertainment (‘video games’) and those created for the purpose of cognitive enhancement (‘cognitive exercises’). Here we consider how specific design factors associated with each tool (e.g., fun, motivation, adaptive mechanics) and the study itself (e.g., participant expectancy, dose effects) can influence cognitive enhancement effects. We finally describe how the development of hybrid interventions that capitalize on strengths of each type of interactive digital media are anticipated to emerge as this field matures.

Ardilla, A. and M. Rosselli (1989). "Neuropsychological characteristics of normal aging." *Developmental Neuropsychology* **5**: 307-320. https://doi.org/10.1080/87565648909540441

A basic neuropsychological battery was given to 346 normal adults. Participant characteristics were balanced according to: (a) age (55 to 60, 61 to 65, 66 to 70, 71 to 75, 76 or older), (b) sex, and (c) educational level (0 to 5 years, 6 to 12 years, more than 12 years of schooling). The items of the neuropsychological battery assessed language, memory, attention, abstraction, and constructional abilities, and also included a behavioral scale. Differences based on educational level were found for 28 of the 29 tests used, and age differences were found for 23, with better performance among younger and more highly educated participants. Sex differences were found for 10 tests, with better performance among males in 9 of these tasks. Few interactions were significant. A factor analysis was performed in which 43 factors were found to explain the total variance. However, a single factor explained 35.9% of the variance this factor was related to visuospatial and visuomotor abilities. A second factor (6% of the variance) was related to verbal learning. A third factor (4.6% of the variance) was clearly related to speed, and a fourth factor (3.9% of the variance) to verbal semantic memory. Implications of these results are discussed.

Au, R., et al. (1995). "Naming ability across the adult life span." *Aging and Cognition* **2**: 300-311. https://doi.org/10.1080/13825589508256605

Longitudinal performance on the Boston Naming Test (BNT) was evaluated in 53 normal subjects aged 30 to 79 who were each tested three times over a 7-year span. Naming performance showed a significant decline over time that was greatest for the oldest subjects. These results confirm that decline in naming is a real in naming ability across the life span reflect more than simply a breakdown in lexical retrieval and that perceptual and semantic processing may be implicated.

Bäckman, L., et al. (2000). "Age-related cognitive deficits mediated by changes in the striatal dopamine system." *Am. J. Psychiatry* **157**: 635-637. https://doi.org/10.1176/ajp.157.4.635

The study examined the influence of losses in dopaminergic function on age-related cognitive deficits. METHOD: Eleven healthy subjects (21-68 years of age) completed a set of cognitive tasks used to assess perceptual speed and episodic memory. D(2) receptor binding was measured in the caudate and the putamen by using positron emission tomography. RESULTS: A gradual age-related deterioration was found for all cognitive tasks and for D(2) binding in both striatal structures. Statistical control of D(2) binding eliminated the age-related cognitive variation, whereas residual effects of D(2) binding were seen after the analysis controlled for age. CONCLUSIONS: D(2) receptor binding is a more important factor than chronological age in accounting for variation in cognitive performance across the adult lifespan. Changes in dopaminergic neurotransmission play an important role in aging-related cognitive decline.

Bansal, K., et al. (2019). "Cognitive chimera states in human brain networks." *Sci Adv* **5 (4)**: 1-14 (eaau8535). https://doi.org/10.1126/sciadv.aau8535

The human brain is a complex dynamical system, and how cognition emerges from spatiotemporal patterns of regional brain activity remains an open question. As different regions dynamically interact to perform cognitive tasks, variable patterns of partial synchrony can be observed, forming chimera states. We propose that the spatial patterning of these states plays a fundamental role in the cognitive organization of the brain and present a cognitively informed, chimera-based framework to explore how large-scale brain architecture affects brain dynamics and function. Using personalized brain network models, we systematically study how regional brain stimulation produces different patterns of synchronization across predefined cognitive systems. We analyze these emergent patterns within our framework to understand the impact of subject-specific and region-specific structural variability on brain dynamics. Our results suggest a classification of cognitive systems into four groups with differing levels of subject and regional variability that reflect their different functional roles.

Barresi, B. A., et al. (2000). "Semantic degradation and lexical access in age-related naming failures." *Aging, Neuropsychology, and Cognition* **7**(3): 169-178. https://doi.org/10.1076/1382-5585(200009)7:3;1-Q;FT169

This study investigated the impaired lexical access and semantic degradation hypotheses as two potential explanations of naming failures in normal aging. Naming responses on the Boston Naming Test (BNT) and Action Naming Test (ANT) were analyzed across three test sessions for 39 adults from three age groups (50s, 60s, and 70s). Failures to name before and after cues were classified as either impaired access if failures occurred at an earlier test session followed by successful naming at a later test session or semantic degradation if naming was successful at an earlier test session followed by failures at a later test session. The results indicated that on both the BNT and ANT all age groups produced more naming failures attrib-uted to impaired access than to semantic degradation. However, for object naming, the failures showed significantly more semantic degradation for people in their 70s compared to the younger age groups. By contrast, for action naming, semantic degradation was negligible, possibly masked by a ceiling effect, and the only age-difference result that approached significance indicated that adults in their 70s produced more naming failures attributed to impaired access than adults in their 50s.

Bartzokis, G., et al. (2003). "White matter structural integrity in healthy aging adults and patients with Alzheimer disease: A magnetic resonance imaging study." *Archives of Neurology* **60,** : 393–398. https://doi.org/10.1001/archneur.60.3.393

Imaging and postmortem studies suggest that frontal lobe white matter (FLWM) volume expands until about the age of 44.6 years and then declines. Postmortem evidence indicates that the structural integrity of myelin sheaths deteriorates during normal aging, especially in late myelinating regions such as the frontal lobes. OBJECTIVES: To assess the integrity of FLWM by magnetic resonance imaging and, thus, to provide an important index of brain aging and its relationship to Alzheimer disease (AD). DESIGN: Cross-sectional study.

SETTING: Two metropolitan university hospitals and AD research centers. PARTICIPANTS: Two hundred fifty-two healthy adults (127 men and 125 women), aged 19 to 82 years, and 34 subjects with AD (16 men and 18 women), aged 59 to 85 years. MAIN OUTCOME MEASURE: Calculated transverse relaxation rate (R(2)) of the FLWM (an indirect measure of the structural integrity of white matter). RESULTS: As expected from prior imaging data on FLWM volume, the quadratic function best represented the relationship between age and the FLWM R(2) (P<.001). In healthy individuals, the FLWM R(2) increased until the age of 38 years and then declined markedly with age. The R(2) of subjects with AD was significantly lower than that of a group of healthy control subjects who were of similar age and sex (P<.001). CONCLUSIONS: The R(2) changes in white matter suggest that the healthy adult brain is in a constant state of change, roughly defined as periods of maturation continuing into middle age followed by progressive loss of myelin integrity. Clinically diagnosed AD is associated with more severe myelin breakdown. Noninvasive measures, such as the determination of the R(2), may have the potential to track prospectively the trajectory of deteriorating white matter integrity during normal aging and the development of AD and, thus, may be a useful marker for medication development aimed at the prevention of AD.

Bastin, C., et al. (2019). "An integrative memory model of recollection and familiarity to understand memory deficits." *Behavioral and Brain Sciences*: 1-66. https://doi.org/10.1017/S0140525X19000621

Humans can recollect past events in details (recollection) and/or know that an object, person or place has been encountered before (familiarity). During the last two decades, there has been intense debate about how recollection and familiarity are organized in the brain. Here, we propose an Integrative Memory model which describes the distributed and interactive neurocognitive architecture of representations and operations underlying recollection and familiarity. In this architecture, the subjective experience of recollection and familiarity arises from the interaction between core systems storing particular kinds of representations shaped by specific computational mechanisms and an attribution system. By integrating principles from current theoretical views about memory functioning, we provide a testable framework to refine the prediction of deficient versus preserved mechanisms in memory-impaired populations. The case of Alzheimer's disease is considered as an example because it entails progressive lesions starting with limited damage to core systems before invading step-by-step most parts of the model-related network. We suggest a chronological scheme of cognitive impairments along the course of Alzheimer's disease, where the inaugurating deficit would relate early neurodegeneration of the perirhinal/anterolateral entorhinal cortex to impaired familiarity for items that need to be discriminated as viewpoint-invariant conjunctive entities. The Integrative Memory model can guide future neuropsychological and neuroimaging studies aiming to understand how such a network allows humans to remember past events, to project into the future and possibly also to share experiences. (**Keywords**: Alzheimer's disease; Cerebral network; Dual-process models of recognition memory; Episodic memory; Familiarity; Fluency; Hippocampus; Perirhinal cortex; Posterior cingulate cortex; Recollection)

Bates, E., et al. (1995). "Production of complex syntax in normal ageing and Alzheimer's disease." *Language and Cognitive Processes* **10**: 487-539. https://doi.org/10.1080/01690969508407113

Word-finding difficulties are among the earliest symptoms of Alzheimer's disease (AD), but most AD patients retain the ability to produce well-formed sentences until the late stages of their disease. This dissociation has been used to argue for a modular distinction between grammar and the lexicon. In this paper, we offer an alternative view. First, we show that grammatical production is impaired in AD patients when grammar is assessed under highly constrained conditions in a film description task. Furthermore, these grammatical deficits are comparable in some respects to the patterns of lexical impairment observed in this and other studies of AD specifically, patients do not produce frank lexical or grammatical errors, but they do find it difficult to access the "best fit" between meaning and form. We propose that differences in the onset time for lexical and grammatical symptoms in AD are due not to a disconnection between modules, but to fundamental differences in the automaticity and/or accessibility of content words and grammatical structures within a unified lexicon that breaks down gradually across the course of this disease.

Bavelier, D. and C. S. Green (2016). "The brain-boosting power of video games." *Scientific American* **315**(1):26-31. https://doi.org/10.1038/scientificamerican0716-26

The article discusses the potential of video games to enhance mental skills. Topics covered include the finding of a study that people who regularly play action games show improved ability to focus on visual details, the ability to make correct decisions under pressure conferred by game playing, and the ability of the video games Call of Duty and Medal of Honor to enhance attention. Also mentioned is the recommendation to customize games for dyslexic children or head-trauma patients. （**Subject terms**: Video games -- Physiological aspects, Mental health, Cognitive ability, Call of Duty (Game), Dyslexic children, Alternative treatment for head injuries)

Bennett, I. J. and D. J. Madden (2013). "Disconnected aging: Cerebral white matter integrity and age-related differences in cognition." *Neuroscience* **276** (2014) 187–205. http://dx.doi.org/10.1016/j.neuroscience.2013.11.026

Cognition arises as a result of coordinated processing among distributed brain regions and disruptions to communication within these neural networks can result in cognitive dysfunction. Cortical disconnection may thus contribute to the declines in some aspects of cognitive functioning observed in healthy aging. Diffusion tensor imaging (DTI) is ideally suited for the study of cortical disconnection as it provides indices of structural integrity within interconnected neural networks. The current review summarizes results of previous DTI aging research with the aim of identifying consistent patterns of age-related differences in white matter integrity, and of relationships between measures of white matter integrity and behavioral performance as a function of adult age. We outline a number of future directions that will broaden our current understanding of these brain–behavior relationships in aging. Specifically, future research should aim to (1) investigate multiple models of age–brain–behavior relationships; (2) determine the tract-specificity versus global effect of aging on white matter integrity; (3) assess the relative contribution of normal variation in white matter integrity versus white matter lesions to age-related differences in cognition; (4) improve the definition of specific aspects of cognitive functioning related to age-related differences in white matter integrity using information processing tasks, and (5) combine multiple imaging modalities (e.g., resting-state and task-related functional magnetic resonance imaging fMRI) with DTI to clarify the role of cerebral white matter integrity in cognitive aging. (Abbreviations: AD axial diffusivity, DTI diffusion tensor imaging, FA fractional anisotropy, FLAIR fluid-attenuated inversion recovery, fMRI functional MRI, HARD Ihigh angular resolution diffusion imaging, MD mean diffusivity, PCA principal component analysis, RD radial diffusivity, WML white matter lesions) (Key words: white matter integrity, diffusion tensor imaging, aging, cognition, magnetic resonance imaging, disconnection)

Benton, A. L., et al. (1981). "Normative observations on neuropsychological test performances in old age." *Journal of Clinical Neuropsychology* **3**(1): 33-42. https://doi.org/10.1080/01688638108403111

As part of a study of dementia, 162 normal volunteers in the age range of 65-84 years were given a battery of nine neuropsychological tests assessing temporal orientation, short-term memory, language functions, and visuoperceptive capacity. When compared to subjects less than 65 years of age, the groups showed little evidence of generalized decline in cognitive function before the age of 80 years. The 80-84 years subgroup showed a higher overall failure rate on the tests than the younger subgroups. Nevertheless, 70% of all subjects in the 80-84 years subgroup made no more than one failure on the nine tests. There were substantial differences among the tests in respect to their sensitivity to the effects of aging. The largest decline in performance was shown on tests of short-term visual memory, serial digit learning, and facial recognition. The other verbal, memory, and visuoperceptive tests were performed well up to the age of 80 years. The findings are interpreted as providing limited support for the hypothesis that normal aging does not necessarily involve a general decline in level of cognitive functioning. The clinical application of the tests that were sensitive or insensitive to the effects of aging is considered

Bergerbest, D., et al. (2009). "Age-associated reduction of asymmetry in prefrontal function and preservation of conceptual repetition priming." *NeuroImage* **45**(1): 237-246. https://doi.org/10.1016/j.neuroimage.2008.10.019

Older adults often show bilateral brain activation, compared to unilateral activation in younger adults, when performing tasks in domains of age-associated cognitive impairment, such as episodic and working memory. Less is known about activation associated with performance in cognitive domains that are typically unaffected by healthy aging. We used event-related functional magnetic resonance imaging to examine age-related patterns in brain activation associated with a form of implicit memory, repetition priming, which is typically preserved in healthy aging. Sixteen younger adults and 15 nondemented older adults performed semantic judgments (abstract/concrete) on single words in a study phase. In a test phase, identical judgments were made for repeated and new words. Younger and older adults showed similar response-time benefits (repetition priming) from repeated semantic classification. Repetition priming was associated with repetition-related reductions of prefrontal activation in both groups, but the patterns of activation differed between groups. Both groups showed similar activation reductions in dorsal left inferior prefrontal cortex (LIPFC), but older adults showed less reduction than younger adults in ventral and anterior LIPFC. Activation reductions were exclusively left-lateralized for younger adults, whereas older adults showed additional reductions in multiple regions of right frontal cortices. Right prefrontal activation reductions in older adults correlated with better repetition priming and better performance on independent tests of semantic processing. Thus, reduced asymmetry of prefrontal activation reductions in healthy aging was related to conceptual repetition priming, a form of learning that is spared in aging, and with the sparing of semantic memory. (**Keywords**: Conceptual repetition priming, Aging, fMRI, Semantic classification, Prefrontal cortex, Memory and Aging Project)

Berggren, R., et al. (2020). "Foreign language learning in older age does not improve memory or intelligence: Evidence from a randomized controlled study." *Psychology and Aging* **35**(2): 212-219. https://doi.org/10.1037/pag0000439

Foreign language learning in older age has been proposed as a promising avenue for combatting age-related cognitive decline. We tested this hypothesis in a randomized controlled study in a sample of 160 healthy older participants (aged 65–75 years) who were randomized to 11 weeks of either language learning or relaxation training. Participants in the language learning condition obtained some basic knowledge in the new language (Italian), but between-groups differences in improvements on latent factors of verbal intelligence, spatial intelligence, working memory, item memory, or associative memory were negligible. We argue that this is not due to either poor measurement, low course intensity, or low statistical power, but that basic studies in foreign languages in older age are likely to have no or trivially small effects on cognitive abilities. We place this in the context of the cognitive training and engagement literature and conclude that while foreign language learning may expand the behavioral repertoire, it does little to improve cognitive processing abilities.

Berndt, R. S., et al. (1997a). "Verb retrieval in aphasia. 1. Characterizing single word impairments." *Brain and Language* **56**(1): 68-106. http://dx.doi.org/10.1016/j.neuroscience.2013.11.026

The ability of aphasic patients to produce words from the grammatical classes of nouns and verbs was investigated in tasks that elicited these types of words in isolation. Eleven chronic aphasic patients produced nouns and verbs in picture naming, videotaped scene naming, sentence completion, naming from definition, and oral reading. Comprehension of the meanings of nouns and verbs was tested in word/picture and word/video scene matching, and appreciation of noun/verb grammatical class differences was tested with two metalinguistic tasks. Five patients demonstrated significantly more difficulty producing verbs than nouns, two patients were significantly more impaired producing nouns than verbs, and the remaining four patients showed no difference between the two classes. There was no improvement in verb production when naming actions presented on videotape, suggesting that selective verb impairments are not attributable to conceptual difficulty in identifying actions in static pictures. Selective noun impairments occurred in the context of severe anomia, as reported in previous studies. Selective verb impairments were demonstrated for both agrammatic and fluent (Wernicke) patients, indicating that such deficits are not necessarily associated with the nonfluent and morphologically impoverished production that is characteristic of agrammatism. There was no indication that single word comprehension was affected in these patients in a manner consonant with their production impairments. Results

are interpreted in light of current models of lexical organization and processing.

Berndt, R. S., et al. (1997b). "Verb retrieval and sentence processing: Dissociation of an established symptom association." *Cortex* **33**(1): 99-114. http://dx.doi.org/10.1016/S0010-9452(97)80007-X

A patient is described with severe anomia who produces verbs significantly better than nouns in action/object naming tasks, but who also has difficulty comprehending and producing semantically reversible sentences. This pattern differs from the frequently-reported association of symptoms involving relative verb/noun retrieval and sentence processing: impaired verb retrieval is typically associated with poor sentence processing, and preserved verb retrieval with spared sentence processing. Brain imaging reveals areas of cerebral ischemia in portions of the territories supplied by the anterior, middle and posterior cerebral arteries. An earlier ischemic episode and extensive cortical collateral circulation are hypothesized to have contributed to this unusual pattern of left cerebral hemisphere damage. The previously-reported association of symptoms that dissociated in this patient was interpreted as reflecting a hemodynamically-influenced probability of joint involvement of neuroanatomical regions subserving functionally distinct aspects of language processing.

Berson, A., et al. (2018). "Epigenetic regulation in neurodegenerative diseases." *Trends in Neurosciences* **41**(9): 587-598. https://doi.org/10.1016/j.tins.2018.05.005

Mechanisms of epigenetic regulation, including DNA methylation, chromatin remodeling, and histone post-translational modifications, are involved in multiple aspects of neuronal function and development. Recent discoveries have shed light on critical functions of chromatin in the aging brain, with an emerging realization that the maintenance of a healthy brain relies heavily on epigenetic mechanisms. Here, we present recent advances, with a focus on histone modifications and the implications for several neurodegenerative diseases including Alzheimer's disease (AD), Huntington's disease (HD), and amyotrophic lateral sclerosis (ALS). We highlight common and unique epigenetic mechanisms among these situations and point to emerging therapeutic approaches. (**Keywords**: Alzheimer’s disease; Huntington’s disease; chromatin; epigenetics; histone modifications; neurodegenerative diseases)

Beste, C., et al. (2009). "Error processing in normal aging and in basal ganglia disorders." *Neuroscience* **159**(1): 143-149. https://doi.org/10.1016/j.neuroscience.2008.12.030

Recently it has been shown that effects of aging and pathologically induced changes of basal ganglia structures may have quite similar effects on cognitive functions mediated by the medial prefrontal cortex. The question appears, if this pattern may be assignable to other cognitive functions that are mediated via the basal ganglia and medial prefrontal brain areas. Error processing is a component of executive functions that also Basal Ganglia Diseases depends on these areas and especially on the anterior cingulate cortex (ACC). Hence we ask, if error processing functions are differentially modulated by normal aging and basal ganglia diseases. Error processing mechanisms in these groups were investigated using a cognitive event-related potential (ERP), the error negativity. Enrolling an extended sample of young and elderly controls, as well as patients with Parkinson's and Huntington's disease, we show that modulations of error processing differ between aging, different basal ganglia diseases. Despite that the examined basal ganglia disorder groups (Parkinson's and Huntington's disease) differ in their age they show similar modulations in error processing, suggesting that aging effects are overridden by pathogenic effects. The study shows that it may be valuable to compare aging not only to different forms of basal ganglia disorders in order to gain knowledge about age- and disease-related mechanisms and the effects of these on cognitive functions. Diseases of the basal ganglia may impact error processing above and beyond the effects of normal aging. Although many aging, Parkinson's disease and Huntington's disease studies on error processing functions have already been published, this study ties together several related observations across all of these groups in one experiment.

Bialystok, E., et al. (2008). "Cognitive control and lexical access in younger and older bilinguals." *Journal of*

Experimental Psychology: Learning, Memory, and Cognition **34**(4): 859-873. https://doi.org/10.1037/0278-7393.34.4.859

Ninety-six participants, who were younger (20 years) or older (68 years) adults and either monolingual or bilingual, completed tasks assessing working memory, lexical retrieval, and executive control. Younger participants performed most of the tasks better than older participants, confirming the effect of aging on these processes. The effect of language group was different for each type of task: Monolinguals and bilinguals performed similarly on working memory tasks, monolinguals performed better on lexical retrieval tasks, and bilinguals performed better on executive control tasks, with some evidence for larger language group differences in older participants on the executive control tasks. These results replicate findings from individual studies obtained using only 1 type of task and different participants. The confirmation of this pattern in the same participants is discussed in terms of a suggested explanation of how the need to manage 2 language systems leads to these different outcomes for cognitive and linguistic functions. (Erratum in *Journal of Experimental Psychology: Learning, Memory, and Cognition* 2009 May 35(3):828)

Bialystok, E., et al. (2004). "**Bilingualism, aging, and cognitive control**: **Evidence from the simon task**." *Psychology and Aging* **19**(2): 290-303. https://doi.org/10.1037/0882-7974.19.2.290

Previous work has shown that bilingualism is associated with more effective controlled processing in children; the assumption is that the constant management of 2 competing languages enhances executive functions (E. Bialystok, 2001). The present research attempted to determine whether this bilingual advantage persists for adults and whether bilingualism attenuates the negative effects of aging on cognitive control in older adults. Three studies are reported that compared the performance of monolingual and bilingual middle-aged and older adults on the Simon task. Bilingualism was associated with smaller Simon effect costs for both age groups; bilingual participants also responded more rapidly to conditions that placed greater demands on working memory. In all cases the bilingual advantage was greater for older participants. It appears, therefore, that controlled processing is carried out more effectively by bilinguals and that bilingualism helps to offset age-related losses in certain executive processes.

Bialystok, E. and J. G. Grundy (2018). "**Science does not disengage**." *Cognition* **170**((2018)): 330-333. https://doi.org/10.1016/j.cognition.2017.10.019

In a recent commentary, Goldsmith and Morton (in press) argue that the results of a study demonstrating smaller sequential congruency effects (SCEs) for bilinguals than for monolinguals (Grundy, Chung-Fat-Yim, Friesen, Mak, & Bialystok, 2017) is incorrect in its interpretation of SCEs. Moreover, their overall framework is that there is no evidence for any cognitive differences between monolingual and bilingual young adults. Here, we provide evidence in support of our original interpretation and challenge their basis for arguing that there are no language group differences on these cognitive measures.

Biou, E., et al. (2019). "Transcranial direct current stimulation in post-stroke aphasia rehabilitation: A systematic review." *Annals of Physical and Rehabilitation Medicine* **62**: 104-121. https://doi.org/10.1016/j.rehab.2019.01.003

Transcranial direct current stimulation (tDCS) **is** a non-invasive tool that induces neuromodulation in the brain. Several studies have shown the effectiveness of tDCS in improving language recovery in post-stroke aphasia. However, this innovative technique is not currently used in routine speech and language therapy (SLT) practice. OBJECTIVE: This systematic review aimed to summarise the role of tDCS in aphasia rehabilitation. METHODS: We searched MEDLINE via PubMed and Scopus on October 5, 2018 for English articles published from 1996 to 2018. Eligible studies involved post-stroke aphasia rehabilitation with tDCS combined or not with SLT. RESULTS: We retained 5 meta-analyses and 48 studies. Among the 48 studies, 39 were randomised controlled trials (558 patients), 2 prospective studies (56 patients), and 5 case studies (5 patients). Two articles were sub-analyses of a randomised clinical trial. Methods used in these studies were heterogeneous. Only 6 studies

did not find a significant effect of tDCS on language performance. As compared with earlier meta-analyses, the 2 latest found significant effects. CONCLUSION: Evidence from published peer reviewed literature is effective for post-stroke aphasia rehabilitation at the chronic stages. tDCS devices are easy to use, safe and inexpensive. They can be used in routine clinical practice by speech therapists for aphasia rehabilitation. However, further studies should investigate the effectiveness in the subacute post-stroke phase and determine the effect of the lesion for precisely identifying the targeted brain areas. We discuss crucial challenges for future studies. (**Keywords:** Aphasia, Rehabilitation, Speech therapy, TDCS)

Blackburn, E. H., et al. (2015). "Human telomere biology: A contributory and interactive factor in aging, disease risks, and protection." *Science* **350**(6265): 1193-1198. https://doi.org/10.1126/science.aab3389

Telomeres are the protective end-complexes at the termini of eukaryotic chromosomes. Telomere attrition can lead to potentially maladaptive cellular changes, block cell division, and interfere with tissue replenishment. Recent advances in the understanding of human disease processes have clarified the roles of telomere biology, especially in diseases of human aging and in some aging-related processes. Greater overall telomere attrition predicts mortality and aging-related diseases in inherited telomere syndrome patients, and also in general human cohorts. However, genetically caused variations in telomere maintenance either raise or lower risks and progression of cancers, in a highly cancer type–specific fashion. Telomere maintenance is determined by genetic factors and is also cumulatively shaped by nongenetic influences throughout human life; both can interact. These and other recent findings highlight both causal and potentiating roles for telomere attrition in human diseases.

Blatter, D. D., et al. (1995). "Quantitative volumetric analysis of brain MR: Normative database spanning 5 decades of life." *American Journal of Neuroradiology.* **16** : 241–251.

To present a normative volumetric database, spanning 5 decades of life, of cerebrospinal fluid, subarachnoid cerebrospinal fluid, total brain volume, total ventricular volume (component ventricular volumes of lateral, temporal horn, and third and fourth ventricles) and estimates of white and gray matter, based on a multispectral segmentation of brain MR. This database is presented as a reference for future studies comparing pathologic states. METHOD: One hundred ninety-four healthy subjects, ranging in age from 16 to 65 years, received standard axial intermediate- and T2-weighted spin-echo MR images. Multispectral segmentation and volume analysis were performed using ANALYZE. RESULTS: Normative volumetric estimates, both uncorrected and corrected for differences in total intracranial volume, were obtained for all subjects and presented by decade and sex. Age-related cerebrospinal fluid changes were evident for both male and female subjects. Most gender differences were eliminated by correction for differences in total intracranial volume. Standard and fast spin-echo acquisition methods gave comparable volume estimates. Total brain volume measurements from MR compare favorably with data from large autopsy series. CONCLUSION: Although there may be limitations to generalizations, these normative data tables can provide a comparison index for contrasting pathologic groups with a normative sample. (**Index terms**: Brain, magnetic resonance Brain, volume) [Comment in: MR methods of measuring changes in brain and cerebrospinal fluid volume with age and menstrual cycle. *American Journal of Neuroradiology* 1996]

Boets, B., et al. (2013). "Intact but less accessible phonetic representations in adults with dyslexia." *Science* **342**(6163): 1251-1254.

Dyslexia is a severe and persistent reading and spelling disorder caused by impairment in the ability to manipulate speech sounds. We combined functional magnetic resonance brain imaging with multivoxel pattern analysis and functional and structural connectivity analysis in an effort to disentangle whether dyslexics' phonological deficits are caused by poor quality of the phonetic representations or by difficulties in accessing intact phonetic representations. We found that phonetic representations are hosted bilaterally in primary and secondary auditory cortices and that their neural quality (in terms of robustness and distinctness) is intact in adults

with dyslexia. However, the functional and structural connectivity between the bilateral auditory cortices and the left inferior frontal gyrus (a region involved in higher-level phonological processing) is significantly hampered in dyslexics, suggesting deficient access to otherwise intact phonetic representations. (**Comment in**: Neuroscience. Faulty brain connections in dyslexia? [*Science*. 2013], Neuroimaging sheds new light on the phonological deficit in dyslexia. [*Trends in Cognitive Sciences.* 2014], Eyeing visual pathways in dyslexia. [*Science*. 2014], Eyeing visual pathways in dyslexia--response. [*Science*. 2014])

Borson, S., et al. (2013). "**Improving dementia care**: **The role of screening and detection of cognitive impairmen**t." *Alzheimer's & Dementia* **9**: 151-159.

The value of screening for cognitive impairment, including dementia and Alzheimer's disease, has been debated for decades. Recent research on causes of and treatments for cognitive impairment has converged to challenge previous thinking about screening for cognitive impairment. Consequently, changes have occurred in health care policies and priorities, including the establishment of the annual wellness visit, which requires detection of any cognitive impairment for Medicare enrollees. In response to these changes, the Alzheimer's Foundation of America and the Alzheimer's Drug Discovery Foundation convened a workgroup to review evidence for screening implementation and to evaluate the implications of routine dementia detection for health care redesign. The primary domains reviewed were consideration of the benefits, harms, and impact of cognitive screening on health care quality. In conference, the workgroup developed 10 recommendations for realizing the national policy goals of early detection as the first step in improving clinical care and ensuring proactive, patient-centered management of dementia.

Bowles, N. L., et al. (1987). "Naming errors in healthy aging and dementia of the Alzheimer type." *Cortex* **23**:519-524. Naming errors were analyzed for healthy younger and older adults and patients with a diagnosis of senile dementia of the Alzheimer type (SDAT). Three types of errors were identified, varying in relatedness to the target word: near synonyms, semantically related naming errors, and unrelated naming errors. Older adults made relatively more related errors than did younger adults. SDAT patients were distinguished by the number of unrelated responses given. In addition, SDAT patients who scored within the normal range were identified by the high number of response attempts relative to the number of initial errors. We suggest that error patterns on naming tasks may potentially serve as clinical markers to distinguish healthy older persons with mild naming disorders from patients with SDAT.

Breedin, S. D., et al. (1998). "Semantic factors in verb retrieval: An effect of complexity." *Brain and Language* **63**(1): 1-31. http://dx.doi.org/10.1006/brln.1997.1923

Aphasic patients often have more difficulty retrieving verbs than nouns. We present data from eight Aphasics demonstrating that they have a selective impairment for verb retrieval. We then explore the role of semantic complexity (i.e., the number of semantic features) in verb retrieval using a delayed repetition/story completion task. The results indicate that six of the patients are better at retrieving semantically complex verbs (e.g., run) than semantically simpler verbs (e.g., go). The results have implications for accounts of the noun/verb dissociation in Aphasia, as well as for theories of verb representation. (**Comment in**: The frequency paradox in disguise: a response to Breedin, Saffran, and Schwartz (1998). [*Brain and Language* 2001])

Bridges, K. A. and D. V. L. Sidtis (2013). "Formulaic language in Alzheimer's disease." *Aphasiology* **27**(7):799-810.

Studies of productive language in Alzheimer's disease (AD) have focused on formal testing of syntax and semantics but have directed less attention to naturalistic discourse and formulaic language. Clinical observations suggest that individuals with AD retain the ability to produce formulaic language long after other cognitive abilities have deteriorated. Aims. This study quantifies production of formulaic expressions in the spontaneous speech of individuals with AD. Persons with early- and late-onset forms of the disease were compared.

Methods & Procedures. Conversational language samples of individuals with early- (n = 5) and late-onset (n = 6) AD and healthy controls (n = 5) were analyzed to determine whether formulaic language, as measured by the number of words in formulaic expressions, differs between groups. Outcomes & Results. Results indicate that individuals with AD, regardless of age of onset, used significantly more formulaic expressions than healthy controls. The early- and late-onset AD groups did not differ on formulaic language measures. Conclusions. These findings contribute to a dual process model of cerebral function, which proposes differing processing principles for formulaic and novel expressions. In this model, subcortical areas, which remain intact into late in the progression of Alzheimer's disease, play an important role in the production of formulaic language. Applications to clinical practice include identifying preserved formulaic language and providing informed counseling to patient and family.

Bridges, K. A., et al. (2013). "Role of subcortical structures in recited speech: Studies in Parkinson's disease." *Journal of Neurolinguistics* **26**: 591-601.

The role of subcortical structures in language function is complex and dependent on language task, with studies increasingly showing subcortical involvement for the production of formulaic language, including recited speech. Individuals with Parkinson's disease (PD), with (n = 6) and without (n = 7) surgical treatment, deep brain stimulation (DBS), were compared to healthy adults (n = 14) to determine whether individuals with subcortical dysfunction produce more errors during a recitation speech task. Participants were asked to recite poems, prayers, and rhymes familiar to them in order to determine the effects of subcortical disease on recited speech ability. When compared with healthy controls, the DBS-OFF group produced significantly more error words, suggesting that deficits in recitation arise with severe states of subcortical dysfunction. Individuals with DBS in the ON or OFF conditions did not differ significantly during the recited speech task. Results support a model of language where large units of overlearned language are at least partially modulated by subcortical structures. (**Keywords**: Parkinson's disease, Dual-process model, Recited speech, Formulaic language)

Briley, P. M. and A. Q. Summerfield (2014). "Age-related deterioration of the representation of space in human auditory cortex." *Neurobiology of Aging* **35**: 633-644.

One of the principal auditory disabilities associated with older age is difficulty in locating and tracking sources of sound. This study investigated whether these difficulties are associated with deterioration in the representation of space in the auditory cortex. In psychophysical tests, half of a group of older (>60 years) adults displayed spatial acuity similar to that of young adults throughout the frontal horizontal plane. The remaining half had considerably poorer spatial acuity at the more peripheral regions of frontal space. Computational modeling of electroencephalographic responses to abrupt location shifts demonstrated marked differences in the spatial tuning of populations of cortical neurons between the older adults with poor spatial acuity on the one hand, and those with good spatial acuity, as well as young adults, on the other hand. In those with poor spatial acuity, cortical responses contained little information with which to distinguish peripheral locations. We demonstrate a clear link between neural responses and spatial acuity measured behaviorally, and provide evidence for age-related changes in the coding of horizontal space. (**Keywords**: Computational modeling, Electro-encephalography (EEG), Older adults, Presbycusis, Psychophysics, Sound localization, Spatial acuity)

Bubbico, G., et al. (2019). "Effects of second language learning on the plastic aging brain: Functional connectivity, cognitive decline, and reorganization." *Front Neurosci* **13**: 423.

Learning a new language requires the use of extensive neural networks and can represent a powerful tool to reorganize brain neuroplasticity. In this study, we analyze how a 4 months long second language learning program (16, 2 h sessions) can lead to functional changes in the brain of healthy elderly individuals. A large number of studies point out a decline of brain-skills with age here it is analyzed how cognition together with functional brain organization can be improved later in life. Twenty-six older adults (59-79 years old) were enrolled in the present study. A complete neuropsychological examination was administered before and after the

intervention to measure global cognition levels, short- and long-term memory, attention, language access and executive functions. At the end of the program, in the intervention group, the results showed a significant improvement in global cognition together with an increased functional connectivity in the right inferior frontal gyrus (rIFG), right superior frontal gyrus (rSFG) and left superior parietal lobule (lSPL). These findings can be added to the current neurobiological breakthroughs of reshaping brain networks with a short language learning practice in healthy elderly subjects. Therefore, learning a foreign-language may represent a potentially helpful cognitive intervention for promoting healthy aging. (**Keywords**: Aging, Brain plasticity, Cognitive decline, Functional connectivity, Resting state, Second language learning)

Burgaleta, M., et al. (2014). "Cognitive ability changes and dynamics of cortical thickness development in healthy children and adolescents." *NeuroImage* **84**: 810-819.

Intelligence quotient (IQ) scores tend to remain stable across the lifespan. Nevertheless, in some healthy individuals, significant decreases or increases in IQ have been observed over time. It is unclear whether such changes reflect true functional change or merely measurement error. Here, we applied surface-based corticometry to investigate vertex-wise cortical surface area and thickness correlates of changes in Full Scale IQ (FSIQ), Performance IQ (PIQ) and Verbal IQ (VIQ) in a representative sample of children and adolescents (n = 188, mean age = 11.59 years) assessed two years apart as part of the NIH Study of Normal Brain Development. No significant associations between changes in IQ measures and changes in cortical surface area were observed, whereas changes in FSIQ, PIQ, and VIQ were related to rates of cortical thinning, mainly in left frontal areas. Participants who showed reliable gains in FSIQ showed no significant changes in cortical thickness on average, whereas those who exhibited no significant FSIQ change showed moderate declines in cortical thickness. Importantly, individuals who showed large decreases in FSIQ displayed the steepest and most significant reductions in cortical thickness. Results support the view that there can be meaningful cognitive ability changes that impact IQ within relatively short developmental periods and show that such changes are associated with the dynamics of cortical thickness development. (**Keywords**: Intelligence, IQ, Brain development, Brain plasticity, Cortical thickness, Verbal IQ, Performance IQ)

Burke, D. M. and D. G. MacKay (1997). "Memory, language, and ageing." *Philosophical Transactions of the Royal Society B* **352**: 1845-1856.

This overview provides both theoretical and empirical reasons for emphasizing practice and familiar skills as a practical strategy for enhancing cognitive functioning in old age. Our review of empirical research on age-related changes in memory and language reveals a consistent pattern of spared and impaired abilities in normal old age. Relatively preserved in old age is memory performance involving highly practised skills and familiar information, including factual, semantic and autobiographical information. Relatively impaired in old age is memory performance that requires the formation of new connections, for example, recall of recent autobiographical experiences, new facts or the source of newly acquired facts. This pattern of impaired new learning versus preserved old learning cuts across distinctions between semantic memory, episodic memory, explicit memory and perhaps also implicit memory. However, familiar verbal information is not completely preserved when accessed on the output side rather than the input side: aspects of language production, namely word finding and spelling, exhibit significant age-related declines. This emerging pattern of preserved and impaired abilities presents a fundamental challenge for theories of cognitive ageing, which must explain why some aspects of language and memory are more vulnerable to the effects of ageing than others. Information-universal theories involving mechanisms such as general slowing that are independent of the type or structure of the information being processed, require additional mechanisms to account for this pattern of cognitive aging. Information-specific theories, where the type or structure of the postulated memory units can influence the effects of cognitive ageing, are able to account for this emerging pattern, but in some cases require further development to account for comprehensive cognitive changes such as general slowing.

Burke, D. M., et al. (1991). "On the tip of the tongue: What causes word finding failures in young and older adults?" *Journal of Memory and Language* **30**(5): 542-579.

This paper develops a new theory of the tip of the tongue (TOT) phenomenon. Within this interactive activation model of speech production, TOTs occur when the connections between lexical and phonological nodes become weakened due to infrequent use, nonrecent use, and aging, causing a reduction in the transmission of priming. Predictions of the theory were examined using retrospective questionnaires, diary procedures, and a laboratory word retrieval task. In Study 1, young, midage, and older adults recorded naturally occurring TOTs in structured diaries during a four week interval in their everyday life. TOT targets were infrequent words in the language, and proper names, the largest category of TOT targets, were the names of acquaintances who had not been contacted recently, especially for older adults. Persistent alternates, i.e., incorrect words that came repeatedly to mind, shared phonology and grammatical class with TOT targets, and delayed TOT resolution. Older adults experienced more TOTs, but fewer persistent alternates. An influence of expectations on these age differences was ruled out by responses to the retrospective questionnaires, which indicated no age differences in expected number of TOTs. In Study 2, the basic results for age and persistent alternates were replicated in the laboratory for experimenter-selected TOT targets. The experimental study also demonstrated that proper names of famous people are especially vulnerable to TOTs in older adults.

Burzynska, A., et al. (2010). "Age-related differences in white matter microstructure: Region-specific patterns of diffusivity." *NeuroImage* **49**: 2104-2112.

We collected MRI diffusion tensor imaging data from 80 younger (20-32 years) and 63 older (60-71 years) healthy adults. Tract-based spatial statistics (TBSS) analysis revealed that white matter integrity, as indicated by decreased fractional anisotropy (FA), was disrupted in numerous structures in older compared to younger adults. These regions displayed five distinct region-specific patterns of age-related differences in other diffusivity properties: (1) increases in both radial and mean diffusivity; (2) increases in radial diffusivity; (3) no differences in parameters other than FA (4) a decrease in axial and an increase in radial diffusivity, and (5) a decrease in axial and mean diffusivity. These patterns suggest different biological underpinnings of age-related decline in FA, such as demyelination, Wallerian degeneration, gliosis, and severe fiber loss, and may represent stages in a cascade of age-related degeneration in white matter microstructure. This first simultaneous description of age-related differences in FA, mean, axial, and radial diffusivity requires histological and functional validation as well as analyses of intermediate age groups and longitudinal samples. (**Keywords**: Axial diffusivity, Fractional anisotropy, Mean diffusivity, Radial diffusivity, Tract-based spatial statistics)

Cabeza, R. (2002). "Hemispheric asymmetry reduction in older adults: The HAROLD model." *Psychology and Aging* **17**(1): 85-100.

A model of the effects of aging on brain activity during cognitive performance is introduced. The model is called HAROLD (hemispheric asymmetry reduction in older adults), and it states that, under similar circumstances, prefrontal activity during cognitive performances tends to be less lateralized in older adults than in younger adults. The model is supported by functional neuroimaging and other evidence in the domains of episodic memory, semantic memory, working memory, perception, and inhibitory control. Age-related hemispheric asymmetry reductions may have a compensatory function or they may reflect a dedifferentiation process. They may have a cognitive or neural origin, and they may reflect regional or network mechanisms. The HAROLD model is a cognitive neuroscience model that integrates ideas and findings from psychology and neuroscience of aging.

Cabeza, R., et al. (2018). "Maintenance, reserve and compensation: The cognitive neuroscience of healthy ageing." *Nature Reviews Neuroscience* **19**(11): 701-710.

Cognitive ageing research examines the cognitive abilities that are preserved and/or those that decline

with advanced age. There is great individual variability in cognitive ageing trajectories. Some older adults show little decline in cognitive ability compared with young adults and are thus termed ‘optimally ageing’. By contrast, others exhibit substantial cognitive decline and may develop dementia. Human neuroimaging research has led to a number of important advances in our understanding of the neural mechanisms underlying these two outcomes. However, interpreting the age-related changes and differences in brain structure, activation and functional connectivity that this research reveals is an ongoing challenge. Ambiguous terminology is a major source of difficulty in this venture. Three terms in particular — compensation, maintenance and reserve — have been used in a number of different ways, and researchers continue to disagree about the kinds of evidence or patterns of results that are required to interpret findings related to these concepts. As such inconsistencies can impede progress in both theoretical and empirical research, here, we aim to clarify and propose consensual definitions of these terms. (Subjects: Cognitive ageing, Cognitive neuroscience, Neural ageing)

Cabeza, R., et al. (1997). "Age-related differences in neural activity during memory encoding and retrieval: A positron emission tomography study." *Journal of Neuroscience* **17**(1): 391-400.

Positron emission tomography (PET) was used to compare regional cerebral blood flow (rCBF) in young (mean 26 years) and old (mean 70 years) subjects while they were encoding, recognizing, and recalling word pairs. A multivariate partial-least-squares (PLS) analysis of the data was used to identify age-related neural changes associated with (1) encoding versus retrieval and (2) recognition versus recall. Young subjects showed higher activation than old subjects (1) in left prefrontal and occipito-temporal regions during encoding and (2) in right prefrontal and parietal regions during retrieval. Old subjects showed relatively higher activation than young subjects in several regions, including insular regions during encoding, cuneus/precuneus regions during recognition, and left prefrontal regions during recall. Frontal activity in young subjects was left-lateralized during encoding and right-lateralized during recall [hemispheric encoding/retrieval asymmetry (HERA)], whereas old adults showed little frontal activity during encoding and a more bilateral pattern of frontal activation during retrieval. In young subjects, activation in recall was higher than that in recognition in cerebellar and cingulate regions, whereas recognition showed higher activity in right temporal and parietal regions. In old subjects, the differences in blood flow between recall and recognition were smaller in these regions, yet more pronounced in other regions. Taken together, the results indicate that advanced age is associated with neural changes in the brain systems underlying encoding, recognition, and recall. These changes take two forms: (1) age-related decreases in local regional activity, which may signal less efficient processing by the old, and (2) age-related increases in activity, which may signal functional compensation. (**Keywords**: positron emission tomography, cerebral blood flow, aging, memory, encoding, retrieval, recognition, recall, frontal lobes, functional reorganization, functional compensation)

Cabeza, R., et al. (2000). "Age-related differences in neural activity during item and temporal-order memory retrieval: A positron emission tomography study." *Journal of Cognitive Neuroscience* **12**(1): 197-206.

Positron emission tomography (PET) was used to investigate the hypothesis that older adults' difficulties with temporal-order memory are related to deficits in frontal function. Young (mean 24.7 years) and old (mean 68.6 years) participants studied a list of words, and were then scanned while retrieving information about what words were in the list (item retrieval) or when they occurred within the list (temporal-order retrieval). There were three main results. First, whereas the younger adults engaged right prefrontal regions more during temporal-order retrieval than during item retrieval, the older adults did not. This result is consistent with the hypothesis that context memory deficits in older adults are due to frontal dysfunction. Second, ventromedial temporal activity during item memory was relatively unaffected by aging. This finding concurs with evidence that item memory is relatively preserved in old adults and with the notion that medial temporal regions are involved in automatic retrieval operations. Finally, replicating the result of a previous study (Cabeza, R., Grady, C. L., Nyberg, L., McIntosh, A. R., Tulving, E., Kapur, S., Jennings, J. M., Houle, S., and Craik, F. I. M., 1997), the old adults showed weaker activations than the young adults in the right prefrontal cortex but stronger activations in the left prefrontal cortex. The age-related increase in left prefrontal activity may be interpreted as compensatory. Taken

together, the results suggest that age-related changes in brain activity are rather process- and region-specific, and that they involve increases as well as decreases in neural activity.

Cabeza, R., et al. (2004). "Task-independent and task-specific age effects on brain activity during working memory, visual attention and episodic retrieval." *Cerebral Cortex* **14**: 364-375.

It is controversial whether the effects of aging on various cognitive functions have the same common cause or several different causes. To investigate this issue, we scanned younger and older adults with functional magnetic resonance imaging (fMRI) while performing three different tasks: working memory, visual attention and episodic retrieval. There were three main results. First, in all three tasks, older adults showed weaker occipital activity and stronger prefrontal and parietal activity than younger adults. The occipital reduction is consistent with the view that sensory processing decline is a common cause in cognitive aging, and the prefrontal increase may reflect functional compensation. Secondly, older adults showed more bilateral patterns of prefrontal activity than younger adults during working memory and visual attention tasks. These findings are consistent with the Hemispheric Asymmetry Reduction in Older Adults (HAROLD) model. Finally, compared to younger adults, older adults showed weaker hippocampal formation activity in all three tasks but stronger parahippocampal activity in the episodic retrieval task. The former finding suggests that age-related hippocampal deficits may have a global effect in cognition, and the latter is consistent with an age-related increase in familiarity-based recognition. Taken together, the results indicate that both common and specific factors play an important role in cognitive aging. (**Keywords**: Frontal, Hippocampus, Lateralization, Magnetic Resonance imaging, Recollection, Reserve. **Topic:** Aging, Adult, Cognition, Hippocampus, Memory, Short-term mental processe,s Functional magnetic resonance imaging, Brain activity, Elderly hippocampal formation, Sensory processing, Visual attention, Cognitive aging)

Cabeza, R., et al., Eds. (2004/2009). *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging*. Oxford: Oxford University Press.

Until very recently**,** our knowledge about the neural basis of cognitive aging was based on two disciplines that had very little contact with each other. Whereas the neuroscience of aging investigated the effects of aging on the brain independently of age-related changes in cognition, the cognitive psychology of aging investigated the effects of aging on cognition independently of age-related changes in the brain. The lack of communication between these two disciplines is currently being addressed by an increasing number of studies that focus on the relationships between cognitive aging and cerebral aging. This rapidly growing body of research has come to constitute a new discipline, which may be called cognitive neuroscience of aging. The goal of this book is to introduce this new discipline. This book is divided into four main sections. **The first section** describes non-invasive measures of cerebral aging, including structural (e.g., volumetric MRI), chemical (e.g., dopamine PET), electrophysiological (e.g., ERPs), and hemodynamic (e.g., fMRI), and discusses how they can be linked to behavioral measures of cognitive aging. T**he second section r**eviews evidence for the effects of aging on neural activity during different cognitive functions, including perception and attention, imagery, working memory, long-term memory, and prospective memory. **The third section** focuses on clinical and applied topics, such as the distinction between healthy aging and Alzheimer's disease and the use of cognitive training to ameliorate age-related cognitive decline. **The last section** describes theories that relate cognitive and cerebral aging, including models accounting for functional neuroimaging evidence and models supported by computer simulations. (**Keywords:** Non-invasive measures, Cerebral aging, Volumetric MRI, Dopamine PET, ERPs, fMRI, Effects of aging, Neural activity, Perception, attention) https://oxford.universitypressscholarship.com/view/10.1093/acprof:oso/9780195156744.001.0001/acprof-9780195156744

Cabeza, R., et al., Eds. (2016). *Cognitive Neuroscience of Aging: Linking Cognitive and Cerebral Aging* (2nd edition). Oxford: Oxford University Press. https://doi.org/10.1093/acprof:oso/9780199372935.001.0001 (including table of contents).

It has been 10 years since the first edition of “The Handbook of the Cognitive Neuroscience of Aging”

was published. The field was in its infancy at that time, and has matured rapidly, as a reading of the present volume will quickly establish. The original chapters often laid out an agenda for directions for future research, and it is quite gratifying to note that the present chapters reflect advances in methodology, basic processes, and health that were called for in the earlier volume. A brief summary of the major contribution to the discipline of each chapter is presented. (Keywords: cognitive aging, cognitive neuroscience, memory, methodology)

Canter, R. G., et al. (2016). "Road to restoring neural circuits for the treatment of Alzheimer's disease" [a review]." *Nature* **539**: 187.

Alzheimer's disease is a progressive loss of memory and cognition, for which there is no cure. Although genetic studies initially suggested a primary role for amyloid-in Alzheimer's disease, treatment strategies targeted at reducing amyloid have failed to reverse cognitive symptoms. These clinical findings suggest that cognitive decline is the result of a complex pathophysiology and that targeting amyloid-alone may not be sufficient to treat Alzheimer's disease. Instead, a broad outlook on neural-circuit-damaging processes may yield insights into new therapeutic strategies for curing memory loss in the disease.

Cantero, J. L., et al. (2018). "Cerebral changes and disrupted gray matter cortical networks in asymptomatic older adults at risk for Alzheimer's disease." *Neurobiology of Aging* **64**(2018): 58-67.

The diagnostic value of cerebrospinal fluid (CSF) biomarkers is well established in Alzheimer's disease, but our current knowledge about how abnormal CSF levels affect cerebral integrity, at local and network levels, is incomplete in asymptomatic older adults. Here, we have collected CSF samples and performed structural magnetic resonance imaging scans in cognitively normal elderly as part of a cross-sectional multicenter study (SIGNAL project). To identify group differences in cortical thickness, white matter volume, and properties of structural networks, participants were split into controls (N = 20), positive amyloid-beta (Abeta1-42(+)) (N = 19), and positive phosphorylated tau (N = 18). The Abeta1-42(+) group exhibited thickening of middle temporal regions, while positive phosphorylated tau individuals showed thinning in the superior parietal and orbitofrontal cortices. Subjects with abnormal CSF biomarkers further showed regional white matter atrophy and more segregated cortical networks, the Abeta1-42(+) group showing heightened isolation of cingulate and temporal cortices. Collectively, these findings highlight the relevance of combining structural brain imaging and connectomics for in vivo tracking of Alzheimer's disease lesions in asymptomatic stages. (**Keywords**: CSF biomarkers, Cortical thickness, Preclinical Alzheimer's disease, SNAP, Structural cortical networks, White matter)

Cao, M., et al. (2014). "Topological organization of the human brain functional connectome across the lifespan." *Developmental Cognitive Neuroscience* **7 (2014)**: 76–93.

Human brain function undergoes complex transformations across the lifespan. We employed resting-state functional MRI and graph-theory approaches to systematically chart the lifespan trajectory of the topological organization of human whole-brain functional networks in 126 healthy individuals ranging in age from 7 to 85 years. Brain networks were constructed by computing Pearson's correlations in blood-oxygenation-level-dependent temporal fluctuations among 1024 parcellation units followed by graph-based network analyses. We observed that the human brain functional connectome exhibited highly preserved non-random modular and rich club organization over the entire age range studied. Further quantitative analyses revealed linear decreases in modularity and inverted-U shaped trajectories of local efficiency and rich club architecture. Regionally heterogeneous age effects were mainly located in several hubs (e.g., default network, dorsal attention regions). Finally, we observed inverse trajectories of long- and short-distance functional connections, indicating that the reorganization of connectivity concentrates and distributes the brain's functional networks. Our results demonstrate topological changes in the whole-brain functional connectome across nearly the entire human lifespan, providing insights into the neural substrates underlying individual variations in behavior and cognition. These results have important implications for disease connectomics because they provide a baseline for evaluating network impairments in age-related neuropsychiatric disorders. (**Keywords**: Functional connectomics, Graph

theory, Lifespan trajectory, Rich club)

Cappelletti, M., et al. (2014). "Number skills are maintained in healthy ageing." *Cognitive Psychology* **69**: 25-45.

Numerical skills have been extensively studied in terms of their development and pathological decline, but whether they change in healthy ageing is not well known. Longer exposure to numbers and quantity-related problems may progressively refine numerical skills, similar to what happens to other cognitive abilities like verbal memory. Alternatively, number skills may be sensitive to ageing, reflecting either a decline of number processing itself or of more auxiliary cognitive abilities that are involved in number tasks. To distinguish between these possibilities we tested 30 older and 30 younger participants on an established numerosity discrimination task requiring to judge which of two sets of items is more numerous, and on arithmetical tasks. Older participants were remarkably accurate in performing arithmetical tasks although their numerosity discrimination (also known as 'number acuity') was impaired. Further analyses indicate that this impairment was limited to numerosity trials requiring inhibiting information incongruent to numerosity (e.g., fewer but larger items), and that this also correlated with poor inhibitory processes measured by standard tests. Therefore, rather than a numerical impairment, poor numerosity discrimination is likely to reflect elderly's impoverished inhibitory processes. This conclusion is supported by simulations with a recent neuro-computational model of numerosity perception, where only the specific degradation of inhibitory processes produced a pattern that closely resembled older participants' performance. Numeracy seems therefore resilient to ageing but it is influenced by the decline of inhibitory processes supporting number performance, consistent with the 'Inhibitory Deficit' Theory. (**Keywords**: Ageing, Computational modelling, Number acuity, Numerical cognition, Numerosity perception)

Caramazza, A. and A. E. Hillis (1991). "Lexical organization of nouns and verbs in the brain." *Nature* **349**(6312): 788-790.

The analysis of neuropsychological disorders of lexical processing has provided important clues about the general organization of the lexical system and the internal structure of the processing components. Reports of patients with selective dysfunction of specific semantic categories such as abstract versus concrete words, living things versus inanimate objects, animals, fruits and vegetables, proper names and so forth, support the hypothesis that the neural organization of the semantic processing component is organized in these categories. There are reports of selective dysfunction of the grammatical categories noun and verb, suggesting that a dimension of lexical organization is the grammatical class of words. But the results reported in these studies have not provided unambiguous evidence concerning two fundamental questions about the nature and the locus of this organization within the lexical system. Is the noun-verb distinction represented in the semantic or in the phonological and orthographic lexicons? Is grammatical-class knowledge represented independently of lexical forms or is it represented separately and redundantly within each modality-specific lexicon? Here we report the performance of two brain-damaged subjects with modality-specific deficits restricted principally (H.W.) or virtually only (S.J.D) to verbs in oral and written production, respectively. The contrasting performance suggests that grammatical-class distinctions are redundantly represented in the phonological and orthographic output lexical components.

Carpenter, C. R., et al. (2011). "Four sensitive screening tools to detect cognitive dysfunction in geriatric emergency department patients: Brief Alzheimer's screen, short blessed test, Ottawa 3DY, and the caregiver-completed AD8." *Academic Emergency Medicine* **18**(4): 374-384.

Cognitive dysfunction, including dementia and delirium, is prevalent in geriatric emergency department (ED) patients, but often remains undetected. One barrier to reliable identification of acutely or chronically impaired cognitive function is the lack of an acceptable screening tool. While multiple brief screening instruments have been derived, ED validation trials have not previously demonstrated tools that are appropriately sensitive for clinical use. OBJECTIVES: The primary objective was to evaluate and compare the Ottawa 3DY (O3DY), Brief Alzheimer's Screen (BAS), Short Blessed Test (SBT), and caregiver-completed AD8 (cAD8) diagnostic test performance for cognitive dysfunction in geriatric ED patients using the Mini Mental Status Exam (MMSE) as

the criterion standard. A secondary objective was to assess the diagnostic accuracy for the cAD8 (which is an informant-based instrument) when used in combination with the other performance-based screening tools. METHODS: In an observational cross-sectional cohort study at one urban academic university-affiliated medical center, trained research assistants (RAs) collected patients' responses on the Confusion Assessment Method for the Intensive Care Unit, BAS, and SBT. When available, reliable caregivers completed the cAD8. The MMSE was then obtained. The O3DY was reconstructed from elements of the MMSE and the BAS. Consenting subjects were non-critically ill, English-speaking adults over age 65 years, who had not received potentially sedating medications prior to or during cognitive testing. Using an MMSE score of ≤23 as the criterion standard for cognitive dysfunction, the sensitivity, specificity, likelihood ratios, and receiver operating characteristic (ROC) area under the curve (AUC) were computed. Venn diagrams were constructed to quantitatively compare the degree of overlap among positive test results between the performance-based instruments. RESULTS: The prevalence of cognitive dysfunction for the 163 patients enrolled with complete data collection was 37%, including 5.5% with delirium. Dementia was self-reported in 3%. Caregivers were available to complete the cAD8 for 56% of patients. The SBT, BAS, and O3DY each demonstrated 95% sensitivity, compared with 83% sensitivity for the cAD8. The SBT had a superior specificity of 65%. No combination of instruments with the cAD8 significantly improved diagnostic accuracy. The SBT provided the optimal overlap with the MMSE. CONCLUSIONS: The SBT, BAS, and O3DY are three brief performance-based screening instruments to identify geriatric patients with cognitive dysfunction more rapidly than the MMSE. Among these three instruments, the SBT provides the best diagnostic test characteristics and overlap with MMSE results. The addition of the cAD8 to the other instruments does not enhance diagnostic accuracy.

Ceponiene, R., et al. (2008). "Modality-specificity of sensory aging in vision and audition: Evidence from event-related potentials." *Brain Research* **1215**: 53-68.

Major accounts of aging implicate changes in processing external stimulus information. Little is known about differential effects of auditory and visual sensory aging, and the mechanisms of sensory aging are still poorly understood. Using event-related potentials (ERPs) elicited by unattended stimuli in younger (M=25.5yrs) and older (M=71.3yrs) subjects, this study examined mechanisms of sensory aging under minimized attention conditions. Auditory and visual modalities were examined to address modality-specificity vs. generality of sensory aging. Between-modality differences were robust. The earlier-latency responses (P1, N1) were unaffected in the auditory modality but were diminished in the visual modality. The auditory N2 and early visual N2 were diminished. Two similarities between the modalities were age-related enhancements in the late P2 range and positive behavior-early N2 correlation, the latter suggesting that N2 may reflect long-latency inhibition of irrelevant stimuli. Since there is no evidence for salient differences in neuro-biological aging between the two sensory regions, the observed between-modality differences are best explained by the differential reliance of auditory and visual systems on attention. Visual sensory processing relies on facilitation by visuo-spatial attention, withdrawal of which appears to be more disadvantageous in older populations. In contrast, auditory processing is equipped with powerful inhibitory capacities. However, when the whole auditory modality is unattended, thalamo-cortical gating deficits may not manifest in the elderly. In contrast, ERP indices of longer-latency, stimulus-level inhibitory modulation appear to diminish with age.

Cervellati, C., et al. (2013). "Oxidative balance, homocysteine, and uric acid levels in older patients with late onset Alzheimer's disease or vascular dementia." *Journal of the Neurological Sciences* **337**(1–2): 156-161.

This study aimed to investigate whether Late Onset Alzheimer's Disease (LOAD) and Vascular Dementia (VAD) might be associated with a distinct profile of oxidative stress (OxS) peripheral markers. Serum levels of hydroperoxides, homocysteine, advanced oxidation protein products, uric acid, thiols, and total and residual antioxidant power were assessed in 103 mild cognitive impairment (MCI), 89 LOAD, 54 VAD patients and 48 Controls. Compared with Controls, a similar oxidative unbalance (high hydroperoxides and low residual antioxidant power) was observed in MCI, LOAD and, although less pronounced, VAD. Moreover, individuals with simultaneously high levels of homocysteine and uric acid, both well-known risk factors for cardiovascular

disease, had a high probability to be affected by VAD (O.R.:10.50 95% C.I.: 2.33-47.2), but not LOAD (O.R.: 3.0 95% C.I.:0.86-10.76) compared with individuals with normal values. Our data suggest that, although they might share a common OxS-related pathogenesis, VAD and LOAD might maintain some distinctive features, with a predominance of "vascular component" in VAD compared with LOAD. (**Keywords**: Dementia, Homocysteine, Late Onset Alzheimer's Disease, Oxidative stress, Uric acid, Vascular Dementia）

Chang, L., et al. (2009). "Effects of age and sex on brain glutamate and other metabolites." *Magnetic Resonance Imaging* **27**: 142-145.

We previously reported the effects of sex and age on brain glutamate, as well as other brain metabolite concentrations, measured with a new technique called TE-averaged PRESS on a 3-T Siemens scanner in four brain regions of 50 healthy subjects. [Sailasuta N, Ernst T, Chang L. Regional variations and the effects of age and gender on glutamate concentrations in the human brain Magn Reson Imaging, 26 (5) (2008), pp. 667-675]. While revising the original IDL processing script for a scanner upgrade, we noted a programming error in the original code that did not use the unsuppressed water signal corrected for T2 decay and percentage of cerebrospinal fluid to calculate the metabolite concentrations. We report here the reanalyzed metabolite concentrations of glutamate and other metabolites that differ from our original article, based on measurements performed on the original 50 as well as the 12 new subjects (total 62 healthy subjects: 39 males and 23 females). Our reanalyzed data no longer show sex differences in brain glutamate levels in four brain regions measured, but we continue to observe significant age-related declines in glutamate, especially in the parietal gray matter and basal ganglia, and to a lesser degree in the frontal white matter. Further analyses confirm that the basal ganglia and frontal white matter glutamate declines were predominantly due to a decline in men, but not women. These findings indicate that brain glutamate concentrations decline markedly with age, and may be especially useful as a marker for brain diseases that are affected by aging. (**Keywords**: Proton magnetic resonance spectroscopy, TE-averaged PRESS, Glutamate)

Chen, C. C., et al. (2019). "Default-mode network activation underlies accurate contextual processing of exclusive disjunctions in older but not younger adults." *NeuroImage* **201**: 116012.

Young adults proactively engage frontoparietal processing of contextual cues to preempt subsequent events. Rather than being preemptive, older adults engage these brain areas reactively upon event occurrences. Reactive frontoparietal processes in older adults, however, might be insufficient for complex contextual neural computations where utilities of contexts are not straightforward but dependent on a set of stimulus-response rules. Applying non-linear logic (XOR) rules in an fMRI experiment, we found higher default-mode network (DMN) activity critical for correctly responding to such contingency in older but not younger adults. Moreover, older individuals with higher proactive cue processing showed better performances with less DMN activity. Thus, DMN processing provides critical support when older adults are faced with complex contextual contingencies. These findings suggest an age-related change in the neurocomputational role of introspective processes in decision-making from young to older adulthood. (**Keywords**: Cognitive aging, Cognitive control, Context processing, Default mode network, Hidden layer, XOR)

Chen, F. C. 陈丰慈, et al. (2018). "Shenti huodong yu laonian danao gongneng: Gongneng xing cigongzhen zaoying de yanjiu huigu 身体活动与老年大脑功能：功能性磁共振造影的研究回顾." *Jiaoyu Xinli Xuebao* 教育心理学报 **50**(2): 363-388. http://epbulletin.epc.ntnu.edu.tw/upload/journal/prog/946195ba_20190124.pdf

本回顾之目的係以静息态与作业相关功能性磁共振造影取向探讨身体活动对老年大脑功能之影响，其中并以横断式与纵贯式研究取向，将身体活动分为心肺功能/有氧训练、太极拳、阻力健身 运动、协调训练、身体活动量，及认知性身体活动等探讨其在老化大脑功能之效益。静息态功能 性磁共振造影取向之结果发现，透过心肺适能与有氧训练与增进老年人大脑功能间有其正向关 联；该正面效益亦发现在针对高龄者的太极拳运动上，然研究对於阻力健身运动之结果仍需更多 研究进一步釐清。作业相关功能性磁共振造影取向之结果则发现，心肺适能与协调训练皆对老年 人大脑功能亦有正面影响。此外，高

身体活动量对一般老年或高风险失智者之大脑功能皆有其效 益。另外，透过认知性身体活动介入可对老年人之大脑处理效率有正面影响。整体而言，过去研 究已为身体活动与老化大脑功能间之正向关联提供科学实證基础，本回顾结果可能提供台湾社会 针对老年族群改善大脑功能之身体活动处方。(关键词：身体活动、执行功能、认知老化、磁共振造影）In this article， we review recent findings of the effects of physical activities on the aging brain and cognitive functions， focusing on functional magnetic resonance imaging (fMRI) results， including resting-state functional magnetic resonance imaging (RS-fMRI) and task-based functional magnetic resonance imaging (TB-fMRI). Moreover， the present articles explored both cross-sectional studies and longitudinal studies that examined the brain function alterations induced by physical activity training， which included cardiovascular fitness/aerobic exercise training， Tai Chi training， resistance exercise/weight training， and coordination exercise training， using measured amounts of physical activity as assessment criteria， and taking into account cognitive-related physical activity responses. Results of these RS-fMRI studies showed that older adults that engaged in cardiovascular fitness and aerobic training showed evidence of increasing brain functions. Furthermore， these positive effects also extended to older adults engaging in Tai Chi training. Also， a few studies focused on resistance exercise training; however， the results of these investigations remain inconsistence and thus will require further confirmation in the future. Results of the TB-fMRI studies indicated that older adults with higher levels of cardiovascular fitness or those engaged in cardiovascular fitness training combined with coordination training， have gained beneficial effects regarding brain functions. Specifically， the positive effects of cardiovascular fitness could be found in both normal and pathological aging populations， including older adults with mild cognitive impairment (MCI). Older adults with higher amounts of physical activity benefited in their brain functions more than older cognitively intact adults， or those with a high risk for dementia. Collectively， the results of previous studies established an experimental basis for assessing positive relationships between physical activities and brain functions， revealing that physical activity approaches might induce different improved brain functions. The consequence of these reviews provides physical activity prescriptions and exercise models relevant to improving brain functions for older populations in the society of Taiwan. (**Keywords**: Cognitive aging、Executive function、Magnetic reasoning imaging、Physical activity)

Chen, J., et al. (2002). "Age-related dedifferentiation of visuospatial abilities." *Neuropsychologia* **40**: 2050-2056.

Forty-eight older adults were tested on a battery of seven speeded visuospatial tasks that were developed by Chen et al. [4] to measure the functions of the ventral and dorsal neural processing streams. Principal components analysis revealed only one factor with an eigenvalue greater than 1.0, and all of the tasks loaded heavily on this general factor. These results are in contrast to those reported in a previous study of young adults in which principal components analysis revealed two factors with eigenvalues greater than 1.0 [4]. Importantly, for young adults the second principal component was a bipolar factor which grouped the tasks based on the neural processing stream (i.e. ventral versus dorsal) whose function they had been designed to assess. The age-related difference in the factor structure of visuospatial abilities apparent from the present results may be interpreted as reflecting an age-related dedifferentiation of the neural processing streams consistent with the results of recent neuroimaging studies [12], [13]. (**Keywords**: Aging, Visuospatial abilities, Ventral stream, Dorsal stream)

Chiarelli, A. M. (2017). "Individual differences in regional cortical volumes across the life span are associated with regional optical measures of arterial elasticity." *NeuroImage* **162**: 199-213.

Aging is often accompanied by changes in brain anatomy and cerebrovascular health. However, the specific relationship between declines in regional cortical volumes and loss of cerebral arterial elasticity is less clear, as only global or very localized estimates of cerebrovascular health have been available. Here we employed a novel tomographic optical method (pulse-DOT) to derive local estimates of cerebral arterial elasticity and compared regional volumetric estimates (obtained with FreeSurfer) with optical arterial elasticity estimates from the same regions in 47 healthy adults (aged 18-75). Between-subject analyses revealed a global correlation between cortical volume and cortical arterial elasticity, which was a significant mediator of the association between age and cortical volume. Crucially, a novel within-subject analysis highlighted the spatial association between regional variability in cortical volumes and arterial elasticity in the same regions. This association

strengthened with age. Gains in the predictability of cortical volumes from arterial elasticity data were obtained by sharpening the resolution up to individual cortical regions. These results indicate that some of the variance of sub-clinical age-related brain atrophy is associated with differences in the status of cerebral arteries, and can help explain the unique patterns of brain atrophy found within each individual. (**Keywords**: Aging, Cerebrovascular health, Diffuse optical tomography (DOT), FreeSurfer, Optical arterial pulse measures (pulse-DOT), Structural magnetic resonance imaging (sMRI))

Choi, J., et al. (2019). "Resting-state prefrontal EEG biomarkers in correlation with MMSE scores in elderly individuals." *Scientific Reports* **9**(1): 10468.

We investigated whether cognitive decline could be explained by resting-state electroencephalography (EEG) biomarkers measured in prefrontal regions that reflect the slowing of intrinsic EEG oscillations. In an aged population dwelling in a rural community (total = 496, males = 165, females = 331), we estimated the global cognitive decline using the Mini-Mental State Examination (MMSE) and measured resting-state EEG parameters at the prefrontal regions of Fp1 and Fp2 in an eyes-closed state. Using a tertile split method, the subjects were classified as T3 (MMSE 28–30, N = 162), T2 (MMSE 25–27, N = 179), or T1 (MMSE ≤ 24, N = 155). The EEG slowing biomarkers of the median frequency, peak frequency and alpha-to-theta ratio decreased as the MMSE scores decreased from T2 to T1 for both sexes ($-5.19 \leq$ t-value ≤ -3.41 for males and $-7.24 \leq$ t-value ≤ -4.43 for females) after adjusting for age and education level. Using a double cross-validation procedure, we developed a prediction model for the MMSE scores using the EEG slowing biomarkers and demographic covariates of sex, age and education level. The maximum intraclass correlation coefficient between the MMSE scores and model-predicted values was 0.757 with RMSE = 2.685. The resting-state EEG biomarkers showed significant changes in people with early cognitive decline and correlated well with the MMSE scores. Resting-state EEG slowing measured in the prefrontal regions may be useful for the screening and follow-up of global cognitive decline in elderly individuals.

Christiansen, M. H. and N. Chater (2016). "The now-or-never bottleneck: A fundamental constraint on language." *Behavioral and Brain Sciences*: e62. https://doi.org/10.1017/S0140525X1500031X

Memory is fleeting**.** New material rapidly obliterates previous material. How, then, can the brain deal successfully with the continual deluge of linguistic input? We argue that, to deal with this "Now-or-Never" bottleneck, the brain must compress and recode linguistic input as rapidly as possible. This observation has strong implications for the nature of language processing: (1) the language system must "eagerly" recode and compress linguistic input; (2) as the bottleneck recurs at each new representational level, the language system must build a multilevel linguistic representation; and (3) the language system must deploy all available information predictively to ensure that local linguistic ambiguities are dealt with "Right-First-Time"; once the original input is lost, there is no way for the language system to recover. This is "Chunk-and-Pass" processing. Similarly, language learning must also occur in the here and now, which implies that language acquisition is learning to process, rather than inducing, a grammar. Moreover, this perspective provides a cognitive foundation for grammaticalization and other aspects of language change. Chunk-and-Pass processing also helps explain a variety of core properties of language, including its multilevel representational structure and duality of patterning. This approach promises to create a direct relationship between psycholinguistics and linguistic theory. More generally, we outline a framework within which to integrate often disconnected inquiries into language processing, language acquisition, and language change and evolution. (**Keywords**: chunking; grammaticalization; incremental interpretation; language acquisition; language evolution; language processing; online learning; prediction; processing bottleneck; psycholinguistics)

Chuang, Y.-F., et al. (2014). "Cardiovascular risks and brain function: A functional magnetic resonance imaging study of executive function in older adults." *Neurobiology of Aging* **35**: 1396-1403.

Cardiovascular (CV) risk factors, such as hypertension, diabetes, and hyperlipidemia are associated with

cognitive impairment and risk of dementia in older adults. However, the mechanisms linking them are not clear. This study aims to investigate the association between aggregate CV risk, assessed by the Framingham general cardiovascular risk profile, and functional brain activation in a group of community-dwelling older adults. Sixty participants (mean age: 64.6 years) from the Brain Health Study, a nested study of the Baltimore Experience Corps Trial, underwent functional magnetic resonance imaging using the Flanker task. We found that participants with higher CV risk had greater task-related activation in the left inferior parietal region, and this increased activation was associated with poorer task performance. Our results provide insights into the neural systems underlying the relationship between CV risk and executive function. Increased activation of the inferior parietal region may offer a pathway through which CV risk increases risk for cognitive impairment. (**Keywords**: Brain function, Cardiovascular risk, Executive function, Framingham risk score, Older adults, fMRI)

Chung, S. C., et al. (2006). "Effects of gender, age, and body parameters on the ventricular volume of Korean people." *Neuroscience Letters* **395**: 155–158.

The purpose of this study was to measure the average ventricular volume of normal Koreans (aged in their 20s or 40s) and to analyze the effects of gender, age, and body parameters, such as height and weight on ventricle size. Magnetic resonance brain images were recorded for 118 people in their 20s (58 men, 60 women) and 100 in their 40s (41 men, 59 women). Using automatic and manual segmentation techniques, the volumes of the lateral and the third and fourth ventricles were calculated. To investigate the different and interactive effects of gender and age on ventricular volume, two-way analysis of variance (ANOVA) with gender and age as independent variables was carried out. Multiple regression analysis was used to investigate the effect of body parameters, such as height and weight according to gender on changes in ventricular volume. The average ventricular volume for people in their 20s was 16.2 cm3, and that for people in their 40s was 24.9 cm3. The average ventricular volume for men and women was 22.9 and 18.1 cm3, respectively. The average ventricular volume for men was greater than that for women, and that for people in their 40s was greater than that in their 20s. Enlargement of the ventricles on aging was more markedly observed in men than in women. There was a positive relationship between the body height and ventricular volume for men but not for women. There was no relationship between weight and ventricular volume for either men or women. (**Keywords**: Gender, Age, Height, Weight, Ventricular volume)

Clarke, E. and J. Stannard (1963). "Aristotle on the anatomy of the brain." *Journal of the History of Medicine and Allied Sciences* **18**: 130-148.

An abbreviated form of this paper was read before the Johns Hopkins Medical History Club on 22 January 1962" (see the 1st page of the article at https://doi.org/10.1093/jhmas/xviii.2.130)

Coffey, C. E., et al. (1998). "Sex differences in brain aging: A quantitative magnetic resonance imaging study." *Arch. Neurol.* **55**(2): 169–179.

Little is known about the effect of sex on age-related changes in brain structure. METHODS: Quantitative magnetic resonance imaging of the brain was performed in 330 elderly (age range, 66-96 years) volunteers living independently in the community, all of whom were participants in the Cardiovascular Health Study. Blinded measurements of global and regional brain size were made from T1-weighted axial images by means of computer-assisted edge detection and trace methods. High measurement reliabilities were obtained. RESULTS: Age-specific changes in brain size were significantly greater in men than women for the peripheral (sulcal) cerebrospinal fluid volume, the lateral (sylvian) fissure cerebrospinal fluid volume, and the parieto-occipital region area. Main effects of age were observed for all the remaining brain regions examined (cerebral hemisphere volume, frontal region area, temporoparietal region area, lateral ventricular volume, and third ventricle volume), but these effects were similar in men and women. Asymmetries in brain structures were not affected by aging in either sex. CONCLUSIONS: Our results are generally consistent with the few published studies on sex differences in brain aging and suggest that, for at least some structures, aging effects may be more apparent in

men than women. The neurobiological bases and functional correlates of these sex differences require further investigation.

Cohen, G. (1979). "Language comprehension in old age." *Cognitive Psychology* **11**: 412-429.

Three experiments examined the effects of aging on comprehension of spoken language. Integrative and constructive aspects of comprehension showed much more marked age-related deficits than registration of surface meaning. Experiment 1 showed that old subjects had difficulty in making inferences based on presented facts. Experiment 2 revealed a similar deficit in old people's ability to detect anomalies in newly presented information by reference to prior everyday knowledge. And Experiment 3, which tested story recall, showed that old subjects were less well able to extract and retain gist information than younger subjects. These difficulties are interpreted as reflecting a limitation in processing capacity such that the demands of concurrently registering surface meaning and simultaneously carrying out integrative and constructive processes exceed capacity in old age.

Colcombe, S. J., et al. (2006). "Aerobic exercise training increases brain volume in aging humans." *The Journals of Gerontology.* Series A, *Biological Sciences and Medical Sciences* **61**(11): 1166-1170.

The present study examined whether aerobic fitness training of older humans can increase brain volume in regions associated with age-related decline in both brain structure and cognition. METHODS: Fifty-nine healthy but sedentary community-dwelling volunteers, aged 60-79 years, participated in the 6-month randomized clinical trial. Half of the older adults served in the aerobic training group, the other half of the older adults participated in the toning and stretching control group. Twenty young adults served as controls for the magnetic resonance imaging (MRI), and did not participate in the exercise intervention. High spatial resolution estimates of gray and white matter volume, derived from 3D spoiled gradient recalled acquisition MRI images, were collected before and after the 6-month fitness intervention. Estimates of maximal oxygen uptake (VO2) were also obtained. RESULTS: Significant increases in brain volume, in both gray and white matter regions, were found as a function of fitness training for the older adults who participated in the aerobic fitness training but not for the older adults who participated in the stretching and toning (nonaerobic) control group. As predicted, no significant changes in either gray or white matter volume were detected for our younger participants. CONCLUSIONS: These results suggest that cardiovascular fitness is associated with the sparing of brain tissue in aging humans. Furthermore, these results suggest a strong biological basis for the role of aerobic fitness in maintaining and enhancing central nervous system health and cognitive functioning in older adults.

Collinge, J. (2016). "Mammalian prions and their wider relevance in neurodegenerative diseases." *Nature* **539**: 217. https://doi.org/10.1038/nature20415

Prions are notorious protein-only infectious agents that cause invariably fatal brain diseases following silent incubation periods that can span a lifetime. These diseases can arise spontaneously, through infection or be inherited. Remarkably, prions are composed of self-propagating assemblies of a misfolded cellular protein that encode information, generate neurotoxicity and evolve and adapt in vivo. Although parallels have been drawn with Alzheimer's disease and other neurodegenerative conditions involving the deposition of assemblies of misfolded proteins in the brain, insights are now being provided into the usefulness and limitations of prion analogies and their aetiological and therapeutic relevance.

Cona, G., et al. (2013). "Age-related decline in attentional shifting: Evidence from ERPS." *Neuroscience Letters* **556**: 129-134.

The present study investigated age-related attentional changes by comparing event-related potentials (ERPs) in young and older adults during a rapid serial visual presentation task. We focused on analyzing the P3a and the N2 in both the target stimulus and the immediately succeeding irrelevant stimulus. As compared with younger adults, older adults exhibited a marked reduction in the amplitude of the P3a and N2 elicited by the stimulus following the target stimulus. Moreover, in younger adults, the P3a and N2 amplitudes did not differ

between both stimuli, whereas in older adults these ERP components were significantly reduced in the subsequent stimulus compared to the target one. The age-related attenuation of P3a and N2 amplitudes for the subsequent stimulus indicates that older adults take longer and have more difficulty shifting their attention from one stimulus to the next one. (**Keywords**: Aging, ERPs, P3a, N2, Attentional shifting, Attention)

Corral-Debrinski, M., et al. (1992). "Mitochondrial DNA deletions in human brain: Regional variability and increase with advanced age." *Nature Genetics* **2**(4): 324 - 329.

We have examined the role of somatic mitochondrial DNA (mtDNA) mutations in human ageing by quantitating the accumulation of the common 4977 nucleotide pair (np) deletion (mtDNA4977) in the cortex, putamen and cerebellum. A significant increase in the mtDNA4977 deletion was seen in elderly individuals. In the cortex, the deleted to total mtDNA ratio ranged from 0.00023 to 0.012 in 67-77 year old brains and up to 0.034 in subjects over 80. In the putamen, the deletion level ranged from 0.0016 to 0.010 in 67 to 77 years old up to 0.12 in individuals over the age of 80. The cerebellum remained relatively devoid of mtDNA deletions. Similar changes were observed with a different 7436 np deletion. These changes suggest that somatic mtDNA deletions might contribute to the neurological impairment often associated with ageing.

Courchesne, E., et al. (2000). "Normal brain development and aging: Quantitative analysis at in vivo MR imaging in healthy volunteers." *Radiology* **216**(3): 672–682.

To quantitate neuroanatomic parameters in healthy volunteers and to compare the values with normative values from postmortem studies. MATERIALS AND METHODS: Magnetic resonance (MR) images of 116 volunteers aged 19 months to 80 years were analyzed with semiautomated procedures validated by means of comparison with manual tracings. Volumes measured included intracranial space, whole brain, gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF). Results were compared with values from previous postmortem studies. RESULTS: Whole brain and intracranial space grew by 25%-27% between early childhood (mean age, 26 months age range, 19-33 months) and adolescence (mean age, 14 years age range, 12-15 years); thereafter, whole-brain volume decreased such that volunteers (age range, 71-80 years) had volumes similar to those of young children. GM increased 13% from early to later (6-9 years) childhood. Thereafter, GM increased more slowly and reached a plateau in the 4th decade it decreased by 13% in the oldest volunteers. The GM-WM ratio decreased exponentially from early childhood through the 4th decade thereafter, it gradually declined. In vivo patterns of change in the intracranial space, whole brain, and GM-WM ratio agreed with published postmortem data. CONCLUSION: MR images accurately depict normal patterns of age-related change in intracranial space, whole brain, GM, WM, and CSF. These quantitative MR imaging data can be used in research studies and clinical settings for the detection of abnormalities in fundamental neuroanatomic parameters.

Craik, F. I. M. and E. Bialystok (2006). "Cognition through the lifespan: Mechanisms of change." *Trends in Cognitive Sciences* **10**(3).

Cognitive abilities rise steeply from infancy to young adulthood and then are either maintained or decline to old age, depending on the specific ability. This pattern suggests corresponding continuities of mechanism and process, but it is striking that the fields of cognitive development and cognitive aging make little contact with each other's methods and theories. In this review we examine reasons for this cultural separation, and show how recent findings from both areas fit a framework couched in terms of cognitive representation and control. These two broad factors have very different lifespan trajectories consideration of their relative growth and decline makes it clear that cognitive aging is not simply ‘development in reverse’. This framework is offered in light of recent interest in finding greater continuity throughout the lifespan and creating a more comprehensive explanation of cognitive function and cognitive change.

Craik, F. I. M. and N. S. Rose (2012). "Memory encoding and aging: A neurocognitive perspective." *Neuroscience and Biobehavioral Reviews* **36**(7): 1729-1739.

This review article surveys the evidence for age-related changes in memory from cognitive and neuroimaging studies. It is probable that the observed declines in episodic memory with increasing age are a consequence of impairments in both acquisition (encoding) and retrieval – possibly for similar reasons – but the present review focuses on the former set of processes. An additional emphasis is on a processing approach to understanding age-related encoding deficiencies we suggest that many problems stem from a decline in the ability to self-initiate deeper semantic processing operations. The article briefly discusses the role of declining sensory and perceptual abilities, but focuses primarily on the nature of processing resources, their consequences for memory acquisition, and on age-related changes in cognition and neural functioning. We also survey the evidence for neuroplasticity in the older brain, and how compensatory activities at behavioral and neural levels can reduce age-related problems. Finally, we review recent studies of brain and cognitive training procedures. Age-related memory problems are real, but there are also grounds for optimism. (**Keywords**: Memory, Encoding, Aging, Attention, Processing resources, Self-initiated activities, Environmental support)

Craik, F. I. M. and T. A. Salthouse, Eds. (2015). *The Handbook of Aging and Cognition***.** (3rd. Ed.). New York, Psychology Press. https://doi.org/10.4324/9780203837665

Cognitive aging is a flourishing area of research. A significant amount of new data, a number of new theoretical notions, and many new research issues have been generated in the past ten years. This new edition reviews new findings and theories, enables the reader to assess where the field is today, and evaluates its points of growth. The chapters are organized to run from reviews of current work on neuroimaging, neuropsychology, genetics and the concept of brain reserve, through the 'mainstream' topics of attention, memory, knowledge and language, to a consideration of individual differences and of cognitive aging in a lifespan context. This edition continues to feature the broad range of its predecessors, while also providing critical assessments of current theories and findings.

Crick, F. and G. Mitchison (1983). "The function of dream sleep." *Nature* **304**: 111-114.

We propose that the function of dream sleep (more properly rapid-eye movement or REM sleep) is to remove certain undesirable modes of interaction in networks of cells in the cerebral cortex. We postulate that this is done in REM sleep by a reverse learning mechanism (see also p. 158), so that the trace in the brain of the unconscious dream is weakened, rather than strengthened, by the dream.

Cruz Gonzalez, P., et al. (2018). "Effects of transcranial direct current stimulation on the cognitive functions in older adults with mild cognitive impairment**:** A pilot study." *Behavioural Neurology* **2018**: Article ID 5971385.5971381-5971314.

The aim of this pilot study was **to** investigate whether the use of anodal transcranial direct current stimulation (tDCS) on the left dorsolateral prefrontal cortex could boost the effects of a cognitive stimulation (CS) programme using a tablet on five older adults with mild cognitive impairment (MCI). Method. A single-subject study of A-B-C-A design was used. After the baseline with the administration of CS (phase A), a sham treatment with CS was applied (B). Following the withdrawal of sham treatment, tDCS was introduced in combination with CS (C). Finally, phase A was replicated a second time. Results. tDCS had a significant effect on processing speed, selective attention, and planning ability tasks in terms of performance and completion time. Conclusion. tDCS appears to have a positive impact on some cognitive components in CS in persons with MCI. Further study on its long-term effects and generalization of power to daily activities is warranted.

Damasio, A. R. and D. Tranel (1993). "Nouns and verbs are retrieved with differently distributed neural systems." *PNAS* **90**: 4957-4960.

In a task designed to elicit the production of verbs, the patients known as AN-1033 and Boswell consistently produced the correct target words, performing no differently from normal controls. However, in a

similar task designed to elicit the production of nouns, both patients performed quite defectively, and their scores were many SDs below those of controls. Language processing was otherwise normal--i.e., there were no impairments in grammar, morphology, phonetic implementation, or prosody reading and writing were normal. In a third patient (KJ-1360), we obtained the reverse outcome--i.e., retrieval of common and proper nouns was preserved, but verb retrieval was defective. Together, the findings in the three patients constitute a double dissociation between noun and verb retrieval. In AN-1033 and Boswell, the lesions are located outside the so-called language areas (left frontoparietal operculum, posterior temporal region, inferior parietal lobule), where damage is associated with aphasia. The region of damage shared by the two patients is in left anterior and middle temporal lobe. This sector of left hemisphere contains systems for the retrieval of nouns that denote concrete entities. We propose that those systems are not essential for the retrieval of verbs and not involved in the vocal implementation of word forms. Those systems perform a two-way lexical-mediation role for concrete nouns and promote the reconstruction of a word form after the processing of sensory-motor characteristics of the entity denoted by that word. The findings in patient KJ-1360, whose lesion is in left premotor cortex, suggest that equivalent mediation systems for verbs are located in the left frontal region.

Daniele, A., et al. (1994). "Evidence for a possible neuroanatomical basis for lexical processing of nouns and verbs." *Neuropsychologia* **32**(11): 1325-1341.

Neuropsychological studies have revealed that brain-damaged patients may show impairments of specific word categories. This study reports the performance of three patients with impairments of the categories noun and verb. The first and second patients, with left frontal lobe atrophy, were impaired in naming and comprehension of verbs. The third patients, with striking atrophy of the left temporal lobe, was disproportionately impaired in naming and comprehension of nouns. These findings suggest that anatomically distinct neural systems in the temporal and frontal lobes of the dominant hemisphere might play a critical role in lexical processing of nouns and verbs, respectively.

Danner, D. D., et al. (2001). "Positive emotions in early life and longevity: Findings from the nun study." *Journal of Personality and Social Psychology* **80**(5): 804-813.

Handwritten autobiographies from 180 Catholic nuns, composed when participants were a mean age of 22 years, were scored for emotional content and related to survival during ages 75 to 95. A strong inverse association was found between positive emotional content in these writings and risk of mortality in late life ($p < .001$). As the quartile ranking of positive emotion in early life increased, there was a stepwise decrease in risk of mortality resulting in a 2.5-fold difference between the lowest and highest quartiles. Positive emotional content in early-life autobiographies was strongly associated with longevity 6 decades later. Underlying mechanisms of balanced emotional states are discussed.

Davis, S. W., et al. (2008). "Que´ pasa? The posterior--anterior shift in aging." *Cerebral Cortex* **18**: 1201-1209.

A consistent finding from functional neuroimaging studies of cognitive aging is an age-related reduction in occipital activity coupled with increased frontal activity. This posterior–anterior shift in aging (PASA) has been typically attributed to functional compensation. The present functional magnetic resonance imaging sought to 1) confirm that PASA reflects the effects of aging rather than differences in task difficulty; 2) test the compensation hypothesis; and 3) investigate whether PASA generalizes to deactivations. Young and older participants were scanned during episodic retrieval and visual perceptual tasks, and age-related changes in brain activity common to both tasks were identified. The study yielded 3 main findings. First, inconsistent with a difficulty account, the PASA pattern was found across task and confidence levels when matching performance among groups. Second, supporting the compensatory hypothesis, age-related increases in frontal activity were positively correlated with performance and negatively correlated with the age-related occipital decreases. Age-related increases and correlations with parietal activity were also found. Finally, supporting the generalizability of the PASA pattern to deactivations, aging reduced deactivations in posterior midline cortex but increased deactivations in medial frontal

cortex. Taken together, these findings demonstrate the validity, function, and generalizability of PASA, as well as its importance for the cognitive neuroscience of aging. (**Keywords**: Aging, Compensation, Deactivation, fMRI, Frontal. **Topic**: Aging, P-aminosalicylic acid, Functional magnetic resonance imaging, Older adult. https://doi.org/10.1093/cercor/bhm155)

de Cabo, R. and M. P. Mattson (2019). "Effects of intermittent fasting on health, aging, and disease." *New England Journal of Medicine* **381**(26): 2541-2551.

Evidence is accumulating that eating in a 6-hour period and fasting for 18 hours can trigger a metabolic switch from glucose-based to ketone-based energy, with increased stress resistance, increased longevity, and a decreased incidence of diseases, including cancer and obesity.

Deming, Y., et al. (2019). "Ms4a gene cluster is a key modulator of soluble trem2 and Alzheimer's disease risk." *Science Translational Medicine* **11**(505): eaau2291.

Genetic variants in triggering receptor expressed on myeloid cells 2 (TREM2) are associated with Alzheimer's disease (AD) risk. Soluble TREM2 (sTREM2) concentrations in cerebrospinal fluid (CSF) change with AD progression, however, genetic modifiers of CSF sTREM2 remain unknown. Deming and colleagues now report two independent genetic associations in the membrane-spanning 4-domains subfamily A (MS4A) gene region. An AD risk variant was associated with reduced CSF sTREM2 concentrations, whereas a different variant leading to reduced AD risk was associated with elevated CSF sTREM2 concentrations. Gene expression analyses and molecular studies of human macrophages validated a functional relationship between MS4A4A and sTREM2 concentrations. Soluble triggering receptor expressed on myeloid cells 2 (sTREM2) in cerebrospinal fluid (CSF) has been associated with Alzheimer's disease (AD). TREM2 plays a critical role in microglial activation, survival, and phagocytosis; however, the pathophysiological role of sTREM2 in AD is not well understood. Understanding the role of sTREM2 in AD may reveal new pathological mechanisms and lead to the identification of therapeutic targets. We performed a genome-wide association study (GWAS) to identify genetic modifiers of CSF sTREM2 obtained from the Alzheimer's Disease Neuroimaging Initiative. Common variants in the membrane-spanning 4-domains subfamily A (MS4A) gene region were associated with CSF sTREM2 concentrations (rs1582763 $P = 1.15 \times 10{-}15$) ; this was replicated in independent datasets. The variants associated with increased CSF sTREM2 concentrations were associated with reduced AD risk and delayed age at onset of disease. The single-nucleotide polymorphism rs1582763 modified expression of the MS4A4A and MS4A6A genes in multiple tissues, suggesting that one or both of these genes are important for modulating sTREM2 production. Using human macrophages as a proxy for microglia, we found that MS4A4A and TREM2 colocalized on lipid rafts at the plasma membrane, that sTREM2 increased with MS4A4A overexpression, and that silencing of MS4A4A reduced sTREM2 production. These genetic, molecular, and cellular findings suggest that MS4A4A modulates sTREM2. These findings also provide a mechanistic explanation for the original GWAS signal in the MS4A locus for AD risk and indicate that TREM2 may be involved in AD pathogenesis not only in TREM2 risk-variant carriers but also in those with sporadic disease.

Dennis, N. A., et al. (2014). "Age-related differences in the neural correlates mediating false recollection." *Neurobiology of Aging* **35**(2): 395-407.

The current study investigated the effects of aging on the neural basis underlying true and false recollection. Although older adults, compared with younger adults, exhibited equivalent rates of true recollection, age differences in true recollection showed a pattern of activity commonly found among previous memory studies (e.g., age-related decreases in occipital and increases in prefrontal cortices), suggesting reduced retrieval of perceptual details associated with encoding items and a greater reliance on top-down compensatory processing. With regard to false recollection, older adults exhibited significantly greater false recollection yet did not exhibit increased neural processing. They did exhibit decreased activity in prefrontal, parahippocampal gyrus, and occipitoparietal cortex, suggesting a reduced reliance on reconstruction processes mediating false recollection in

young. An individual differences analysis in older adults found false recollection rates predicted activity in several regions, including bilateral middle/superior temporal gyrus. Taken together, these results indicate that increases in false recollection in aging may be mediated by reduced access to encoding-related details as well as reliance on semantic gist and familiarity-related neural activity.

Desgranges, B., et al. (2007). "Anatomical and functional alterations in semantic dementia: A voxel-based MRI and PET study." *Neurobiology of Aging* **28**(12): 1904-1913.

Rare studies have used magnetic resonance imaging (MRI) and voxel-based morphometry (VBM) to assess atrophy, and only two positron emission tomography (PET) studies used SPM to examine functional changes in semantic dementia (SD). Our aim was to highlight both morphological and functional abnormalities in a same group of 10 SD patients, in the entire brain, using a "state of the art" methodology (optimized VBM procedure, PET data corrected for partial volume effects and voxel-based analyses). We also used an extensive neuropsychological battery. We showed that main alterations concerned the left temporal lobe, in accordance with the striking impairment of semantic memory in SD patients, as well as the hippocampal region, which may partly explain their moderate episodic memory deficits. Hypometabolism was more extensive than grey matter loss in both temporal lobes, and specifically concerned the orbitofrontal areas, consistent with the moderate impairment of executive functions and behavioural changes. While PET is more sensitive than MRI, there is striking concordance between morphological and functional abnormalities, which contrasts with the discordance observed in Alzheimer's disease and might be a typical feature of SD.

Diederich, A., et al. (2008). "Assessing age-related multisensory enhancement with the time-window-of-integration model." *Neuropsychologia* **46**(10): 2556-2562.

Although from multisensory research a great deal is known about how the different senses interact, there is little knowledge as to the impact of aging on these multisensory processes. In this study, we measured saccadic reaction time (SRT) of aged and young individuals to the onset of a visual target stimulus with and without an accessory auditory stimulus occurring (focused attention task). The response time pattern for both groups was similar: mean SRT to bimodal stimuli was generally shorter than to unimodal stimuli, and mean bimodal SRT was shorter when the auditory accessory was presented ipsilaterally rather than contralaterally to the target. The elderly participants were considerably slower than the younger participants under all conditions but showed a greater multisensory enhancement, that is, they seem to benefit more from bimodal stimulus presentation. In an attempt to weigh the contributions of peripheral sensory processes relative to more central cognitive processes possibly responsible for the difference in the younger and older adults, the time-window-of-integration (TWIN) model for crossmodal interaction in saccadic eye movements developed by the authors was fitted to the data from both groups. The model parameters suggest that (i) there is a slowing of the peripheral sensory processing in the elderly, (ii) as a result of this slowing, the probability of integration is smaller in the elderly even with a wider time-window-of-integration, and (iii) multisensory integration, if it occurs, manifests itself in larger neural enhancement in the elderly; however, because of (ii), on average the integration effect is not large enough to compensate for the peripheral slowing in the elderly. (**Keywords**: Multisensory integration, Time-window-of-integration, Saccadic eye movement)

Duan, H., et al. (2003). "Age-related dendritic and spine changes in corticocortically projecting neurons in macaque monkeys." *Cerebral Cortex* **13**(9): 950-961.

Alterations in neuronal morphology occur in primate cerebral cortex during normal aging, vary depending on the neuronal type, region and cortical layer, and have been related to memory and cognitive impairment. We analyzed how such changes affect a specific subpopulation of cortical neurons forming long corticocortical projections from the superior temporal cortex to prefrontal area 46. These neurons were identified by retrograde transport in young and old macaque monkeys. Dendritic arbors of retrogradely labeled neurons were visualized in brain slices by intracellular injection of Lucifer Yellow, and reconstructed three-dimensionally using

computer-assisted morphometry. Total dendritic length, numbers of segments, numbers of spines, and spine density were analyzed in layer III pyramidal neurons forming the projection considered. Sholl analysis was used to determine potential age-related changes in dendritic complexity. We observed statistically significant age-related decreases in spine numbers and density on both apical and basal dendritic arbors in these projection neurons. On apical dendrites, changes in spine numbers occurred mainly on the proximal dendrites but spine density decreased uniformly among the different branch orders. On basal dendrites, spine numbers and density decreased preferentially on distal branches. Regressive dendritic changes were observed only in one particular portion of the apical dendrites, with the general dendritic morphology and extent otherwise unaffected by aging. In view of the fact that there is no neuronal loss in neocortex and hippocampus in old macaque monkeys, it is possible that the memory and cognitive decline known to occur in these animals is related to rather subtle changes in the morphological and molecular integrity of neurons subserving identifiable neocortical association circuits that play a critical role in cognition.

Duzel, E., et al. (2016). "Can physical exercise in old age improve memory and hippocampal function?" *Brain* **139**: 662-673.

Physical exercise can convey a protective effect against cognitive decline in ageing and Alzheimer's disease. While the long-term health-promoting and protective effects of exercise are encouraging, it's potential to induce neuronal and vascular plasticity in the ageing brain is still poorly understood. It remains unclear whether exercise slows the trajectory of normal ageing by modifying vascular and metabolic risk factors and/or consistently boosts brain function by inducing structural and neurochemical changes in the hippocampus and related medial temporal lobe circuitry—brain areas that are important for learning and memory. Hence, it remains to be established to what extent exercise interventions in old age can improve brain plasticity above and beyond preservation of function. Existing data suggest that exercise trials aiming for improvement and preservation may require different outcome measures and that the balance between the two may depend on exercise intensity and duration, the presence of preclinical Alzheimer's disease pathology, vascular and metabolic risk factors and genetic variability. (**Keywords**: hippocampus, exercise, cerebral blood flow, Alzheimer's disease, memory. **Topic**: Aging, Alzheimer's disease, Exercise, Hippocampus, Memory, Older adult. Subject: Dementia)

Editor (2018). "Focus on neurodegenerative disease." *Nature Neuroscience* **21**(10): 1293-1293.

We tend to think of neurodegenerative diseases as separate clinical entities that target different brain regions with distinct pathology and symptoms. However, when considered at the genetic, molecular, or cellular level, certain players and patterns crop up again and again, such as early vascular dysfunction, the aggregation and spread of misfolded proteins, selective vulnerability of particular neurons, and activation of immune responses, to name but a few. Should we consider such pathological phenomena as arising from common mechanisms that play out across different brain regions and cell types, or as simply the same steps along a shared pathway to neurodegeneration? In this issue, we present a collection of Reviews describing recent advances in our understanding of neurodegenerative disease, the commonalities and differences between the major pathologies, and the gaps in our knowledge that still need to be addressed.

Emery, V. O. (2000). "Language impairment in dementia of the Alzheimer type: A hierarchical decline?" *Int J Psychiatry Med* **30**(2): 145-164.

Progressive memory impairment **is** the primary cognitive feature of Alzheimer's disease. Systematic attention to progressive language impairment is under-appreciated. The purpose of this article is to apply the semiotic language framework to organize the disparate findings on language impairment in DAT. METHOD: The semiotic system is hierarchical, going from simple to more complex units of language, with the hierarchical ranks of phonology, morphology, syntax, semantics. This language hierarchy is used as an organizing tool to provide a context for the discrete data on language decline in DAT. Studies relating to language impairment in DAT were

identified through an exhaustive computerized search (Medline and Psych Info Database) of available literature spanning the last forty years in which 615 references were examined. Papers were selected for review if reference were made to any one or more of the language parameters of phonology, morphology, syntax, semantics, or to any components or indicators of these parameters, such as sound production, naming, grammar, sentence processing, verbal comprehension in Alzheimer patients. RESULTS: There appears to be an overall relation between language decline and complexity of language both across and within the hierarchical ranks. There also appears to be an associated negative relation between sequence in language development and language decline. Language forms learned last in the sequence of language development are the most complex and appear to be first to deteriorate. CONCLUSIONS: The decline of language in DAT appears to be hierarchical in nature. Further understanding of this hierarchical language decline depends in part on nosologic clarification and subtyping of DAT.

Faragher, R. G. A. and D. Kipling (1998). "How might replicative senescence contribute to human ageing?" *BioEssays* **20**(12): 985-991.

Cell senescence **is** the limited ability of primary human cells to divide when cultured in vitro. This eventual cessation of division is accompanied by a specific set of changes in cell physiology, morphology, and gene expression. Such changes in phenotype have the potential to contribute to human ageing and age-related diseases. Until now, senescence has largely been studied as an in vitro phenomenon, but recent data have for the first time directly demonstrated the presence of senescent cells in aged human tissues. Although a direct causal link between the ageing of whole organisms and the senescence of cells in culture remains elusive, a large body of data is consistent with cell senescence contributing to a variety of pathological changes seen in the aged. This review considers the in vitro phenotype of cellular senescence and speculates on the various possible routes whereby the presence of senescent cells in old bodies may affect different tissue systems.

Ferreira, D., et al. (2014). "Cognitive decline is mediated by gray matter changes during middle-age." *Neurobiology of Aging* **35**(5): 1086-1094.

The present theoretical framework of Alzheimer's disease proposes that pathophysiological changes occur 10-20 years before the diagnosis of dementia. We addressed the question of how age-related changes in gray matter mediate the cognitive performance during middle age. Eighty-two participants (40-50 years, ±2) were assessed with a comprehensive neuropsychological battery covering a broad spectrum of cognitive domains and components. Mediation effects were studied with hierarchical regression and bootstrapping analysis. Results showed that more vulnerable cognitive components were related to executive functioning and in a lesser degree to processing speed. Age-related differences in gray matter mainly involved the frontal lobes. Moreover, age-related differences in visuoconstructive, visuospatial functions, reaction time, and mental flexibility and executive control were mediated by several gray matter regions. It is important to increase the knowledge of the impact of brain changes on cognitive function during middle age. To define the early stages of the aging process may allow early detection of pathologic changes and therapeutic interventions. (**Keywords**: Bootstrapping analyses, Cognitive decline, Early aging, Gray matter changes, Hierarchical regression analyses, Mediation effect, Middle age)

Feyereisen, P. (1997). "A meta-analytic procedure shows an age-related decline in picture naming: Comments on Goulet, Ska." *Journal of Speech, Language & Hearing Research* **40**(6): 1328-1333.

In the conclusion of their review of the literature, Goulet, Ska, and Kahn (1994) found no clear evidence that picture-naming accuracy declines with advancing age. However, another conclusion can be drawn if one considers the subset of studies in which means and standard deviations of picture-naming accuracy are reported for different age groups: below 50, between 50 and 69, and from 70 years of age upwards. A meta-analysis of these data showed that naming accuracy was similar in the younger and the intermediate groups but that the

performance of the older group was significantly different from that of the younger groups. Thus, the problem of inconsistencies in research findings can be resolved when meta-analytic methods are used. (more details about the paper: Examines the 1994 research findings of Goulet, Ska, and Kahn on age-related changes in picture-naming accuracy by using a meta-analytic statistical procedure, heterogeneity of the estimated effect sizes, influence of the selection of the items in a naming test on the outcomes of statistical analyses, potential causal factors of difficulties in cognitive skills.)

Fix, S. T., et al. (2015). "Using visual evoked potentials for the early detection of amnestic mild cognitive impairment: A pilot investigation." *International Journal of Geriatric Psychiatry* **30**: 72–79.

Amnesic mild cognitive impairment (MCIa) is often characterized as an early stage of Alzheimer's dementia (AD). The latency of the P2, an electroencephalographic component of the flash visual evoked potential (FVEP), is significantly longer in those with AD or MCIa when compared with controls. The present investigation examined the diagnostic accuracy of several FVEP-P2 procedures in distinguishing people with MCIa and controls. METHODS. The latency of the FVEP-P2 was measured in participants exposed to a single flash condition and five double flash conditions. The double flash conditions had different inter-stimulus intervals between the pair of strobe flashes. RESULTS. Significant group differences were observed in the single flash and two of the double flash conditions. One of the double flash conditions (100 ms) displayed a higher predictive accuracy than the single flash condition, suggesting that this novel procedure may have more diagnostic potential. Participants with MCIa displayed similar P2 latencies across conditions, while controls exhibited a consistent pattern of P2 latency differences. These differences demonstrate that the double stimulation procedure resulted in a measurable refractory effect for controls but not for those with MCIa. CONCLUSIONS. The pattern of P2 group differences suggests that those with MCIa have compromised cholinergic functioning that results in impaired visual processing. Results from the present investigation lend support to the theory that holds MCIa as an intermediate stage between normal healthy aging and the neuropathology present in AD. Measuring the FVEP-P2 during several double stimulation conditions could provide diagnostically useful information about the health of the cholinergic system. (**Keywords**: AD, Alzheimer, FVEP, MCI, P2, Acetylcholine, Flash Visual Evoked Potential, Mild Cognitive Impairment)

Folstein, M., et al. (1985). "Meaning of cognitive impairment in the elderly." *Journal of the American Geriatrics Society* **33**(4): 228-235.

In order to determine the meaning of cognitive impairment in community dwelling elderly, 3,481 adults were interviewed in their homes using the Mini-Mental State Examination. Ninety-six per cent of the population aged 18-64 scored 23 or higher, whereas 80 per cent of the population 65 and over scored 23 or higher. Individuals with low scores were suffering from a variety of psychiatric disorders including dementia. Thirty-three per cent of the elderly population scoring in the range of 0-23 had no diagnosable DSM-III condition. Prevalence of dementia from all causes was 6.1 per cent of the population over age 65. Two per cent of the population over age 65 were diagnosed as having Alzheimer's disease.

Folstein, M. F., et al. (1975). "Mini-mental state: A practical method for grading the cognitive state of patients for the clinician." *Journal of Psychiatric Research* **12**(3): 189-198.

The Mini-Mental State (MMS) is a short standardized form devised for the serial testing of the cognitive mental state in patients on a neurogeriatric ward, as well as for consecutive admission to a hospital. The MMS was found to be quick (5-10 min to administer), easy to use (11 questions), and acceptable to patients and testers. When given to 69 patients with dementia, depression with cognitive impairment, and depression (Sample A), the test proved to be valid and reliable. It was able to separate the 3 diagnostic groups, it reflected clinical cognitive change, it did not change in patients thought to be cognitively stable, and it was correlated with the WAIS scores. Standardization of the test by administration to 63 normal elderly Ss and 137 patients (Sample B) indicated that the score of 20 or less was found essentially only in patients with dementia, delirium, schizophrenia, or affective

disorder, but not in normal elderly people or in patients with a primary diagnosis of neurosis and personality disorder. The MMS was useful in quantitatively estimating the severity of cognitive impairment, in serially documenting cognitive change, and in teaching residents a method of cognitive assessment.

Fox, N. C. and R. C. Petersen (2013). "The g8 dementia research summit—a starter for eight**?**" *Lancet* **382**(9909 (December 14)): 1968-1969.

On Dec 11, 2013, holding the presidency of the G8, the UK hosts a Dementia Summit in London to try to reach agreement on a new international approach on dementia research. Given the long list of problems facing the G8, why has Prime Minister David Cameron chosen to put dementia research centre stage? Although the devastating impact of dementia on patients and families has long been recognised, it is the projections for future numbers of affected individuals and the economic consequences that have surely focused the minds of international leaders.

Fu, H., et al. (2018). "**Selective** vulnerability in neurodegenerative diseases." *Nature Neuroscience* **21**(10): 1350-1358.

Neurodegenerative diseases have two general characteristics that are so fundamental we usually take them for granted. The first is that the pathology associated with the disease only affects particular neurons (‘selective neuronal vulnerability’); the second is that the pathology worsens with time and impacts more regions in a stereotypical and predictable fashion. The mechanisms underpinning selective neuronal and regional vulnerability have been difficult to dissect, but the recent application of whole-genome technologies, the development of mouse models that reproduce spatial and temporal features of the pathology, and the identification of intrinsic morphological, electrophysiological, and biochemical properties of vulnerable neurons are beginning to shed some light on these fundamental features of neurodegenerative diseases. Here we detail our emerging understanding of the underlying biology of selective neuronal vulnerability and outline some of the areas in which our understanding is incomplete.

Fultz, N. E., et al. (2019). "Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep." *Science* **366**(6465): 628-631.

Sleep is essential for both cognition and maintenance of healthy brain function. Slow waves in neural activity contribute to memory consolidation, whereas cerebrospinal fluid (CSF) clears metabolic waste products from the brain. Whether these two processes are related is not known. We used accelerated neuroimaging to measure physiological and neural dynamics in the human brain. We discovered a coherent pattern of oscillating electrophysiological, hemodynamic, and CSF dynamics that appears during non–rapid eye movement sleep. Neural slow waves are followed by hemodynamic oscillations, which in turn are coupled to CSF flow. These results demonstrate that the sleeping brain exhibits waves of CSF flow on a macroscopic scale, and these CSF dynamics are interlinked with neural and hemodynamic rhythms.

Galdo-Alvarez, S., et al. (2009). "Age-related prefrontal over-recruitment in semantic memory retrieval: Evidence from successful face naming and the tip-of-the-tongue state." *Biological Psychology* **82**(1): 89-96.

Studies that have attempted to determine the effects of aging on the brain neural sources of memory retrieval have reported two contrasting age effects: under-recruitment and over-recruitment of several prefrontal areas. However, the causes for these effects are still a matter of debate. In order to study the underlying factors that cause the effects, we compared brain activation in young and older adults, in a successful word retrieval condition, and a failed word retrieval condition: the tip-of-the-tongue state. For this, we used the event-related potentials technique and neural source estimation with low-resolution tomographies. The results showed that the older adults did not display under-recruitment in any brain area in comparison with the young adults. However, they displayed additional prefrontal activation that varied depending on the processing stage and the condition, which supports the hypothesis of selective over-recruitment in older adults. (**Keywords**: Semantic memory

retrieval, Matched conditions, Over-recruitment, Prefrontal cortex, Event-related potentials, LORETA)

Galli, R. L., et al. (2002). "Fruit polyphenolics and brain aging nutritional interventions: Targeting age-related neuronal and behavioral deficits." *Annals of the New York Academy of Sciences* **959**: 128-132.

Nutritional interventions, in this case, increasing dietary intake of fruits and vegetables, can retard and even reverse age-related declines in brain function and in cognitive and motor performance in rats. Our lab has shown that as Fischer 344 rats age their brains are increasingly vulnerable to oxidative stress. Dietary supplementation with fruit or vegetable extracts high in antioxidants (e.g., blueberry, BB, spinach, respectively) can decrease this vulnerability to oxidative stress as assessed in vivo by examining reductions in neuronal signaling and behavioral deficits and in vitro via H2O2-induced decrements in striatal synaptosomal calcium buffering. Examinations have also revealed that BB supplementations are effective in antagonizing other age-related changes in brain and behavior, as well as decreasing indices of inflammation and oxidative stress in gastrocnemius and quadriceps muscles. In ongoing studies we are attempting to determine the most effective BB polyphenolic components. To date, the anthocyanins show the most efficacy in penetrating the cell membrane and in providing antioxidant protection. In sum, our results indicate that increasing dietary intake of fruits and vegetables high in antioxidant activity may be an important component of a healthy living strategy designed to maximize neuronal and cognitive functioning into old age. (MeSH: Aging/physiology*, Brain/physiology*, Cognitive decline*, Diet Therapy*, Dietary Supplements*, Flavonoids*, Fruit*/chemistry, Vegetables*/chemistry, Antioxidants*, Phenols/administration & dosage*, Polymers/administration & dosage* Plant Extracts*

García-Pentón, L., et al. (2014). "Anatomical connectivity changes in the bilingual brain." *NeuroImage* **84**:495–504.

How the brain deals with more than one language and whether we need different or extra brain language sub-networks to support more than one language remain unanswered questions. Here, we investigate structural brain network differences between early bilinguals and monolinguals. Using diffusion-weighted MRI (DW-MRI) tractography techniques and a network-based statistic (NBS) procedure, we found two structural sub-networks more connected by white matter (WM) tracts in bilinguals than in monolinguals confirming WM brain plasticity in bilinguals. One of these sub-networks comprises left frontal and parietal/temporal regions, while the other comprises left occipital and parietal/temporal regions and also the right superior frontal gyrus. Most of these regions have been related to language processing and monitoring suggesting that bilinguals develop specialized language sub-networks to deal with the two languages. Additionally, a complex network analysis showed that these sub-networks are more graph-efficient in bilinguals than monolinguals and this increase seems to be at the expense of a whole-network graph-efficiency decrease. (**Keywords**: Bilingualism, Efficiency, Language, Network, Tractography)

Gathercole, V. C. M., et al. (2014). "Does language dominance affect cognitive performance in bilinguals? Lifespan evidence from preschoolers through older adults on card sorting, Simon, and metalinguistic tasks." *Frontiers in Psychology* **5**: Article 11. https://doi.org/10.3389/fpsyg.2014.00011

This study explores the extent to which a bilingual advantage can be observed for three tasks in an established population of fully fluent bilinguals from childhood through adulthood. Welsh-English simultaneous and early sequential bilinguals, as well as English monolinguals, aged 3 years through older adults, were tested on three sets of cognitive and executive function tasks. Bilinguals were Welsh-dominant, balanced, or English-dominant, with only Welsh, Welsh and English, or only English at home. Card sorting, Simon, and a metalinguistic judgment task (650, 557, and 354 participants, respectively) reveal little support for a bilingual advantage, either in relation to control or globally. Primarily there is no difference in performance across groups, but there is occasionally better performance by monolinguals or persons dominant in the language being tested, and in one case-in one condition and in one age group-lower performance by the monolinguals. The lack of evidence for a bilingual advantage in these simultaneous and early sequential bilinguals suggests the need for much closer scrutiny of what type of bilingual might demonstrate the reported effects, under what conditions, and why.

(**Keywords**: Executive function, Bilingual children, Language balance, Language dominance, Dimensional change, Card sort task, Simon task, Metalinguistic task, Welsh bilinguals)

Gems, D. and L. Partridge (2008). "Stress-response hormesis and aging: 'That which does not kill us makes us stronger'." *Cell Metabolism* **7**(3): 200-203.

Hormesis refers to the beneficial effects of a treatment that at a higher intensity is harmful. In one form of hormesis, sublethal exposure to stressors induces a response that results in stress resistance. The principle of stress-response hormesis is increasingly finding application in studies of aging, where hormetic increases in life span have been seen in several animal models.

Georgiou-Karistianis, N., et al. (2006). "Age-related differences in cognitive function using a global local hierarchical paradigm." *Brain Resaerch* **1124**(1): 86-95.

While research suggests that normal ageing is associated with compromised divided attentional processing abilities, such studies are comparatively few in comparison to other areas of attention (e.g. selective attention). The current study sought to examine age-related effects in divided attention using a global/local paradigm in three normal healthy age groups: younger adults (20–40 years), middle-aged (40–60 years), and older adults (61–80 years). In three experiments we sought to examine the ability to process local/global stimuli, ability to divide and switch attention, as well as the Influence of a cue on target performance. Experiment 1 revealed global precedence and interference for all age groups. Older adults were overall significantly slower in their response times. Experiments 2 and 3 suggest an age-related impairment in dividing and switching attention, which may begin as early as middle age. The findings are considered to reflect reduced inhibitory mechanisms, as well as possible neurobiological changes in the normal ageing process. (**Keywords**: Ageing, Divided attention, Attention, Global, Local, Older adults)

Giroud, N., et al. (2019). "Bridging the brain structure—brain function gap in prosodic speech processing in older adults." *Neurobiology of Aging* **80**: 116-126.

Age-related decline in speech perception may result in difficulties partaking in spoken conversation and potentially lead to social isolation and cognitive decline in older adults. It is therefore important to better understand how age-related differences in neurostructural factors such as cortical thickness (CT) and cortical surface area (CSA) are related to neurophysiological sensitivity to speech cues in younger and older adults. Age-related differences in CT and CSA of bilateral auditory-related areas were extracted using FreeSurfer in younger and older adults with normal peripheral hearing. Behavioral and neurophysiological sensitivity to prosodic speech cues (word stress and fundamental frequency of oscillation) was evaluated using discrimination tasks and a passive oddball paradigm, while EEG was recorded, to quantify mismatch negativity responses. Results revealed (a) higher neural sensitivity (i.e., larger mismatch negativity responses) to word stress in older adults compared to younger adults, suggesting a higher importance of prosodic speech cues in the speech processing of older adults, and (b) lower CT in auditory-related regions in older compared to younger individuals, suggesting neuronal loss associated with aging. Within the older age group, less neuronal loss (i.e., higher CT) in a right auditory-related area (i.e., the supratemporal sulcus) was related to better performance in fundamental frequency discrimination, while higher CSA in left auditory-related areas was associated with higher neural sensitivity toward prosodic speech cues as evident in the mismatch negativity patterns. Overall, our results offer evidence for neurostructural changes in aging that are associated with differences in the extent to which left and right auditory-related areas are involved in speech processing in older adults. We argue that exploring age-related differences in brain structure and function associated with decline in speech perception in older adults may help develop much needed rehabilitation strategies for older adults with central age-related hearing loss.

Glahn, et al. (2013). "Genetic basis of neurocognitive decline and reduced white-matter integrity in normal human brain aging." *PNAS* **110**(47): 19006–19011.

Identification of genes associated with brain aging should markedly improve our understanding of the biological processes that govern normal age-related decline. However, challenges to identifying genes that facilitate successful brain aging are considerable, including a lack of established phenotypes and difficulties in modeling the effects of aging per se, rather than genes that influence the underlying trait. In a large cohort of randomly selected pedigrees (n = 1,129 subjects), we documented profound aging effects from young adulthood to old age (18-83 y) on neurocognitive ability and diffusion-based white-matter measures. Despite significant phenotypic correlation between white-matter integrity and tests of processing speed, working memory, declarative memory, and intelligence, no evidence for pleiotropy between these classes of phenotypes was observed. Applying an advanced quantitative gene-by-environment interaction analysis where age is treated as an environmental factor, we demonstrate a heritable basis for neurocognitive deterioration as a function of age. Furthermore, by decomposing gene-by-aging (G × A) interactions, we infer that different genes influence some neurocognitive traits as a function of age, whereas other neurocognitive traits are influenced by the same genes, but to differential levels, from young adulthood to old age. In contrast, increasing white-matter incoherence with age appears to be nongenetic. These results clearly demonstrate that traits sensitive to the genetic influences on brain aging can be identified, a critical first step in delineating the biological mechanisms of successful aging. (**Keywords**: Diffusion tensor imaging, Fractional anisotropy, Gene x environment interaction, Genetic correlation, Neurocognition)

Gonzalez-Burgos, L., et al. (2019). "Cognitive compensatory mechanisms in normal aging: A study on verbal fluency and the contribution of other cognitive functions." *Aging* **11**(12): 4090-4106.

Verbal fluency has been widely studied in cognitive aging. However, compensatory mechanisms that maintain its optimal performance with increasing age are not completely understood. Using cross-sectional data, we investigated differentiation and dedifferentiation processes in verbal fluency across the lifespan by analyzing the association between verbal fluency and numerous cognitive measures within four age groups (N=446): early middle-age (32-45 years), late middle-age (46-58 years), early elderly (59-71 years), and late elderly (72-84 years). ANCOVA was used to investigate the interaction between age and fluency modality. Random forest models were conducted to study the contribution of cognition to semantic, phonemic, and action fluency. All modalities declined with increasing age, but semantic fluency was the most vulnerable to aging. The most prominent reduction in performance was observed during the transition from middle-age to early elderly, when cognitive variables stopped contributing (differentiation), and new cognitive variables started contributing (dedifferentiation). Lexical access, processing speed, and executive functions were among the most contributing functions. We conclude that the association between age and verbal fluency is masked by age-specific influences of other cognitive functions. Differentiation and dedifferentiation processes can coexist. This study provides important data for better understanding of cognitive aging and compensatory processes. (**Keywords**: aging, compensation, differentiation, random forest, verbal fluency)

Good, C. D., et al. (2001). "A voxel-based morphometric study of ageing in 465 normal adult human brains." *NeuroImage* **14**(1): 21-36. https://doi.org/10.1006/nimg.2001.0786

Voxel-based-morphometry (VBM) is a whole-brain, unbiased technique for characterizing regional cerebral volume and tissue concentration differences in structural magnetic resonance images. We describe an optimized method of VBM to examine the effects of age on grey and white matter and CSF in 465 normal adults. Global grey matter volume decreased linearly with age, with a significantly steeper decline in males. Local areas of accelerated loss were observed bilaterally in the insula, superior parietal gyri, central sulci, and cingulate sulci. Areas exhibiting little or no age effect (relative preservation) were noted in the amygdala, hippocampi, and entorhinal cortex. Global white matter did not decline with age, but local areas of relative accelerated loss and preservation were seen. There was no interaction of age with sex for regionally specific effects. These results corroborate previous reports and indicate that VBM is a useful technique for studying structural brain correlates of ageing through life in humans. (**Keywords:** Ageing, Normal, MRI, Voxel based morphometry)

Gordon-Salant, S. and P. J. Fitzgibbons (2001). "Sources of age-related recognition difficulty for time-compressed speech." *Journal of Speech, Language, and Hearing Research* **44**(4): 709-719.

Older people frequently show poorer recognition of rapid speech or time-compressed speech than younger listeners. The present investigation sought to determine if the age-related problem in recognition of time-compressed speech could be attributed primarily to a decline in the speed of information processing or to a decline in processing brief acoustic cues. The role of the availability of linguistic cues on recognition performance was examined also. Younger and older listeners with normal hearing and with hearing loss participated in the experiments. Stimuli were sentences, linguistic phrases, and strings of random words that were unmodified in duration or were time compressed with uniform time compression or with selective time compression of consonants, vowels, or pauses. Age effects were observed for recognition of unmodified random words, but not for sentences and linguistic phrases. Analysis of difference scores (unmodified speech versus time-compressed speech) showed age effects for time-compressed sentences and phrases. The forms of time compression that were notably difficult for older listeners were uniform time compression and selective time compression of consonants. Indeed, poor performance in recognizing uniformly time-compressed speech was attributed primarily to difficulty in recognizing speech that incorporated selective time compression of consonants. Hearing loss effects were observed also for most of the listening conditions, although these effects were independent of the aging effects. In general, the findings support the notion that the problems of older listeners in recognizing time-compressed speech are associated with difficulty in processing the brief, limited acoustic cues for consonants that are inherent in rapid speech.

Goyal, M. S., et al. (2019). "Persistent metabolic youth in the aging female brain." *PNAS*: 3251-3255.

Sex differences influence **b**rain morphology and physiology during both development and aging. Here we apply a machine learning algorithm to a multiparametric brain PET imaging dataset acquired in a cohort of 20- to 82-year-old, cognitively normal adults (n = 205) to define their metabolic brain age. We find that throughout the adult life span the female brain has a persistently lower metabolic brain age-relative to their chronological age-compared with the male brain. The persistence of relatively younger metabolic brain age in females throughout adulthood suggests that development might in part influence sex differences in brain aging. Our results also demonstrate that trajectories of natural brain aging vary significantly among individuals and provide a method to measure this. (**Erratum in**: Correction for Goyal et al., Persistent metabolic youth in the aging female brain. [Proc Natl Acad Sci U S A. 2019]) (**Keywords**: Brain aging, Brain metabolism, Machine learning, Neoteny, Sex differences. MeSH: Aginging/physiology*, Attention/physiology*, Brain/physiology*, Cognition/physiology*)

Gross, C. G. (1995). "Aristotle on the brain." *Neuroscientist* **1**(4): 245-250.

Aristotle argued that the heart was the center of of sensation and movement. By contrast, his predecessors, such as the Hippocratic doctors, attributed these functions to the brain. This article examines Aristotle's views on brain function in the context of his time and considers their subsequent influence on the development of the brain sciences. (**Keywords**: Aristotle, History of science, Greek science, Localization of function)

Growdon, J. H. and B. T. Hyman (2014). "Apoe genotype and brain development." *JAMA Neurology* **71**(1):7-8.

The observation that inheritance of the apolipoprotein E (APOE) ε4 allele predisposes dramatically to Alzheimer disease (AD) was first reported in 1993[1] and has been replicated in hundreds of studies thereafter. It is one of the most robust genetic associations with common disease discovered in all of medicine, yet despite 20 years of research, the reason that APOE ε4 has such a profound increase of risk in AD remains uncertain. Several facts are clear: (1) the APOE ε4 genotype predisposes toward AD pathology, primarily with amyloid deposits[2]; (2) the predisposition is relatively specific because the effect of the APOE ε4 genotype on other neurodegenerative diseases is either minimal or absent[3]; (3) the APOE ε4 genotype predisposes toward an earlier age at onset of AD dementia[2,4] and appears to be additive in this effect of earlier age at onset even in the presence of other AD-predisposing genes like PS1 or even Down syndrome and (4) the APOE ε4 genotype is associated with

diminished glucose metabolism in posterior brain regions in a pattern characteristic of AD even in healthy, nondemented individuals.[5] The article by Dean et al[6] in this issue builds on these observations that the APOE ε4 genotype is associated with an early cerebral blood flow phenotype even in middle-aged individuals at risk for AD and asks just how early in the life span an APOE ε4 effect on the brain can be observed. They carried out an observational study on infants between the ages of 2 and 25 months and astonishingly found evidence for morphological changes in brain areas that would be susceptible for AD-related neuropathological changes decades later. Specifically, among ε4 carriers, gray matter volume and myelin water fraction were lower in the precuneus, posterior and middle cingulate, and lateral temporal and medial occipitotemporal regions than in ε4 noncarriers, whereas these measures were greater in frontal regions. These observations prompted Dean et al to speculate that the APOE ε4 genotype is a more powerful genetic predeterminant of AD than previously expected. The results also raise intriguing questions about just "when" AD-related brain alterations might be considered to start.

Grüter, T. and C.-C. Carbon (2010). "Escaping attention " *Science* **328**: 435-436.

Cognitive neuroscience continues to unravel complex perceptional and cognitive processes of the human brain, in part by combining functional and anatomical aspects into network models. For example, the "dual-route" computational model of reading aloud (lexical and nonlexical routes from print to speech) has provided insights into how the process works and where its pathological variants, such as dyslexia (1), may originate. As well, the standard model for how we recognize other people's faces (2) has emerged from behavioral studies and sparse neuropsychological evidence available in the 1980s, and by more recent functional magnetic imaging studies of brain activity (3) and genetic analysis (4– 6). Still, we are only beginning to understand the brain's cognitive function. One limitation is that static functional models of cognition remain a rough approximation of the brain's dynamic processing power. Another challenge is that some cognitive dysfunctions may not be so obvious.

Hagiwara, K., et al (2013). "Age-related changes across the primary and secondary somatosensory areas: An analysis of neuromagnetic oscillatory activities**.**" *Clinical Neurophysiology* **125**(5): 1021-1029.

Age-related changes are well documented in the primary somatosensory cortex (SI). Based on previous somatosensory evoked potential studies, the amplitude of N20 typically increases with age probably due to cortical disinhibition. However, less is known about age-related change in the secondary somatosensory cortex (SII). The current study quantified age-related changes across SI and SII mainly based on oscillatory activity indices measured with agnetoencephalography. METHODS: We recorded somatosensory evoked magnetic fields (SEFs) to right median nerve stimulation in healthy young and old subjects and assessed major SEF components. Then, we evaluated the phase-locking factor (PLF) for local field synchrony on neural oscillations and the weighted phase-lag index (wPLI) for cortico-cortical synchrony between SI and SII. RESULTS: PLF was significantly increased in SI along with the increased amplitude of N20m in the old subjects. PLF was also increased in SII associated with a shortened peak latency of SEFs. wPLI analysis revealed the increased coherent activity between SI and SII. CONCLUSIONS: Our results suggest that the functional coupling between SI and SII is influenced by the cortical disinhibition due to normal aging. SIGNIFICANCE: We provide the first electrophysiological evidence for age-related changes in oscillatory neural activities across the somatosensory areas. （**Keywords**: Secondary somatosensory area (SII), Aging, Oscillatory activity, Phase-locking factor (PLF), Weighted phase-lag index (wPLI), Cortical disinhibition）

Hamann, S., et al. (2002). "Impaired fear conditioning in Alzheimer's disease." *Neuropsychologia* **40**(8): 1187-1195.

Classical conditioning of the fear response is a basic form of nondeclarative (nonconscious) memory that mediates both normal and pathological responses to aversive stimuli. Because fear conditioning critically depends on the amygdala, a medial temporal lobe structure that frequently undergoes significant pathological changes early in the course of Alzheimer's disease (AD), we hypothesized that fear conditioning would be impaired in patients with mild to moderate AD. We examined simple classical fear conditioning in a group of 10 patients with probable

AD and 14 demographically matched, neurologically intact elderly controls. During conditioning, one stimulus (e.g. a green rectangle, the conditioned stimulus (CS+)), was paired with an aversive stimulus (a loud noise, the unconditioned stimulus (US)) using a partial reinforcement conditioning schedule. The opponent color (e.g. red rectangle), the CS−, was never paired with the US. The elderly controls acquired robust fear responses as demonstrated by their differential skin-conductance responses to the CS+ and CS−. In contrast, the AD group showed a marked impairment in conditioning, failing to exhibit significant conditioned fear responses. This failure to acquire conditioned responses could not be attributed to diminished responding by patients, relative to controls, to the aversive US. The results indicate that fear conditioning, an amygdala-dependent form of memory, is impaired in AD. These findings complement previous reports of impairments in declarative emotional memory in AD by demonstrating that a basic form of nondeclarative emotional memory is also impaired in AD. (**Keywords**: Conditioning, Amygdala, memory, Aversive nondeclarative, Emotion)

Han et al. (2019). "Laonianren yuyan nengli de xiangguan yanjiu 老年人语言能力的相关研究" (study on linguistic competence of the elderly) *Shijie Zuixin Yixue Xinxi Wenzhai* 世界最新医学信息文摘 *(*World latest medicine information) **19**(28): 110-111,114.

近年来，我国人口老龄化的趋势逐渐递增，患有认知功能障碍的老年人也随之越来越多，老年人的生活质量受到了严重影响，社会负担也大大的增加。认知障碍体现在计算、执行、理解、判断、记忆和语言能力等功能中的一项或多项受损，作为认知功能的重要组成部分，语言能力的早期变化对识别认知功能减退具有重要的意义，研究语言能力的影响因素也显得尤为重要。本文采用文献资料法，从多个数据库搜索相关文献资料，综述多篇文献得出以下结论：老年人语言能力的衰老与阿尔茨海默症、帕金森综合征等多种神经退行性疾病有关；语言能力与很多因素都具有相关性，明确教育水平对语言能力的影响，确定了下一步的研究方向。(关键词：老龄化；语言能力；认知功能障碍；教育水平） ABSTRACT: In recent years, the trend of population aging in China has gradually increased, and the number of elderly people with cognitive dysfunction has also increased. The quality of life of the elderly has been seriously affected, and the social burden has also increased greatly. Cognitive impairments include the impairment of calculation, execution, understanding, Judgment, memory and linguistic competence. As an important part of cognitive function, linguistic competence is very important. In this paper, we use the literature method to search related literatures from multiple databases, and summarize several literatures. In conclusion, linguistic competence of the elderly is related to various neurological diseases such as Alzheimer's disease and Parkinson's syndrome. The linguistic competence is related to many factors, and we clarify the relationship between educational level and linguistic competence and determines the direction of the next study. (**Keywords**: Aging, Linguistic competence, Cognitive dysfunction, Education level)

Harman, D. (1956). "Aging: A theory based on free radical and radiation chemistry." *Journals of Gerontology.* **11**(3): 298-300.

Aging and the degenerative diseases associated with it are attributed basically to the deleterious side attacks of free radicals on cell constituents and on the connective tissues. The free radicals probably arise largely through reactions involving molecular oxygen catalyzed in the cell by the oxidative enzymes and in the connective tissues by traces of metals such as iron, cobalt, and manganese.

Harris, M. A. and T. Wolbers (2014). "How age-related strategy switching deficits affect wayfinding in complex environments." *Neurobiology of Aging* **35**(5): 1095-1102.

Although most research on navigation in aging focuses on allocentric processing deficits, impaired strategy switching may also contribute to navigational decline. Using a specifically designed task involving navigating a town-like virtual environment, we assessed the ability of young and old participants to switch from following learned routes to finding novel shortcuts. We found large age differences in the length of routes taken during testing and in use of shortcuts, as, while nearly all young participants switched from the egocentric route-following strategy to the allocentric wayfinding strategy, none of the older participants stably switched. Although

secondary tasks confirmed that older participants were impaired both at strategy switching and allocentric processing, the difficulty in using shortcuts was selectively related to impaired strategy switching. This may in turn relate to dysfunction of the prefrontal-noradrenergic network responsible for coordinating switching behavior. We conclude that the large age difference in performance at the shortcutting task demonstrates for the first time, how strategy switching deficits can have a severe impact on navigation in aging. (**Keywords**: Aging, Navigation, Strategy switching, Shortcutting, Route learning, Virtual reality)

Häuser, K. I., et al. (2019). "Effects of aging and dual-task demands on the comprehension of less expected sentence continuations: Evidence from pupillometry." *Frontiers in Psychology* **10**: Article 709.

Prior studies on language processing in aging have shown that older adults experience integration difficulties for contextually unpredictable target words (as indicated by low cloze probabilities in prior ratings), and that such comprehension difficulties are more likely to occur under more demanding processing conditions (e.g., dual-task situations). However, these effects have primarily been demonstrated for conditions when cloze probability of the linguistic stimuli was very low. The question we asked here was do dual-task demands also impair comprehension when target words provide a good, but not perfect, match with prior context? We used a dual-task design, consisting of a sentence comprehension and secondary motor tracking task. Critical target words were those which were not perfectly predictable based on context (words with a cloze probability of 0.7), as opposed to words that were near perfectly predictable based on context (cloze probabilities of 0.99). As a measure to index online processing difficulty for less expected target words, we took into account participants' pupil size. Separate mixed effects models were fit for language comprehension, motor tracking, and pupil size, showing the following: (1) dual-task demands led to age-related comprehension difficulties when target words were less expected (as opposed to very highly expected), (2) integration difficulty in older adults was related to cognitive overload as less expected sentence continuations progressed over time, resulting in behavioral trade-offs between language comprehension and motor tracking, and (3) lower levels of working memory were predictive of whether or not older adults experienced cognitive overload when processing less expected words. In sum, more demanding processing conditions lead to comprehension impairments when words are highly unpredictable based on context, as many prior studies showed. Comprehension impairments among older individuals also occur for conditions when words provide a good, but not perfect, match with prior context. Higher working memory capacity can alleviate such impairments in older adults, thereby suggesting that only high-WM older adults have sufficient cognitive resources to pre-activate words that complete a sentence context plausibly, but not perfectly. (**Keywords**: Aging, Context use, Dual task, Language, Pupillometry, Sentence comprehension)

He, Y.-H., et al. (2014). "MtDNA content contributes to healthy aging in Chinese: A study from nonagenarians and centenarians." *Neurobiology of Aging* **35**(7): 1779. e1771-1774.

Mitochondrial DNA (mtDNA) content plays an important role in energy production and sustaining normal physiological function. A decline in the mtDNA content and subsequent dysfunction cause various senile diseases, with decreasing mtDNA content observed in the elderly individuals with age-related diseases. In contrast, the oldest old individuals, for example, centenarians, have a delayed or reduced prevalence of these diseases, suggesting centenarians may have a different pattern of the mtDNA content, enabling them to keep normal mitochondrial functions to help delay or escape senile diseases. To test this hypothesis, a total of 961 subjects, consisting of 424 longevity subjects and 537 younger control subjects from Hainan and Sichuan provinces of China, were recruited for this study. The mtDNA content was found to be inversely associated with age among the age of group 40-70 years. Surprisingly, no reduction of mtDNA content was observed in nonagenarians and centenarians, instead, these oldest old showed a significant increase than the elderly people aged between 50 and 70 years. The results suggest the higher mtDNA content may convey a beneficial effect to the longevity of people through assuring sufficient energy supply. (**Keywords**: Mitochondrial DNA: Copy number, Aging, Longevity, Age-related diseases)

Hedden, T. and J. D. E. Gabrieli (2004). "Insights into the ageing mind: A view from cognitive neuroscience." *Nature Reviews Neuroscience* **5**: 87-96.

As we grow older, we may grow wiser, but we can also experience memory loss and cognitive slowing that can interfere with our daily routines. The cognitive neuroscience of human ageing, which relies largely on neuroimaging techniques, relates these cognitive changes to their neural substrates, including structural and functional changes in the prefrontal cortex, medial temporal lobe regions and white matter tracts. Much remains unknown about how normal ageing affects the neural basis of cognition, but recent research on individual differences in the trajectory of ageing effects is helping to distinguish normal from pathological origins of age-related cognitive changes. This review summarizes recent work in the cognitive neuroscience of ageing, with an emphasis on human neuropsychological and neuroimaging research, that demonstrates the varied nature of age-related neural and psychological changes. We discuss several of the most pressing issues in the cognitive neuroscience of ageing in an attempt to sketch a research agenda for the future.

Heemels, M.-T. (2016). "Neurodegenerative diseases." *Nature Insight* **539**: 179.

The prevalence of neurodegenerative disorders is increasing, owing — in part — to extensions in lifespan. Currently, there is no cure for any of these diseases, although not for lack of trying. The hard work and dedication that goes into unravelling mechanisms of disease is discernible from this collection of reviews. Each summarises our knowledge, highlights exciting advances and provides ample inspiration for future research. The signs of the passage of time are clearly visible in the brain. Tony Wyss-Coray synthesizes current knowledge on brain ageing and neurodegeneration and explores the prospect of stalling, or even resetting, the clock. Growing evidence suggests that genetic, cellular and circuit dysregulation results from, and can lead to, cellular and cognitive hallmarks of Alzheimer's disease. Li-Huei Tsai, Rebecca Canter and Jay Penney argue for a multipronged approach to the treatment of this common form of dementia. Paul Taylor, Robert Brown and Don Cleveland discuss emerging themes and mechanisms that underlie amyotrophic lateral sclerosis (also known as Lou Gehrig's disease or motor neuron disease), a progressive degeneration of motor neurons in the brain and spinal cord. Parkinson's disease is characterized by the progressive death of dopamine neurons. Asa Abeliovich and Aaron Gitler propose that the accumulation of cellular damage eventually overwhelms the protein-disposal mechanisms of these neurons. John Collinge considers the wider relevance of mammalian prions for neurodegenerative diseases. And Roland Riek and David Eisenberg provide a structural perspective on neurodegeneration through the properties of protein aggregates, the hallmarks of various neurodegenerative disorders. They explore the self-replication, cell-to-cell transmission and toxicity of these amyloids. We hope that this collection will not only stimulate further research on neurodegenerative diseases but also direct more funding towards this area — as a greater understanding will reveal new opportunities for therapeutic intervention. Nature is pleased to acknowledge the financial support of Eli Lilly and Company in producing this Insight. As always, Nature carries sole responsibility for all editorial content. (**Subjects**: Diseases, Genetics, Neuroscience, Structural biology)

Henrich, J., et al. (2010). "Most people are not weird." *Nature* **466**(1): 29. https://doi.org/10.1038/466029a

To understand human psychology, behavioural scientists must stop doing most of their experiments on Westerners, argue Joseph Henrich, Steven J. Heine and Ara Norenzayan. Much research on human behaviour and psychology assumes that everyone shares most fundamental cognitive and affective processes, and that findings from one population apply across the board. A growing body of evidence suggests that this is not the case. Experimental findings from several disciplines indicate considerable variation among human populations in diverse domains, such as visual perception, analytic reasoning, fairness, cooperation, memory and the heritability of IQ1,2. This is in line with what anthropologists have long suggested: that people from Western, educated, industrialized, rich and democratic (WEIRD) societies — and particularly American undergraduates — are some of the most psychologically unusual people on Earth1.

Ho, M.-C., et al (2012). "Age-related changes of task-specific brain activity in normal aging." *Neuroscience Letters* **507**(1): 78-83.

An important question in healthcare for older patients is whether age-related changes in cortical reorganization can be measured with advancing age. This study investigated the factors behind such age-related changes, using time-frequency analysis of event-related potentials (ERPs). We hypothesized that brain rhythms was affected by age-related changes, which could be reflected in the ERP indices. An oddball task was conducted in two experimental groups, namely young participants (N=15 mean age 23.7±2.8 years) and older participants (N=15 mean age 70.1±7.9 years). Two types of stimuli were used: the target (1 kHz frequency) and standard (2 kHz frequency). We scrutinized three ERP indices: event-related spectral power (ERPSP), inter-trial phase-locking (ITPL), and event-related cross-phase coherence (ERPCOH). Both groups performed equally well for correct response rate. However, the results revealed a statistically significant age difference for inter-trial comparison. Compared with the young, the older participants showed the following age-related changes: (a) power activity decreased, however, an increase was found only in the late (P3, 280-450 ms) theta (4-7 Hz) component over the bilateral frontal and temporo-frontal areas (b) low phase-locking in the early (N1, 80-140 ms) theta band over the parietal/frontal (right) regions appeared (c) the functional connections decreased in the alpha (7-13 Hz) and beta (13-30 Hz) bands, but no difference emerged in the theta band between the two groups. These results indicate that age-related changes in task-specific brain activity for a normal aging population can be depicted using the three ERP indices.

Hoffman, P. (2018). "An individual differences approach to semantic cognition: Divergent effects of age on representation, retrieval and selection." *Scientific Reports* **8**: 1-13.

Semantic cognition refers to the appropriate use of acquired knowledge about the world. This requires representation of knowledge as well as control processes which ensure that currently-relevant aspects of knowledge are retrieved and selected. Although these abilities can be impaired selectively following brain damage, the relationship between them in healthy individuals is unclear. It is also commonly assumed that semantic cognition is preserved in later life, because older people have greater reserves of knowledge. Here, semantic cognition was assessed in 100 young and older adults. Despite having a broader knowledge base, older people showed specific impairments in semantic control, performing more poorly than young people when selecting among competing semantic representations. Conversely, they showed preserved controlled retrieval of less salient information from the semantic store. Breadth of semantic knowledge was positively correlated with controlled retrieval but was unrelated to semantic selection ability, which was instead correlated with non-semantic executive function. These findings indicate that three distinct elements contribute to semantic cognition: semantic representations that accumulate throughout the lifespan, processes for controlled retrieval of less salient semantic information, which appear age-invariant, and mechanisms for selecting task-relevant aspects of semantic knowledge, which decline with age and may relate more closely to domain-general executive control.

Holtzman, D. and J. Ulrich (2019). "Senescent glia spell trouble in Alzheimer's disease." *Nature Neuroscience* **22**(5): 683-684.

Comment on "Senolytic therapy alleviates Aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model" [Zhang, P. et al. Nat Neurosci. 2019. https://doi.org/10.1038/s41593-019-0372-9: DNA damage or cellular stresses can induce senescence, and increased senescence with aging contributes to age-associated tissue damage, inflammation and disease. Zheng [Zhang] and colleagues report increased senescent oligodendrocyte progenitor cells around amyloid plaques. Therapeutically eliminating these senescent cells may influence the onset and progression of Alzheimer's disease pathology.

Horváth, J., et al. (2009). "Age-related differences in distraction and reorientation in an auditory task." *Neurobiology of Aging* **30**(7): 1157-1172.

Behavioral and event-related potential measures of distraction and reorientation were obtained from children (6 years), young (19-24 years) and elderly adults (62-82 years) in an auditory distraction-paradigm. Participants performed a go/nogo duration discrimination task on a sequence of short and long (50-50%) tones. In children, reaction times were longer and discrimination (d') scores were lower than in adults. Occasionally (15%), the pitch of the presented tones was changed. The task-irrelevant feature variation resulted in longer reaction times and lower d' scores with no significant differences between the three groups. Task-irrelevant changes affected the N1 amplitude and elicited the mismatch negativity, N2b, P3 and reorienting negativity (RON) sequence of event-related brain potentials. In children, the P3 latency was the same as in young adults. However, the RON component was delayed by about 100ms. In the elderly, P3 and RON were uniformly delayed by about 80ms compared to young adults. This pattern of results provides evidence that distraction influences different processing stages in the three groups. Restoration of the task-optimal attention set was delayed in children, whereas in the elderly, the triggering of involuntary attention-switching required longer time.

Horvath, S. and K. Raj (2018). "DNA methylation-based biomarkers and the epigenetic clock theory of ageing." *Nature Reviews Genetics* **19**: 371-384.

Identifying and validating molecular targets of **i**nterventions that extend the human health span and lifespan has been difficult, as most clinical biomarkers are not sufficiently representative of the fundamental mechanisms of ageing to serve as their indicators. In a recent breakthrough, biomarkers of ageing based on DNA methylation data have enabled accurate age estimates for any tissue across the entire life course. These 'epigenetic clocks' link developmental and maintenance processes to biological ageing, giving rise to a unified theory of life course. Epigenetic biomarkers may help to address long-standing questions in many fields, including the central question: why do we age?

Howard Jr., J. H. and Darlene V. Howard (2013). "Aging mind and brain: Is implicit learning spared in healthy aging**?**." *Frontiers in Psychology* **4**: Article 817.

It is often held that although explicit learning declines in the course of normal aging, implicit learning is relatively preserved. Here we summarize research from our group which leads us to argue that some forms of implicit learning do decline with adult age. In particular, we propose that there are age-related declines in implicit learning of probabilistic sequential relationships that occur across the adult lifespan, and that they reflect, at least in part, age-related striatal dysfunction. We first review behavioral evidence supporting this age-related decline and then evidence from patient groups, genetics, and neuroimaging supporting this striatal dysfunction hypothesis. (**Keywords**: Aging, Cognition, Cognitive neuroscience, Implicit learning, Striatal dysfunction)

Hsu, J.-L., et al. (2008). "Gender differences and age-related white matter changes of the human brain: A diffusion tensor imaging study." *NeuroImage* **39**(2): 566-577.

Cerebral white matter undergoes various changes with normal aging. This study investigated the association between age, gender, and the global and regional fractional anisotropy (FA) and mean diffusivity (MD) in 145 adults (30 to 80 years old) using diffusion tensor magnetic resonance imaging. We studied sixteen regions of interest in both hemispheres to search for regions that display age- and gender-related white matter changes and also performed a complementary voxel-based analysis without any hypothesis a priori. On a global scale, our results indicate that the full brain FA was negatively correlated with age. The regional analysis showed that the anterior corpus callosum, the bilateral anterior and posterior internal capsule, and the posterior periventricular regions had the most significant age-related FA decrease. On the other hand, the FA in the temporal and occipital regions was not correlated with age. However, in contrast to males, females overall had a significantly lower FA in the right deep temporal regions. More gender differences in precentral, cingulate, and anterior temporal white matter areas were also found, suggesting that microstructural white matter organization in these regions may have a sexual dimorphism. Such differences were mainly due to the increase in diffusion perpendicular to fiber tracts. (**Keywords**: Aging, Gender, White matter, Diffusion tensor imaging, Fractional anisotropy, Voxel-based morphometry)

Huth, A. G., et al (2016). "Natural speech reveals the semantic maps that tile human cerebral cortex." *Nature* **532** 453-472. https://doi.org/410.1038/nature17637

The meaning of language is represented in regions of the cerebral cortex collectively known as the 'semantic system'. However, little of the semantic system has been mapped comprehensively, and the semantic selectivity of most regions is unknown. Here we systematically map semantic selectivity across the cortex using voxel-wise modelling of functional MRI (fMRI) data collected while subjects listened to hours of narrative stories. We show that the semantic system is organized into intricate patterns that seem to be consistent across individuals. We then use a novel generative model to create a detailed semantic atlas. Our results suggest that most areas within the semantic system represent information about specific semantic domains, or groups of related concepts, and our atlas shows which domains are represented in each area. This study demonstrates that data-driven methods—commonplace in studies of human neuroanatomy and functional connectivity—provide a powerful and efficient means for mapping functional representations in the brain.

Ishizaki, J., et al (1998). "Normative, community-based study of mini-mental state in elderly adults: The effect of age and educational level." *Journal of Gerontology: Psychological Sciences* **538**(6): 359-363.

We investigated community-based data of the Mini-Mental State Examination (MMSE) scores of elderly residents along with the effects of age and educational level. MMSE was planned for all residents over 65 years of age in a town in northern Japan. The number of elders who took the MMSE was 2,266 (90%). The score significantly declined with age and lower educational level, although no effect of sex was apparent. For the MMSE subitems, all the values except for that of naming showed effects of both age and educational level. Those screened by MMSE who fell in the range of cognitive impairment (< 24) accounted for 21.8% and those with severe cognitive impairment (< 18) constituted 6.0%. Despite the differences in language and culture, the mean scores are remarkably similar between Japan and other countries. This is the first normative, community-based study of MMSE among elderly adults in Japan. (**Topic**: Educational status, Internship and residency, Languages mini-mental state examination, Cognitive impairment, Elderly, Medical residencies, Naming function, Towns, Community)

Ising, C., et al. (2019). "Nlrp3 inflammasome activation drives tau pathology." *Nature* **575**(7784): 669-673.

Alzheimer's disease is characterized by the accumulation of amyloid-beta in plaques, aggregation of hyperphosphorylated tau in neurofibrillary tangles and neuroinflammation, together resulting in neurodegeneration and cognitive decline1. The NLRP3 inflammasome assembles inside of microglia on activation, leading to increased cleavage and activity of caspase-1 and downstream interleukin-1β release2. Although the NLRP3 inflammasome has been shown to be essential for the development and progression of amyloid-beta pathology in mice3, the precise effect on tau pathology remains unknown. Here we show that loss of NLRP3 inflammasome function reduced tau hyperphosphorylation and aggregation by regulating tau kinases and phosphatases. Tau activated the NLRP3 inflammasome and intracerebral injection of fibrillar amyloid-beta-containing brain homogenates induced tau pathology in an NLRP3-dependent manner. These data identify an important role of microglia and NLRP3 inflammasome activation in the pathogenesis of tauopathies and support the amyloid-cascade hypothesis in Alzheimer's disease, demonstrating that neurofibrillary tangles develop downstream of amyloid-beta-induced microglial activation.

Jia, Jianping et al. (2014). "The prevalence of dementia in urban and rural areas of china." *Alzheimer's & Dementia* **10**(1): 1–9.

The Chinese population has been aging rapidly and the country's economy has experienced exponential growth during the past three decades. The goal of this study was to estimate the changes in the prevalence of dementia, Alzheimer's disease (AD), and vascular dementia (VaD) among elderly Chinese individuals and to

analyze differences between urban and rural areas. METHODS: For the years 2008 to 2009, we performed a population-based cross-sectional survey with a multistage cluster sampling design. Residents aged 65 years and older were drawn from 30 urban (n = 6096) and 45 rural (n = 4180) communities across China. Participants were assessed with a series of clinical examinations and neuropsychological measures. Dementia, AD, and VaD were diagnosed according to established criteria via standard diagnostic procedures. RESULTS: The prevalence of dementia, AD, and VaD among individuals aged 65 years and older were 5.14% (95% CI, 4.71-5.57), 3.21% (95% CI, 2.87-3.55), and 1.50% (95% CI, 1.26-1.74), respectively. The prevalence of dementia was significantly higher in rural areas than in urban ones (6.05% vs. 4.40%, P < .001). The same regional difference was also seen for AD (4.25% vs. 2.44%, P < .001) but not for VaD (1.28% vs. 1.61%, P = .166). The difference in AD was not evident when the sample was stratified by educational level. Moreover, the risk factors for AD and VaD differed for urban and rural populations. CONCLUSIONS: A notably higher prevalence of dementia and AD was found in rural areas than in urban ones, and education might be an important reason for the urban-rural differences. (**Keywords**: Dementia Alzheimer's disease, Vascular dementia, Prevalence, Risk factors)

Jonkers, R. and R. Bastiaanse (1998). "How selective are selective word class deficits? Two case studies of action and object naming." *Aphasiology* **12**(3): 245-256.

In this article two case studies of fluent aphasic speakers are presented. Both patients performed significantly worse on an action-naming task than on an object-naming task, whereas comprehension of verbs was spared. The items of the action-naming test were controlled not only for the well-known factors that may influence word retrieval (e.g., word-frequency and imageability), but also for other variables that might be of relevance-that is, instrumentality, name relation to a noun and transitivity. Although both patients retrieved nouns better than verbs, word class as such did not seem to be the discriminating factor. In one patient name relation to a noun was particularly helpful in verb retrieval (verbs related in name to nouns were retrieved as easily as nouns in general), whereas in the other patient transitivity demonstrated an effect: he retrieved transitive verbs significantly better than intransitive verbs. It will be argued that the often-made distinction between verbs and nouns may be too rough, and may create artefacts. More careful matching on linguistic and extralinguistic criteria is necessary to learn more about the cognitive representation of verbs and nouns, and to obtain a better understanding of the effect of brain damage on word retrieval.

Kaiser, L. G., et al. (2005). "Age-related glutamate and glutamine concentration changes in normal human brain: 1h MR spectroscopy study at 4 T." *Neurobiology of Aging* **26**(2): 665-672.

Proton magnetic resonance spectroscopy was performed at 4 T to determine effects of age, region and gender on glutamate and glutamine in the normal human brain. Furthermore, glutamate and glutamine alterations with age were tested for correlations with other cerebral metabolites. Two 8 cm3 volumes were selected in corona radiata and mesial motor cortex in normal subjects (N = 24) between 24 and 68 years old. Older subjects had lower glutamate concentration in the motor cortex compared to younger subjects ($p < 0.001$). In corona radiata, older subjects demonstrated a trend in higher glutamine compared to younger subjects ($p = 0.05$). Glutamate in the motor cortex was positively correlated with glutamine, N-acetyl aspartate and creatine. Reduced glutamate and N-acetyl aspartate in the motor cortex is consistent with neuronal loss/shrinkage with age. In conclusion, different patterns in association with normal aging in these brain regions were detected in this study. (**Keywords**: Glutamate, Glutamine, Aging, Motor neurons, Spectroscopy 4 T, Metabolites)

Kemp, J., et al. (2014). "Age-related decrease in sensitivity to electrical stimulation is unrelated to skin conductance: An evoked potentials study." *Clinical Neurophysiology* **125**(3): 602-607.

With aging**,** kin is likely to become less hydrated, thereby increasing its resistance to electrical current. This, rather than sensorial/perceptual differences per se, may be the primary cause of differences between younger and older adults in somatosensorial perception in response to electrical stimuli. METHODS: To assess whether

aging alters the perception of electrical stimulation, we compared the perceived intensity of electrical stimuli in younger and older subjects, considering both setpoint intensities and the actual intensities of the current passing through subjects' skin. This resulted in reliable information about electrical somatosensory perception in both groups at equivalent received amounts of current. Somatosensory evoked potentials (SEPs) enabled the objective evaluation of somatosensitivity in both groups. RESULTS: At equivalent received intensities, the mean ratings were significantly lower in older than in younger subjects. SEPs confirmed these results, with older adults having longer latencies and reduced amplitudes. CONCLUSIONS: Our results suggest that age-related decreases in somatosensitivity to electrical stimuli are not due to cutaneous physiological changes. SIGNIFICANCE: Age-related increases in electrical somatosensorial and pain thresholds seem to be more attributable to dysfunctions of the peripheral and/or central nervous system, than to non-optimal activation of somatosensorial receptors/nerve fibers due to cutaneous physiological changes. (**Keywords**: Aging, Electrical stimulations, Evoked potentials, Received intensity, Setpoint intensity, Skin conductance, Somatosensitivity)

Kennedy, J. L., et al. (2003). "The genetics of adult-onset neuropsychiatric disease: Complexities and conundra?" *Science* **302**: 822-826.

Genetic factors play a major role in the etiology of adult-onset neurodegenerative and neuropsychiatric disorders. Several highly penetrant genes have been cloned for rare, autosomal-dominant, early-onset forms of neurodegenerative diseases. These genes have provided important insights into the mechanisms of these diseases (often altering neuronal protein processing). However, the genes associated with inherited susceptibility to late-onset neurodegenerative diseases, schizophrenia, and bipolar disorder appear to have smaller effects and are likely to interact with each other (and with nongenetic factors) to modulate susceptibility and/or disease phenotype. Several strategies have recently been applied to address this complexity, leading to the identification of a number of candidate susceptibility loci/genes.

Klaassen, E. B., et al (2013). "Working memory in middle-aged males: Age-related brain activation changes and cognitive fatigue effects." *Biological Psychology* **96**: 134-143.

We examined the effects of aging and cognitive fatigue on working memory (WM) related brain activation using functional magnetic resonance imaging. Age-related differences were investigated in 13 young and 16 middle-aged male school teachers. Cognitive fatigue was induced by sustained performance on cognitively demanding tasks (compared to a control condition). Results showed a main effect of age on left dorsolateral prefrontal and superior parietal cortex activation during WM encoding greater activation was evident in middle-aged than young adults regardless of WM load or fatigue condition. An interaction effect was found in the dorsomedial prefrontal cortex (DMPFC) WM load-dependent activation was elevated in middle-aged compared to young in the control condition, but did not differ in the fatigue condition due to a reduction in activation in middle-aged in contrast to an increase in activation in the young group. These findings demonstrate age-related activation differences and differential effects of fatigue on activation in young and middle-aged adults. (**Keywords**: Aging, Cognitive fatigue, Functional magnetic resonance imaging, Working memory)

Knight, B. (2009). "The ageing brain." *The Lancet Neurology* **8**(6): 516-517.

The *Healthy Ageing Brain* addresses a wide range of ageing-related phenomena from a unique perspective that combines cognitive neuroscience with attachment theory to focus on social and emotional aspects of adult development and ageing. Cozolino's developmental focus is informed by a solid understanding of child and adolescent development and how increased knowledge in these fields has changed our understanding of the ongoing development of the brain into adolescence, young adulthood, and now later life. He chooses a determinedly optimistic perspective on adult development in general, and brain changes in particular, that is refreshing against a background of societal negativity regarding ageing. This negativity is even more pronounced in much of neuroscience, which has a perspective on ageing that the late British gerontologist Tom Kitwood referred to as “neurological determinism”.

Koenig, T., et al. (2002). "Millisecond by millisecond, year by year: Normative EEG microstates and developmental stages." *NeuroImage* **16**(1): 41-48. https://doi.org/10.1006/nimg.2002.1070

Most studies of continuous EEG data have used frequency transformation, which allows the quantification of brain states that vary over seconds. For the analysis of shorter, transient EEG events, it is possible to identify and quantify brain electric microstates as subsecond time epochs with stable field topography. These microstates may correspond to basic building blocks of human information processing. Microstate analysis yields a compact and comprehensive repertoire of short lasting classes of brain topographic maps, which may be considered to reflect global functional states. Each microstate class is described by topography, mean duration, frequency of occurrence and percentage analysis time occupied. This paper presents normative microstate data for resting EEG obtained from a database of 496 subjects between the age of 6 and 80 years. The extracted microstate variables showed a lawful, complex evolution with age. The pattern of changes with age is compatible with the existence of developmental stages as claimed by developmental psychologists. The results are discussed in the framework of state dependent information processing and suggest the existence of biologically predetermined top-down processes that bias brain electric activity to functional states appropriate for age-specific learning and behavior. (**Keywords**: EEG, maturation, microstate, development, normative data)

Komes, J., et al. (2014). "Fluency affects source memory for familiar names in younger and older adults: Evidence from event-related brain potentials." *NeuroImage* **92**((2014)): 90-105.

A current debate in memory research is whether and how the access to source information depends not only on recollection, but on fluency-based processes as well. In three experiments, we used event-related brain potentials (ERPs) to examine influences of fluency on source memory for famous names. At test, names were presented visually throughout, whereas visual or auditory presentation was used at learning. In Experiment 1, source decisions following old/new judgments were more accurate for repeated relative to non-repeated visually and auditorily learned names. ERPs were more positive between 300 and 600ms for visually learned as compared to both auditorily learned and new names, resembling an N400 priming effect. In Experiment 2, we omitted the old/new decision to more directly test fast-acting fluency effects on source memory. We observed more accurate source judgments for repeated versus non-repeated visually learned names, but no such effect for repeated versus non-repeated auditorily learned names. Again, an N400 effect (300-600ms) differentiated between visually and auditorily learned names. Importantly, this effect occurred for correct source decisions only. We interpret it as indexing fluency arising from within-modality priming of visually learned names at test. This idea was further supported in Experiment 3, which revealed an analogous pattern of results in older adults, consistent with the assumption of spared fluency processes in older age. In sum, our findings suggest that fluency affects person-related source memory via within-modality repetition priming in both younger and older adults. (**Keywords**: Cognitive aging, ERPs, Familiar names, Fluency, N400, Priming, Source memory)

Kowald, A. and T. B. L. Kirkwood (2014). "Transcription could be the key to the selection advantage of mitochondrial deletion mutants in aging." *PNAS* **111**(8): 2972-2977.

The mitochondrial theory of aging is widely popular but confronted by several apparent inconsistencies. On the one hand, mitochondrial energy production is of central importance to the health and proper functioning of cells, and single-cell studies have shown that mtDNA deletion mutants accumulate in a clonal fashion in various mammalian species, displacing the wild-type mtDNAs. On the other hand, no explanation exists yet for the clonal expansion of mtDNA mutants that is compatible with experimental observations. We present here a new idea based on the distinctive connection between transcription and replication of metazoan mtDNA. Bioinformatic analysis of mtDNA deletion spectra strongly supports the predictions of this hypothesis and identifies specific candidates for proteins involved in transcriptional control of mtDNA replication. Computer simulations show the mechanism to be compatible with the available data from short- and long-lived mammalian species. (**Keywords**: mathematical model, mitochondrial mutations)

Kuo, M. C. C., et al. (2014). "Age-related effects on perceptual and semantic encoding in memory." *Neuroscience* **261**: 95-106.

This study examined the age-related subsequent memory effect (SME) in perceptual and semantic encoding using event-related potentials (ERPs). Seventeen younger adults and 17 older adults studied a series of Chinese characters either perceptually (by inspecting orthographic components) or semantically (by determining whether the depicted object makes sounds). The two tasks had similar levels of difficulty. The participants made studied or unstudied judgments during the recognition phase. Younger adults performed better in both conditions, with significant SMEs detected in the time windows of P2, N3, P550, and late positive component (LPC). In the older group, SMEs were observed in the P2 and N3 latencies in both conditions but were only detected in the P550 in the semantic condition. Between-group analyses showed larger frontal and central SMEs in the younger sample in the LPC latency regardless of encoding type. Aging effect appears to be stronger on influencing perceptual than semantic encoding processes. The effects seem to be associated with a decline in updating and maintaining representations during perceptual encoding. The age-related decline in the encoding function may be due in part to changes in frontal lobe function. (**Keywords**: aging, event-related potentials, perceptual encoding processing, semantic processing, subsequent memory effect)

Kuzmina, E., et al. (2019). "What influences language impairment in bilingual aphasia? A meta-analytic review." *Frontiers in Psychology* **10**: Article 445.

Patterns of language impairment in multilingual speakers with post-stroke aphasia are diverse: in some cases the language deficits are parallel, that is, all languages are impaired relatively equally, whereas in other cases deficits are differential, that is, one language is more impaired than the other(s). This diversity stems from the intricate structure of the multilingual language system, which is shaped by a complex interplay of influencing factors, such as age of language acquisition, frequency of language use, premorbid proficiency, and linguistic similarity between one's languages. Previous theoretical reviews and empirical studies shed some light on these factors, however no clear answers have been provided. The goals of this review were to provide a timely update on the increasing number of reported cases in the last decade and to offer a systematic analysis of the potentially influencing variables. One hundred and thirty cases from 65 studies were included in the present systematic review and effect sizes from 119 cases were used in the meta-analysis. Our analysis revealed better performance in L1 compared to L2 in the whole sample of bilingual speakers with post-stroke aphasia. However, the magnitude of this difference was influenced by whether L2 was learned early in childhood or later: those who learned L2 before 7 years of age showed comparable performance in both of their languages contrary to the bilinguals who learned L2 after 7 years of age and showed better performance in L1 compared to L2. These robust findings were moderated mildly by premorbid proficiency and frequency of use. Finally, linguistic similarity did not appear to influence the magnitude of the difference in performance between L1 and L2. Our findings from the early bilingual subgroup were in line with the previous reviews which included mostly balanced early bilinguals performing comparably in both languages. Our findings from the late bilingual subgroup stressed the primacy of L1 and the importance of age of L2 learning. In addition, the evidence from the present review provides support for theories emphasizing the role of premorbid proficiency and language use in language impairment patterns in bilingual aphasia. (**Keywords**: Bilingual aphasia, Language use, Linguistic similarity, Meta-analysis, Premorbid proficiency, Stroke)

La Joie, R., et al (2014). "Intrinsic connectivity identifies the hippocampus as a main crossroad between Alzheimer's and semantic dementia-targeted networks**.**" *Neuron* **81**: 1417-1428.

Alzheimer's disease (AD) and semantic dementia (SD) are both characterized by severe atrophy in the hippocampus, a brain region underlying episodic memory paradoxically; episodic memory is relatively preserved in SD. Here, we used intrinsic connectivity analyses and showed that the brain networks differentially vulnerable to each disease converge to the hippocampus in the healthy brain. As neurodegeneration is thought to spread

within preexisting networks, the common hippocampal atrophy in both diseases is likely due to its location at the crossroad between both vulnerable networks. Yet, we showed that in the normal brain, these networks harbor different functions, with episodic memory relying on the AD-vulnerable network only. Overall, disease-associated cognitive deficits seem to reflect the disruption of targeted networks more than atrophy in specific brain regions: in AD, over hippocampal atrophy, episodic memory deficits are likely due to disconnection within a memory-related network.

LaBar, K. S., et al. (2004). "Impact of healthy aging on awareness and fear conditioning." *Behavioral Neuroscience* **118**(5): 905-915.

Fear conditioning has provided a useful model system for studying associative emotional learning, but the impact of healthy aging has gone relatively unexplored. The present study investigated fear conditioning across the adult life span in humans. A delay discrimination task was employed using visual conditioned stimuli and an auditory unconditioned stimulus. Awareness of the reinforcement contingencies was assessed in a postexperimental interview. Compared with young adult participants, middle-aged and older adults displayed reductions in unconditioned responding, discriminant conditioning, and contingency awareness. When awareness and overall arousability were taken into consideration, there were no residual effects of aging on conditioning. These results highlight the importance of considering the influence of declarative knowledge when interpreting age-associated changes in discriminative conditioned learning.

LaBarge, E., et al. (1986). "Performance of normal elderly on the Boston naming test**.**" *Brain and Language* **27**(2): 380-384.

The Boston Naming Test has enjoyed increasing use in many research studies since its introduction. However, there is little normative data on the age group above 60 years of age. This study presents data from a sample of 58 well-defined healthy elderly males and females between the ages of 60 and 85. In comparison with published normative data, our sample has higher means, smaller standard deviations, and narrower ranges. These results suggest that aging alone does not significantly alter recognition-cued word-finding ability as defined by the Boston Naming Test. Also, there is remarkably consistent performance throughout our age range.

Lecouvey, G., et al. (2019). "An impairment of prospective memory in mild Alzheimer's disease: A ride in a virtual town." *Frontiers in Psychology* **10**: Article 241. https://doi.org/210.3389/fpsyg.2019.00241

Research suggests that prospective memory (PM) is impaired from the very early stages of Alzheimer's Aldisease (AD). We sought to further characterize this impairment in patients with mild AD, using a virtual reality (VR) task to provide ecological assessment of PM. Methods: Fifteen cognitively normal older individuals (76.47 years old ± 4.14, MMSE: 28.80 ± 1.21), and 17 patients with mild AD (79.29 years old ± 4.45, MMSE: 22.82 ± 2.83) were asked to recall the prospective and retrospective components of seven intentions in a virtual town task. Six intentions were event-based, where the prospective cue was either highly (three intentions) or weakly (three intentions) associated with the retrospective component. The remaining intention was time-based. All participants completed a neuropsychological assessment of episodic memory, semantic memory and executive functioning. Non-parametric tests were used to compare the two groups on the different intentions types and components. Correlations between cognition and PM scores were then realized to further understand the cognitive correlates of the PM impairment in patients with AD. Results: Overall, patients with Alzheimer disease recalled fewer intentions than controls, with the retrospective component and time-based intentions being the most challenging for them. The strength of the association between the prospective and retrospective components, however, had no effect on their performance. Event-based PM impairment, as well as deficit in the recall of prospective component correlated with memory and executive functions performance. Conclusion: PM is impaired in AD. Both automatic and controlled processes of PM retrieval are disturbed. This study also confirms the reliability of VR for assessing complex cognitive functions such as PM. （**Keywords**: Alzheimer's disease, Event-based, Intentions, Prospective, Component, Retrospective Component, Time-based, Virtual reality)

Lee, H.-C., et al. (1994). "Differential accumulations of 4,977 bp deletion in mitochondrial DNA of various tissues in human ageing." *Biochimica et Biophysica Acta* **1226**(1): 37-43.

Several types of deletions in mitochondrial DNA (mtDNA) have been recently identified in various tissues of old humans. In order to determine whether there are differences in the incidence and proportion of deleted mtDNAs in different tissues during human ageing, we examined the 4,977 bp deletion in mtDNA of various tissues from subjects of different ages. Total DNA was extracted from each of the biopsied tissues and was serially diluted by two-fold with distilled water. A 533 bp DNA fragment was amplified by PCR from total mtDNA using a pair of primers L3304-3323 and H3817-3836, and another 524 bp PCR product was amplified from 4,977 bp deleted mtDNA by identical conditions using another pair of primers L8150-8166 and H13631-13650. The maximum dilution fold of each sample that still allowed the ethidium bromide-stained PCR product (533 bp or 524 bp) in the agarose gel to be visible under UV light illumination was taken as the relative abundance of the mtDNA (wild-type or mutant) in the original sample. By this method, we were able to determine the proportion of deleted mtDNA in human tissues. **We found** that the 4,977 bp deletion started to appear in the second and third decades of life in human muscle and liver tissues. But the deletion was not detectable in the testis until the age of 60 years. Moreover, the proportion of deleted mtDNA varied greatly in different tissues. Among the tissues examined, muscle was found to harbor higher proportion of deleted mtDNA than the other tissues. The average proportion of the 4,977 bp deleted mtDNA of the muscle from subjects over 70 years old was approximately 0.06%, and that of the liver and the testis was 0.0076% and 0.05%, respectively. These findings suggest that the frequency and proportion of the deleted mtDNA in human tissues increase with age and that the mtDNA deletions occur more frequently and abundantly in high energy-demanding tissues during the ageing process of the human. (**Keywords**: Mitochondrial DNA, Deletion, Human ageing, Muscle, Liver, Testis)

Lei, X. et al. (2019). "Jing lu zhiliudian ciji dui laohua he Alzheimer bing renzhi gongneng yingxiang de yanjiu jinzhan 经颅直流电刺激对老化和阿尔茨海默病认知功能影响的研究进展" (Effects of transcranial direct current stimulation on cognitive function after aging and Alzheimer's disease) (review)." *Zhongguo Kangfu Lilun yu Shijian* 中国康复理论与实践 (Chinese journal of rehabilitation theory and practice) **25** (3): 255-260. http://www.cjrtponline.com/CN/abstract/abstract7467.shtml

老化导致认知功能下降，包括记忆、注意、语言和执行等功能。阿尔茨海默病(AD)是一种与年龄密切相关的进行性神经退行性疾病,认知功能下降是其核心症状 之一。经颅直流电刺激(tDCS)已被应用于健康老年人和AD患者，改善生理和病理性老化相关的认知障碍。tDCS能改善老年人的记忆(情景记忆、语义记 忆和工作记忆)、语言、错误感知和注意功能，其效果受教育水平、刺激参数和个人任务基线成绩等多种因素影响。tDCS也能改善AD患者的认知功能，效果受 解剖差异、疾病严重程度、刺激参数以及评估工具等因素影响。认知训练与tDCS结合可进一步增强老年人和AD患者认知功能。(关键词：老化，阿尔茨海默病，经颅直流电刺激，认知功能，综述) Aging leads to cognitive decline, including memory, attention, language and execution. Alzheimer's disease(AD) is a progressive neurodegenerative disorder closely related to age. Decreased cognitive function is one of its core symptoms. Transcranial direct current stimulation(tDCS) has been used in old healthy adults and AD patients to improve aging-related cognitive impairment. tDCS can improve memory (situational memory, semantic memory and working memory), language, error awareness and attentional functions in the old adults, which were influenced by many factors, such as education levels, stimulation parameters and individual task baseline scores, etc. For AD patients, tDCS may improve their cognitive function, which is influenced by the factors as anatomical differences, severity of disease, stimulation parameters and assessment tools,etc. Cognitive training combined with tDCS can further improve cognitive function in old adults and AD patients. (**Keywords**: aging, Alzheimer's disease, transcranial direct current stimulation (tDCS), cognitive function, review)

Leinenga, G. and J. Götz (2015). "Scanning ultrasound removes amyloid-β and restores memory in an Alzheimer's disease mouse model." *Science Translational Medicine* **7**(278): 278ra233-278ra233.

Amyloid-β (Aβ) peptide has been implicated in the pathogenesis of Alzheimer's disease (AD). We present a nonpharmacological approach for removing Aβ and restoring memory function in a mouse model of AD

in which Aβ is deposited in the brain. We used repeated scanning ultrasound (SUS) treatments of the mouse brain to remove Aβ, without the need for any additional therapeutic agent such as anti-Aβ antibody. Spinning disk confocal microscopy and high-resolution three-dimensional reconstruction revealed extensive internalization of Aβ into the lysosomes of activated microglia in mouse brains subjected to SUS, with no concomitant increase observed in the number of microglia. Plaque burden was reduced in SUS-treated AD mice compared to sham-treated animals, and cleared plaques were observed in 75% of SUS-treated mice. Treated AD mice also displayed improved performance on three memory tasks: the Y-maze, the novel object recognition test, and the active place avoidance task. Our findings suggest that repeated SUS is useful for removing Aβ in the mouse brain without causing overt damage, and should be explored further as a noninvasive method with therapeutic potential in AD. (**Comment in**: Alzheimer disease: scanning ultrasound elicits amyloid-β clearance in mice. [*Nature Reviews Neurology* 2015]

Leung, P.-C. (2014). *The Asian Way of Exercises Yoga & Qigong— For the Health of Body & Mind*. (Pp. 8) Hong Kong: Institute of Chinese Medicine, Chinese University of Hong Kong.

Yoga originated from India and is becoming popular worldwide. Qigong originated from China and is less known outside China. Interestingly, both Indian Yoga and Chinese Qigong emphasize on three common components in their fundamental practices, viz. (i) stretching of muscles, tendons and ligaments when thousands of proprioceptive receptors which initiate the "gate theory" of neurological control of pain perception are stimulated; (ii) controlled breathing which harmonizes the somatic and autonomic systems of neurological activities; and (iii) the wonderful outcome after such simple voluntary efforts, a state of tranquility of the mind, which could be understood as Meditation. A comprehensive review on the reports on Yoga and Qigong practices affecting the physiological processes and mental states of the practitioners is completed to provide reliable information about the value of the practices. Result of the review shows that there are sufficient evidences today, after many carefully planned research studies, on the supportive effects of both Yoga and Qigong on not only neuromuscular pathologies but also problems in cardiovascular, pulmonary and most remarkably, mental health. Yoga and Qigong practices are good for both the body and mind. (**Keywords**: Yoga; Qigong; Body-mind health)

Leyns, C. E. G., et al. (2019). "TREM2 function impedes tau seeding in neuritic plaques." *Nature Neuroscience* **22**: 1217–1222. https://doi.org/10.1038/s41593-019-0433-0

Variants in the triggering receptor expressed on myeloid cells 2 (TREM2) have been associated with increased risk for sporadic, late-onset Alzheimer's disease. Here we show that germline knockout of Trem2 or the TREM2R47H variant reduces microgliosis around amyloid-β plaques and facilitates the seeding and spreading of neuritic plaque tau aggregates. These findings demonstrate a key role for TREM2 and microglia in limiting the development of peri-plaque tau pathologies.

Li, H., et al. (2014). "Trajectories of age-related cognitive decline and potential associated factors of cognitive function in senior citizens of Beijing**.**" *Current Alzheimer Research* **11**(8): 806-816.

With a longer life expectancy and an increased prevalence of neurodegenerative diseases, investigations on trajectories of cognitive aging have become exciting and promising. This study aimed to estimate the patterns of age-related cognitive decline and the potential associated factors of cognitive function in community-dwelling residents of Beijing, China. In this study, 1248 older adults aged 52-88 years [including 175 mild cognitive impairment (MCI) subjects] completed a battery of neuropsychological scales. The personal information, including demographic information, medical history, eating habits, lifestyle regularity and leisure activities, was also collected. All cognitive function exhibited an age related decline in normal volunteers. Piece-wise linear fitting results suggested that performance on the Auditory Verbal Learning Test remained stable until 58 years of age and continued to decline thereafter. The decline in processing speed and executive function began during the early 50's. Scores on visual-spatial and language tests declined after 66 years of age. The decline stage of the general mental status ranged from 63 to 70 years of age. However, the MCI group did not exhibit an obvious age-

related decline in most cognitive tests. Multivariate linear regression analyses indicated that education, gender, leisure activities, diabetes and eating habits were associated with cognitive abilities. These results indicated various trajectories of age-related decline across multiple cognitive domains. We also found different patterns of age related cognitive decline between MCI and normal elderly. These findings could help improve the guidance of cognitive intervention program and have implications for public policy issues.

Li, Y. et al. (2016). "Laonianren yanyu jiaoj zhangai diaocha fenxi 老年人言语交际障碍调查分析 (investigation on speech communication disorders among the elderly people)." *Renkou Xue Kan* 人口学刊 （population journal） **38(2016)**(2): 87-90.

老龄化社会是一个不可避免的世界趋势，如何改善老年人的言语交际质量已经成为全世界面临的共同课题。笔者针对当前我国老年群体的言语交际障碍成因和现状进行了系统的社会调研。研究发现，随着年龄增长，老年人产生显著的功能性听力下降。在60岁以上老人中，听力减退者占68%；在40~60岁期间，女性听力减退的速度高于男性。在进入老年阶段后，很多老年人心理状态产生变化：主动和他人交际的意愿降低；不喜欢和不同的交际对象交流；日均与他人沟通的时间减少等。（关键词：老年人；言语交际；交际障碍）Aging society has been an inevitable global trend. How to improve the quality of speech communication among the elderly has been a common topic all over the world. We conduct a systematic research on the causes and current situation of speech communicative disorders among elderly people in China. The results are as follows: firstly, the elderly people show significant functional hearing loss because of aging. Hearing loss occurs in 68% of people is older than 60 years old. The rate of hearing loss among females aged 40 to 60 years old is higher than that among males within the same age range. Secondly, entering the ranks of the elderly, many old people occur some psychological changes: elderly people generally become less willing to communicate with others; the elderly generally dislike to communicate with different communicative objects the time which the old people spend daily communicating with others has reduced, etc. (Key Words: Elderly people, Speech communication, Communicative disorders)

Lichtenthaler, S. F. and G. Guner (2019). "Pathology-linked protease caught in action: Structural snapshots of γ-secretase yied insight for drug development." *Science* **363**(6428): 690-691.

The intramembrane protease γ-secretase has fundamental functions in animals, including signal transduction during embryogenesis and tissue homeostasis in adulthood. γ-Secretase cleaves its numerous substrates within their single transmembrane domains (TMDs), largely independently of their amino acid sequence. Abnormal cleavage of the substrates Notch and amyloid precursor protein (APP) is linked to leukemia and Alzheimer's disease (AD), respectively, making γ-secretase an important drug target for both diseases (1). Yet, chronic use of γ-secretase inhibitors (GSIs), such as in patients with AD, led to severe side effects, resulting from cleavage inhibition not only of the disease-relevant substrate APP but likely also of other substrates. Thus, there is a clear need to develop substrate-selective GSIs, but this requires a detailed understanding of how γ-secretase recognizes, binds, and cleaves its substrates. On page 708 of this issue, Zhou et al. (2) and another study by Yang et al. (3) provide a major step in this direction. Zhou et al. reveal the cryo–electron microscopy (cryo-EM) structure of human γ-secretase with its bound substrate, a fragment of APP. Yang et al. report a structure of γ-secretase, but bound with Notch. Together, the two studies demonstrate that binding of different substrates occurs in a similar manner and that both γ-secretase and substrate undergo specific structural rearrangements for substrate positioning in the active site. This has major implications for understanding the mechanism of γ-secretase and its function in signal transduction and AD, and for future development of substrate-specific GSIs with fewer side effects. (**Comment on** "Recognition of the amyloid precursor protein by human γ-secretase" [Science. 2019]: Science. 2019 Feb 15, 363(6428). P. ii: eaaw0930. https://doi.org/10.1126/science.aaw0930. Epub 2019)

Lin, C., et al. (2019). "Increased brain entropy of resting-state FMRI mediates the relationship between depression severity and mental health-related quality of life in late-life depressed elderly." *Journal of Affective Disorders* **250**: 270-277.

Entropy analysis is a computational method used to quantify the complexity in a system, and loss of brain complexity is hypothesized to be related to mental disorders. Here, we applied entropy analysis to the resting-state functional magnetic resonance imaging (rs-fMRI) signal in subjects with late-life depression (LLD), an illness combined with emotion dysregulation and aging effect. METHODS: A total of 35 unremitted depressed elderly and 22 control subjects were recruited. Multiscale entropy (MSE) analysis was performed in the entire brain, 90 automated anatomical labeling-parcellated ROIs, and five resting networks in each study participant. LIMITATIONS: Due to ethical concerns, all the participants were under medication during the study. RESULTS: Regionally, subjects with LLD showed decreased entropy only in the right posterior cingulate gyrus but had universally increased entropy in affective processing (putamen and thalamus), sensory, motor, and temporal nodes across different time scales. We also found higher entropy in the left frontoparietal network (FPN), which partially mediated the negative correlation between depression severity and mental components of the quality of life, reflecting the possible neural compensation during depression treatment. CONCLUSION: MSE provides a novel and complementary approach in rs-fMRI analysis. The temporal-spatial complexity in the resting brain may provide the adaptive variability beneficial for the elderly with depression. (**Keywords**: Depression, Entropy, Late-life, Quality of life, Resting-state fMRI)

Lindenberger, U. and U. Mayr (2014). "Cognitive aging: Is there a dark side to environmental support?" *Trends in Cognitive Sciences* **18**(1): 7-15.

It has been known for some time that memory deficits among older adults increase when self-initiated processing is required and decrease when the environment provides task-appropriate cues. We propose that this observation is not confined to memory but can be subsumed under a more general developmental trend. In perception, learning or memory, and action management, older adults often rely more on external information than younger adults do, probably both as a direct reflection and indirect adaptation to difficulties in internally triggering and maintaining cognitive representations. This age-graded shift from internal towards environmental control is often associated with compromised performance. Cognitive aging research and the design of aging-friendly environments can benefit from paying closer attention to the developmental dynamics and implications of this shift. (**Keywords**: Cognitive aging, Cognitive control, Environmental support, Self-initiated processing)

Lipnicki, D. M., et al. (2019). "Determinants of cognitive performance and decline in 20 diverse ethno-regional groups: A cosmic collaboration cohort study." *PLOS Medicine* **16**(7): e1002853-e1002853.

With no effective treatments for cognitive decline or dementia, improving the evidence base for modifiable risk factors is a research priority. This study investigated associations between risk factors and late-life cognitive decline on a global scale, including comparisons between ethno-regional groups. METHODS AND FINDINGS: We harmonized longitudinal data from 20 population-based cohorts from 15 countries over 5 continents, including 48,522 individuals (58.4% women) aged 54-105 (mean = 72.7) years and without dementia at baseline. Studies had 2-15 years of follow-up. The risk factors investigated were age, sex, education, alcohol consumption, anxiety, apolipoprotein E ε4 allele (APOE*4) status, atrial fibrillation, blood pressure and pulse pressure, body mass index, cardiovascular disease, depression, diabetes, self-rated health, high cholesterol, hypertension, peripheral vascular disease, physical activity, smoking, and history of stroke. Associations with risk factors were determined for a global cognitive composite outcome (memory, language, processing speed, and executive functioning tests) and Mini-Mental State Examination score. Individual participant data meta-analyses of multivariable linear mixed model results pooled across cohorts revealed that for at least 1 cognitive outcome, age (B = -0.1, SE = 0.01), APOE*4 carriage (B = -0.31, SE = 0.11), depression (B = -0.11, SE = 0.06), diabetes (B = -0.23, SE = 0.10), current smoking (B = -0.20, SE = 0.08), and history of stroke (B = -0.22, SE = 0.09) were independently associated with poorer cognitive performance ($p < 0.05$ for all), and higher levels of education (B = 0.12, SE = 0.02) and vigorous physical activity (B = 0.17, SE = 0.06) were associated with better performance ($p < 0.01$ for both). Age (B = -0.07, SE = 0.01), APOE*4 carriage (B = -0.41, SE = 0.18), and diabetes (B = -0.18, SE = 0.10) were independently associated with faster cognitive decline ($p < 0.05$ for all). Different effects between Asian people and white people included stronger associations for Asian people between ever smoking and poorer

cognition (group by risk factor interaction: B = -0.24, SE = 0.12), and between diabetes and cognitive decline (B = -0.66, SE = 0.27 $p < 0.05$ for both). Limitations of our study include a loss or distortion of risk factor data with harmonization, and not investigating factors at midlife. CONCLUSIONS: These results suggest that education, smoking, physical activity, diabetes, and stroke are all modifiable factors associated with cognitive decline. If these factors are determined to be causal, controlling them could minimize worldwide levels of cognitive decline. However, any global prevention strategy may need to consider ethno-regional differences.

Liu, T., et al. (2010). "The effects of age and sex on cortical sulci in the elderly." *NeuroImage* **51**(1): 19-27.

A large number of structural brain studies using magnetic resonance imaging (MRI) have reported age-related cortical changes and sex difference in brain morphology. Most studies have focused on cortical thickness or density, with relatively few studies of cortical sulcal features, especially in the elderly. In this paper, we report global sulcal indices (g-SIs) of both cerebral hemispheres and the average sulcal span in six prominent sulci, as observed in T1-weighted scans obtained from a large community cohort of 319 non-demented individuals aged between 70 and 90 years (mean=78.06+/-4.75 male/female=149/170), using automated methods. Our results showed that for both hemispheres, g-SIs had significant negative correlations with age in both men and women. Using an interactive effect analysis, we found that g-SIs for men declined faster with age than that for women. The widths of all six sulcal spans increased significantly with age, with largest span increase occurring in the superior frontal sulcus. Compared to women, men had significantly wider sulcal spans for all sulci that were examined. Our findings suggest that both age and sex contribute to significant cortical gyrification differences and variations in the elderly. This study establishes a reference for future studies of age-related brain changes and neurodegenerative diseases in the elderly. (**Keywords**: Aging, Sex, Cortex, Sulcus, MRI)

Liu, T., et al. (2011). "The relationship between cortical sulcal variability and cognitive performance in the elderly." *NeuroImage* **56**(3): 865-873.

The relationship between cognitive functions and brain structure has been of long-standing research interest. Most previous research has attempted to relate cognition to volumes of specific brain structures or thickness of cortical regions, with relatively few studies examining other features such as cortical surface anatomy. In this study, we examine the relationship between cortical sulcal features and cognitive function in a sample (N=316) of community-dwelling subjects aged between 70 and 90 years (mean=78.06±4.75 male/female=130/186) who had detailed neuropsychological assessments and brain MRI scans. Using automated methods on 3D T1-weighted brain scans, we computed global sulcal indices (g-SIs) of the whole brain and average sulcal spans of five prominent sulci. The g-SI, which reflects the complexity of sulcal folds across the cerebral hemispheres, showed a significant positive correlation with performance in most cognitive domains including attention/processing speed, memory, language and executive function. Regionally, a negative correlation was found between some cognitive functions and sulcal spans, i.e. poorer cognitive performance was associated with a wider sulcal span. Of the five cognitive domains examined, the performance of processing speed was found to be correlated with the spans of most sulci, with the strongest correlation being with the superior temporal sulcus. Memory did not show a significant correlation with any individual sulcal index, after correcting for age and sex. Of the five sulci measured, the left superior temporal sulcus showed the highest sensitivity, with significant correlations with performances in all cognitive domains except memory, after controlling for age, sex, years of education and brain size. The results suggest that regionally specific sulcal morphology is associated with cognitive function in elderly individuals. Research highlights: ► We examined 3D cortical sulci of healthy elderly in multiple cognitive domains. ► Sulcal complexity was associated with better cognitive functions. ► Processing speed showed the largest range of correlations with sulcal measures. ► No significant relationship between sulcal morphology and memory was found. (**Keywords**: Brain, Cortex, Aging, MRI, Sulcus, Cognition)

Llano, D. A., et al. (2011). "Derivation of a new ADAS-cog composite using tree-based multivariate analysis prediction of conversion from mild cognitive impairment to Alzheimer disease." *Alzheimer Disease and*

Associated Disorders **25**(1): 73-84.

Model-based statistical approaches were used to compare the ability of the Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-cog), cerebrospinal fluid (CSF), fluorodeoxyglucose positron emission tomography and volumetric magnetic resonance imaging (MRI) markers to predict 12-month progression from mild cognitive impairment (MCI) to Alzheimer disease (AD). Using the Alzheimer's Disease Neuroimaging Initiative (ADNI) data set, properties of the 11-item ADAS-cog (ADAS.11), the 13-item ADAS-cog (ADAS.All) and novel composite scores were compared, using weighting schemes derived from the Random Forests (RF) tree-based multivariate model. Weighting subscores using the RF model of ADAS. All enhanced discrimination between elderly controls, MCI and AD patients. The ability of the RF-weighted ADAS-cog composite and individual scores, along with neuroimaging or biochemical biomarkers to predict MCI to AD conversion over 12 months was also assessed. Although originally optimized to discriminate across diagnostic categories, the ADAS. All, weighted according to the RF model, did nearly as well or better than individual or composite baseline neuroimaging or CSF biomarkers in prediction of 12-month conversion from MCI to AD. These suggest that a modified subscore weighting scheme applied to the 13-item ADAS-cog is comparable to imaging or CSF markers in prediction of conversion from MCI to AD at 12 months.

Lockhart, S. N., et al. (2014). "White matter hyperintensities are associated with visual search behavior independent of generalized slowing in aging." *Neuropsychologia* **52**: 93-101.

A fundamental controversy is whether cognitive decline with advancing age can be entirely explained by decreased processing speed, or whether specific neural changes can elicit cognitive decline, independent of slowing. These hypotheses are anchored by studies of healthy older individuals where age is presumed the sole influence. Unfortunately, advancing age is also associated with asymptomatic brain white matter injury. We hypothesized that differences in white matter injury extent, manifest by MRI white matter hyperintensities (WMH), mediate differences in visual attentional control in healthy aging, beyond processing speed differences. We tested young and cognitively healthy older adults on search tasks indexing speed and attentional control. Increasing age was associated with generally slowed performance. WMH were also associated with slowed search times independent of processing speed differences. Consistent with evidence attributing reduced network connectivity to WMH, these results conclusively demonstrate that clinically silent white matter injury contributes to slower search performance indicative of compromised cognitive control, independent of generalized slowing of processing speed. See also, Graphical Abstract: https://ars.els-cdn.com/content/image/1-s2.0-S0028393213003552-fx1_lrg.jpg (**Keywords**: Cognitive control, Visual attention, Aging, Cerebrovascular disease, Cognitive neuroscience, Neuroimaging)

Lu, T., et al. (2014). "Rest and stress resistance in ageing and Alzheimer's disease." *Nature* **507**(7493): 448–454.

Human neurons are functional over an entire lifetime, yet the mechanisms that preserve function and protect against neurodegeneration during ageing are unknown. Here we show that induction of the repressor element 1-silencing transcription factor (REST also known as neuron-restrictive silencer factor, NRSF) is a universal feature of normal ageing in human cortical and hippocampal neurons. REST is lost, however, in mild cognitive impairment and Alzheimer's disease. Chromatin immunoprecipitation with deep sequencing and expression analysis show that REST represses genes that promote cell death and Alzheimer's disease pathology, and induces the expression of stress response genes. Moreover, REST potently protects neurons from oxidative stress and amyloid β-protein toxicity, and conditional deletion of REST in the mouse brain leads to age-related neurodegeneration. A functional orthologue of REST, Caenorhabditis elegans SPR-4, also protects against oxidative stress and amyloid β-protein toxicity. During normal ageing, REST is induced in part by cell non-autonomous Wnt signalling. However, in Alzheimer's disease, frontotemporal dementia and dementia with Lewy bodies, REST is lost from the nucleus and appears in autophagosomes together with pathological misfolded proteins. Finally, REST levels during ageing are closely correlated with cognitive preservation and longevity. Thus, the activation state of REST may distinguish neuroprotection from neurodegeneration in the ageing brain. (**Erratum in Addendum**: REST and stress resistance in ageing and Alzheimer's disease. *Nature* 2016])

(**Comment in** 1) Alzheimer's disease: A protective factor for the ageing brain. [*Nature* 2014] 2) Neurodegeneration: Ageing neurons need REST. [*Nature Reviews Neuroscience* 2014] 3) REST as a new therapeutic target for neurodegenerative disorders. [*Movement Disorder*. 2014] 4) Alternative REST Splicing Underappreciated. [*eNeuro* 2018])

Lu, T., et al. (2004). "Gene regulation and DNA damage in the ageing human brain." *Nature* **429**(6994): 883-891.

The ageing of the human brain is a cause of cognitive decline in the elderly and the major risk factor for Alzheimer's disease. The time in life when brain ageing begins is undefined. Here we show that transcriptional profiling of the human frontal cortex from individuals ranging from 26 to 106 years of age defines a set of genes with reduced expression after age 40. These genes play central roles in synaptic plasticity, vesicular transport and mitochondrial function. This is followed by induction of stress response, antioxidant and DNA repair genes. DNA damage is markedly increased in the promoters of genes with reduced expression in the aged cortex. Moreover, these gene promoters are selectively damaged by oxidative stress in cultured human neurons, and show reduced base-excision DNA repair. Thus, DNA damage may reduce the expression of selectively vulnerable genes involved in learning, memory and neuronal survival, initiating a programme of brain ageing that starts early in adult life. (**Subjects by ProQuest:** Gene regulation, DNA damage, Aging, Brain, Cortex, Plasticity (synaptic), Mitochondria, Cognitive ability, Learning, Memory)

Luo, L. and F. I. M. Craik (2008). "Aging and memory: A cognitive approach." *Canadian Journal of Psychiatry* **53**(6): 346-353.

This article describes changes in memory during the normal aging process from the standpoint of cognitive psychology. There is now a great deal of evidence to show that memory is not one single function but may be described in terms of different memory systems that show differential effects of aging. For example, memory for procedures, and some perceptual memory functions, show few age-related changes, whereas working memory, episodic memory, and prospective memory decline substantially in the course of normal aging. Memory for facts and knowledge (semantic memory) holds up well in older individuals provided that the information is used frequently, although the ability to retrieve highly specific information (such as names) typically declines. The article discusses current theoretical accounts of the effects of aging; different theorists have attributed the changes in memory and cognition to mental slowing, declining attentional resources, an inability to inhibit unwanted information, and a decline in cognitive control. Other suggestions include the notion that memory performance in older adults is particularly vulnerable when the need for self-initiated processing is greatest; conversely, performance is greatly helped by the provision of environmental support. The practical implications of these research findings and ideas include the point that clinical memory assessments should incorporate tests designed to measure the different aspects of memory functioning. (Key Words: aging, memory, cognitive functions, attentional resources, inhibition, executive functions, encoding and retrieval, memory for context, false memory, prospective memory, memory assessment)

MacKay, A. J., et al. (2002). "Noun and verb retrieval in healthy aging." *Journal of the International Neuropsychological Society* **8**: 764–770.

This study tests the hypothesis that retrieval of object and action names declines at different rates with age. Uncued and cued performance on the Boston Naming Test (BNT) and the Action Naming Test (ANT) were examined for 171 individuals from 50 to 88 years old. To control for differences in item difficulty, a subset of items from each of the two tests was selected for which uncued performance was equivalent in individuals in their 50s. With this matched set of items, differences in action and object naming were tested in the 60s and 70+ age groups. Although age-related decline in name retrieval was observed for both the BNT and the ANT subsets, no differences between object and action retrieval were found. Our results, thus, do not confirm previous studies reporting that object names and action names are differentially retrieved with aging. We discuss these new findings

in relation to evidence of dissociations in object and action naming in brain-damaged individuals.

Marie¨n, P., et al. (1998). "Normative data for the Boston naming test in native Dutch-speaking Belgian elderly." *Brain and Language* **65**: 447-467.

A normative study of the 60-item version of the Boston Naming Test (BNT) was performed in a group of 200 native Dutch-speaking Flemish elderly. Analysis of test results revealed that BNT performance in Dutch is significantly affected by age, years of education, and gender. Error analysis disclosed verbal semantic paraphasias to occur as the most frequent error type (1/3 errors). "Don't know responses," verbal semantic paraphasias, and adequate circumlocutions were found on at least 30 different BNT items and constituted the most diffusely distributed error types. Following a careful review of other normative BNT studies, group characteristics rather than cultural differences were found to account for the difference in the overall mean scores. Our study surprisingly revealed that, as far as American-English, Australian-English and Dutch-speaking elderly are concerned, linguistics does not have an impact on the overall mean BNT score. A linguistic impact, however, clearly holds on the qualitative levels of performance, reflected by fundamental differences in the error distribution in different languages. Language-related BNT characteristics therefore stress the need for specific adaptations of norms.

Marshall, J., et al. (1998). "Verb retrieval and sentence production in aphasia." *Brain and Language* **63**(2): 159-183.

This paper presents a subject with a selective verb retrieval deficit. Nouns were produced more successfully than verbs in spontaneous speech, picture naming and when naming to definition. The word class effect was not observed in comprehension tasks, reading aloud or writing. This indicated that it was due to a specific problem in accessing verbs' phonological representations from semantics. The second part of the paper explores the implications of the verb deficit for sentence production. Analyses of narrative speech revealed a typically agrammatic profile, with minimal verb argument structure and few function words and inflections. Two investigations suggested that the sentence deficit was at least partly contingent upon the verb deficit. In the first, the subject was asked to produce a sentence with the aid of a provided noun or verb. The noun cues were not effective in eliciting sentences, whereas verb cues were. The second investigation explored the effects of therapy aiming to improve verb retrieval. This therapy resulted in better verb retrieval and improved sentence production with those verbs. These findings suggest that an inability to access verbs' phonological representations can severely impair sentence formulation. Implications for models of sentence production are considered.

Mathys, H., et al. (2019). "Single-cell transcriptomic analysis of Alzheimer's disease." *Nature* **570**(7761): 332-337.

Alzheimer's disease **is a** pervasive neurodegenerative disorder, the molecular complexity of which remains poorly understood. Here, we analysed 80,660 single-nucleus transcriptomes from the prefrontal cortex of 48 individuals with varying degrees of Alzheimer's disease pathology. Across six major brain cell types, we identified transcriptionally distinct subpopulations, including those associated with pathology and characterized by regulators of myelination, inflammation, and neuron survival. The strongest disease-associated changes appeared early in pathological progression and were highly cell-type specific, whereas genes upregulated at late stages were common across cell types and primarily involved in the global stress response. Notably, we found that female cells were overrepresented in disease-associated subpopulations, and that transcriptional responses were substantially different between sexes in several cell types, including oligodendrocytes. Overall, myelination-related processes were recurrently perturbed in multiple cell types, suggesting that myelination has a key role in Alzheimer's disease pathophysiology. Our single-cell transcriptomic resource provides a blueprint for interrogating the molecular and cellular basis of Alzheimer's disease.

Matsunaga, R., et al. (2012). "Magnetoencephalography evidence for different brain subregions serving two musical cultures." *Neuropsychologia* **50**(14): 3218-3227.

Individuals who have been exposed to two different musical cultures (bimusicals) can be differentiated from those exposed to only one musical culture (monomusicals). Just as bilingual speakers handle the distinct

language-syntactic rules of each of two languages, bimusical listeners handle two distinct musical-syntactic rules (e.g., tonal schemas) in each musical culture. This study sought to determine specific brain activities that contribute to differentiating two culture-specific tonal structures. We recorded magnetoencephalogram (MEG) responses of bimusical Japanese nonmusicians and amateur musicians as they monitored unfamiliar Western melodies and unfamiliar, but traditional, Japanese melodies, both of which contained tonal deviants (out-of-key tones). Previous studies with Western monomusicals have shown that tonal deviants elicit an early right anterior negativity (mERAN) originating in the inferior frontal cortex. In the present study, tonal deviants in both Western and Japanese melodies elicited mERANs with characteristics fitted by dipoles around the inferior frontal gyrus in the right hemisphere and the premotor cortex in the left hemisphere. Comparisons of the nature of mERAN activity to Western and Japanese melodies showed differences in the dipoles' locations but not in their peak latency or dipole strength. These results suggest that the differentiation between a tonal structure of one culture and that of another culture correlates with localization differences in brain subregions around the inferior frontal cortex and the premotor cortex.

Mattson, M. P. (2004). "Pathways towards and away from Alzheimer's disease." *Nature* **430**(7000): 631-639.

Slowly but surely, Alzheimer's disease (AD) patients lose their memory and their cognitive abilities, and even their personalities may change dramatically. These changes are due to the progressive dysfunction and death of nerve cells that are responsible for the storage and processing of information. Although drugs can temporarily improve memory, at present there are no treatments that can stop or reverse the inexorable neurodegenerative process. But rapid progress towards understanding the cellular and molecular alterations that are responsible for the neuron's demise may soon help in developing effective preventative and therapeutic strategies.

Mazzon, G., et al. (2019). "Connected speech deficit as an early hallmark of CSF-defined Azheimer's disease and correlation with cerebral hypoperfusion pattern." *Current Alzheimer Research* **16**(6): 483.

Diagnosis of prodromal Alzheimer's disease (AD) still represents a hot topic and there is a growing interest for the detection of early and non-invasive biomarkers. Although progressive episodic memory impairment is the typical predominant feature of AD, communicative difficulties can be already present at the early stages of the disease. Objective: This study investigated the narrative discourse production deficit as a hallmark of CSF defined prodromal AD and its correlation with cerebral hypoperfusion pattern. Methods: Narrative assessment with a multilevel procedure for discourse analysis was conducted on 28 subjects with Mild Cognitive Impairment (15 MCI due to AD, 13 MCI non-AD) and 28 healthy controls. The diagnostic workup included CSF AD biomarkers. Cerebral hypoperfusion pattern was identified by SPECT image processing. Results: The results showed that the discourse analysis of global coherence and lexical informativeness indexes allowed to identify MCI due to AD from MCI non-AD and healthy subjects. These findings allow to hypothesize that the loss of narrative efficacy could be a possible early clinical hallmark of Alzheimer's disease. Furthermore, a significant correlation of global coherence and lexical informativeness reduction with the SPECT hypoperfusion was found in the dorsal aspect of the anterior part of the left inferior frontal gyrus, supporting the hypothesis that this area has a significant role in communicative efficacy, and in particular, in semantic selection executive control. Conclusion: This study contributes to the understanding of the neural networks for language processing and their involvement in prodromal Alzheimer's disease. It also suggests an easy and sensitive tool for clinical practice that can help identifying individuals with prodromal Alzheimer's disease. (**Keywords**: Alzheimer's Disease, Biomarker, Connected speech, Functional neuroimaging, Language disorders, Mild Cognitive Impairment)

Mehta, J. and J. Jerger (2014). "Variation in semantic priming across age groups: An AERP study." *International Journal of Audiology* **53**: 235-242.

To study the semantic priming effect on words across the life span by means of auditory event-related potentials (AERPs). Design: Participants heard a series of three words (S1, S2, and S3). The task was to indicate whether S2 was in the same semantic category as S3. Semantic priming was quantified as the difference between

AERPs to the second word when it was semantically related to the first word (S2-R) or unrelated to the first word (S2-UR). Interest was focused entirely on the processing negativity (PN) component of the AERP to S2. The purpose of S3 was to delay the task decision so that the LPC generated by the decision would not confound the measurement of the PN component to S2. Sample: Ten children (9–11 years), 11 young adults (20–30 years), and 10 seniors (60–70 years). Results: The semantic priming effect was evident in the difference between peak amplitude of the PN component of the AERP to S2R and S2UR in all three groups. Children showed a clear asymmetry favoring the left hemisphere. In young adults, the asymmetry still favored the left hemisphere, but the degree of asymmetry was less robust. In the case of seniors, the priming effect was greater over the right hemisphere. Conclusion: Results suggest that all age groups benefit from contextual support, as evidenced by the semantic priming effect. However, differences in hemispheric asymmetry of activation indicate that perhaps seniors may need to recruit additional, but somewhat different brain resources to manage otherwise largely automatic tasks. (**Keywords**: Semantic priming, Auditory event-related potential, Processing negativity, Age groups, Hemispheric asymmetry)

Meunier, D., et al. (2009). "Age-related changes in modular organization of human brain functional networks." *NeuroImage* **44**(3): 715-723.

Graph theory allows us to quantify any complex system, e.g., in social sciences, biology or technology, that can be abstractly described as a set of nodes and links. Here we derived human brain functional networks from fMRI measurements of endogenous, low frequency, correlated oscillations in 90 cortical and subcortical regions for two groups of healthy (young and older) participants. We investigated the modular structure of these networks and tested the hypothesis that normal brain aging might be associated with changes in modularity of sparse networks. Newman's modularity metric was maximised and topological roles were assigned to brain regions depending on their specific contributions to intra- and inter-modular connectivity. Both young and older brain networks demonstrated significantly non-random modularity. The young brain network was decomposed into 3 major modules: central and posterior modules, which comprised mainly nodes with few inter-modular connections, and a dorsal fronto-cingulo-parietal module, which comprised mainly nodes with extensive inter-modular connections. The mean network in the older group also included posterior, superior central and dorsal fronto-striato-thalamic modules but the number of intermodular connections to frontal modular regions was significantly reduced, whereas the number of connector nodes in posterior and central modules was increased.

Miceli, G., et al. (1988). "Patterns of dissociation in comprehension and production of nouns and verbs." *Aphasiology* **2**: 351-358.

Theoretical analysis and experimental evidence converge in support of model of the lexicon which assumes that lexical information is represented in a number of independent lexical components. This distributed model of the lexical system assumes that there are independent input and output lexical components which, in turn, consist of independent orthographic and phonological lexical components. The input lexicons are connected to the output lexicons through a lexical-semantic components. (Caramazza 1988) … In this paper we report differential patterns of dissociations in comprehension and production of verbs and nouns in several aphasic patients. ... **The implications of** these results for the functional architecture of the lexical system are straightforward: not only is it the case that the lexicon is organized by grammatical class but this organizational principle is duplicated for input and output subcomponents of the lexical system (see Caramazza 1988, for discussion). A functional architecture of the lexical system of the form proposed here has considerable prima facie plausibility. After all, we want the relevant lexical distinctions to be represented at just those levels where they would serve a useful purpose. In the present case we want form class information to be represented both in the input and output components of the lexicon so that it may be exploited in sentence comprehension (input) and sentence production (output). (from the 1st 3 paragraphs of the article)

Miceli, G., et al. (1984). "On the basis for the agrammatic's difficulty in producing main verbs." *Cortex* **20**: 207-220.

Current theories of agrammatism do not provide a clear explanation for the co-occurrence of omission of grammatical markers and main verbs in this disorder. This study tested the hypothesis that the two symptom features have distinct underlying causes. Specifically, that the omission of main verbs in agrammatic speech is caused, at least in part, by a lexical (as opposed to a syntactic) deficit. Agrammatic and anomic aphasics and normal controls were given an object and action naming test. Agrammatic patients showed a marked impairment in naming actions in contrast to anomic aphasics and normal controls who named actions better than objects. The action naming impairment in agrammatic patients was interpreted as evidence for the lexical deficit hypothesis of verb omission in the speech of these patients and as a demonstration that agrammatism is a heterogeneous disorder that implicates damage to both lexical and syntactic mechanisms.

Mikkelsen, U. R., et al. (2013). "Life-long endurance exercise in humans: Circulating levels of inflammatory markers and leg muscle size." *Mechanisms of Ageing and Development* **134**(11-12): 531-540.

Human aging is associated with a loss of skeletal muscle and an increase in circulating inflammatory markers. It is unknown whether endurance training (Tr) can prevent these changes. Therefore, we studied 15 old trained (O-Tr) healthy males and, for comparison, 12 old untrained (O-Un), 10 Young-Tr (Y-Tr) and 12 Young-Un (Y-Un). Quadriceps size, VO2 peak, CRP, IL-6, TNF-α and its receptors, suPAR, lipid profile, leucocytes and glucose homeostasis were measured. Tr was associated with an improved insulin profile ($p<0.05$), and lower leucocyte ($p<0.05$) and triglyceride levels ($p<0.05$), independent of age. Aging was associated with poorer glucose control ($p<0.05$), independent of training. The age-related changes in waist circumference, VO2 peak, cholesterol, LDL, leg muscle size, CRP and IL-6 were counteracted by physical activity ($p<0.05$). A significant increase in suPAR with age was observed ($p<0.05$). Most importantly, life-long endurance exercise was associated with a lower level of the inflammatory markers CRP and IL-6 ($p<0.05$), and with a greater thigh muscle area ($p<0.05$), compared to age-matched untrained counterparts. These findings in a limited group of individuals suggest that regular physical endurance activity may play a role in reducing some markers of systemic inflammation, even within the normal range, and in maintaining muscle mass with aging. (**Keywords,** Master athletes, Cytokines, Aging, Skeletal muscle mass, Low-grade inflammation, **Abbreviations**: CRP C-reactive protein, HDL high density lipoprotein, HOMA-IR, homeostatic model assessment – insulin resistance, IL-6, interleukin 6, IPAQ, International Physical Activity Questionnaire, LDL, low density lipoprotein, MET, metabolic equivalent of task, MRI, magnetic resonance image, OGTT, oral glucose tolerance test, Q-CSA, quadriceps cross sectional area, QUICKI, quantitative insulin sensitivity check index, sTNFR, soluble TNF receptor, suPAR, soluble urokinase plasminogen activator receptor, Tr, trained, TNF-α, tumor necrosis factor alpha, Un, untrained, VO2 peak, peak oxygen consumption)

Milner, B., et al. (1998). "Cognitive neuroscience and the study of memory." *Neuron* **20**: 445-468.

The neurosciences have grown rapidly over the last half century. This growth has been stimulated by two important developments. First, molecular biology has transformed cellular neurobiology and has led to a new conceptual framework for signaling, a molecular framework that encompasses not only signaling in nerve cells but in all the cells of the body. Second, work on brain and cognition, which was traditionally associated with a number of different disciplines, has merged into a single discipline: cognitive neuroscience. This has provided a new framework for the study of memory, perception, action, language, and perhaps even conscious awareness. In this review, we will consider the second development by focusing on one aspect of cognitive neuroscience: recent progress in memory research. In so doing, we also want to consider the broader question: to what degree can these two independent and disparate strands—molecular neurobiology and cognitive neuroscience—be united? Can molecular biology enlighten the study of cognitive processes, such as learning and memory, as it has other areas of biology, such as development? In turn, can cognitive neuroscience define novel phenomena that will lead to a completely new set of molecular mechanisms and insights?

Mobley, A. S., et al. (2014). "Aging in the olfactory system." *Trends in Neurosciences* **37**(2): 77-84.

With advancing age, the ability of humans to detect and discriminate odors declines. In light of the rapid progress in analyzing molecular and structural correlates of developing and adult olfactory systems, the paucity of information available on the aged olfactory system is startling. A rich literature documents the decline of olfactory acuity in aged humans, but the underlying cellular and molecular mechanisms are largely unknown. Using animal models, preliminary work is beginning to uncover differences between young and aged rodents that may help address the deficits seen in humans, but many questions remain unanswered. Recent studies of odorant receptor (OR) expression, synaptic organization, adult neurogenesis, and the contribution of cortical representation during aging suggest possible underlying mechanisms and new research directions. (**Keywords**: Adult neurogenesis, Aging, Odorant receptor, Olfactory cortex, Rostral migratory stream, Synaptic organization)

Mohrin, M., et al. (2015). "A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging." *Science* **347**(6228): 1374-1377.

Deterioration of adult stem cells accounts for much of aging-associated compromised tissue maintenance. How stem cells maintain metabolic homeostasis remains elusive. Here, we identified a regulatory branch of the mitochondrial unfolded protein response (UPR(mt)), which is mediated by the interplay of SIRT7 and NRF1 and is coupled to cellular energy metabolism and proliferation. SIRT7 inactivation caused reduced quiescence, increased mitochondrial protein folding stress (PFS(mt)), and compromised regenerative capacity of hematopoietic stem cells (HSCs). SIRT7 expression was reduced in aged HSCs, and SIRT7 up-regulation improved the regenerative capacity of aged HSCs. These findings define the deregulation of a UPR(mt)-mediated metabolic checkpoint as a reversible contributing factor for HSC aging. (Comment in: Stem cells. Holding your breath for longevity. [Science. 2015] Stem cells: SIRT7, the UPR and HSC ageing. [Nat Rev Mol Cell Biol. 2015])

Monaghan, P. and S. G. Roberts (2019). "Cognitive influences in language evolution: Psycholinguistic predictors of loan word borrowing." *Cognition* **186**: 147-158.

Languages change due to social, cultural, and cognitive influences. In this paper, we provide an assessment of these cognitive influences on diachronic change in the vocabulary. Previously, tests of stability and change of vocabulary items have been conducted on small sets of words where diachronic change is imputed from cladistics studies. Here, we show for a substantially larger set of words that stability and change in terms of documented borrowings of words into English and into Dutch can be predicted by psycholinguistic properties of words that reflect their representational fidelity. We found that grammatical category, word length, age of acquisition, and frequency predict borrowing rates, but frequency has a non-linear relationship. Frequency correlates negatively with probability of borrowing for high-frequency words, but positively for low-frequency words. This borrowing evidence documents recent, observable diachronic change in the vocabulary enabling us to distinguish between change associated with transmission during language acquisition and change due to innovations by proficient speakers. (**Keywords**: Language evolution, Vocabulary change, Loan-words, Frequency, Age of acquisition, Word length, Language acquisition, Language incrementation)

Monetta, L., et al. (2007). "Age-related changes in the processing of the metaphorical alternative meanings of words." *Journal of Neurolinguistics* **20**(4): 277-284.

The goal of this study was to contribute to a better understanding of the relative impacts of age and the occurrence of a right-hemisphere lesion on the processing of the non-literal alternative meanings of words. Eighty healthy individuals participated in this study. Participants were divided into two groups: the older group included participants between 50 and 65 years old whereas the younger group included participants between 20 and 30 years old. Participants performed a semantic pairing task involving metaphorical and non -metaphorical alternative meanings of words and a countdown task. There were two different task presentation conditions: (1) non-interfering context task in which participants completed the main task (word-triad task) without any interference, and (2) interfering-context task in which the word-triad task and the countdown task were executed simultaneously. The main results indicated an age-related change in the processing of the non-literal alternative

meanings of words. The most interesting result was that the resource-limiting condition had an impact only on the young adult group. (**Author Keywords**: Aging, Cognitive resource processing, Metaphors, Non-literal language. **Keywords Plus**: Cognitive resources hypothesis, Brain-damaged patients, Right-hemisphere, Reduction, Capacity, FMRI. **Research Area:** Linguistics; Neuroimaging; Neurosciences; Psychology, Experimental)

Moreno-Jiménez, E. P., et al (2019). "Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease." *Nature Medicine* **25**: 554-560.

The hippocampus is one of the most affected areas in Alzheimer's disease (AD)1. Moreover, this structure hosts one of the most unique phenomena of the adult mammalian brain, namely, the addition of new neurons throughout life2. This process, called adult hippocampal neurogenesis (AHN), confers an unparalleled degree of plasticity to the entire hippocampal circuitry3,4. Nonetheless, direct evidence of AHN in humans has remained elusive. Thus, determining whether new neurons are continuously incorporated into the human dentate gyrus (DG) during physiological and pathological aging is a crucial question with outstanding therapeutic potential. By combining human brain samples obtained under tightly controlled conditions and state-of-the-art tissue processing methods, we identified thousands of immature neurons in the DG of neurologically healthy human subjects up to the ninth decade of life. These neurons exhibited variable degrees of maturation along differentiation stages of AHN. In sharp contrast, the number and maturation of these neurons progressively declined as AD advanced. These results demonstrate the persistence of AHN during both physiological and pathological aging in humans and provide evidence for impaired neurogenesis as a potentially relevant mechanism underlying memory deficits in AD that might be amenable to novel therapeutic strategies. (Comment in A fresh look at adult neurogenesis. [*Nature Medicine*. 2019])

Morris, J. C., et al. (2019). "Assessment of racial disparities in biomarkers for Alzheimer disease." *JAMA Neurol* **76**(3): 264-273.

IMPORTANCE: Racial differences in molecular biomarkers for Alzheimer disease may suggest race-dependent biological mechanisms. OBJECTIVE: To ascertain whether there are racial disparities in molecular biomarkers for Alzheimer disease. DESIGN, SETTING, AND PARTICIPANTS: A total of 1255 participants (173 African Americans) were enrolled from January 1, 2004, through December 31, 2015, in longitudinal studies at the Knight Alzheimer Disease Research Center at Washington University and completed a magnetic resonance imaging study of the brain and/or positron emission tomography of the brain with Pittsburgh compound B (radioligand for aggregated amyloid-β) and/or cerebrospinal fluid (CSF) assays for the concentrations of amyloid-β42, total tau, and phosphorylated tau181. Independent cross-sectional analyses were conducted from April 22, 2016, to August 27, 2018, for each biomarker modality with an analysis of variance or analysis of covariance including age, sex, educational level, race, apolipoprotein E (APOE) ε4 allele status, and clinical status (normal cognition or dementia). All biomarker assessments were conducted without knowledge of the clinical status of the participants. MAIN OUTCOMES AND MEASURES: The primary outcomes were hippocampal volumes adjusted for differences in intracranial volumes, global cerebral amyloid burden as transformed into standardized uptake value ratios (partial volume corrected), and CSF concentrations of amyloid-β42, total tau, and phosphorylated tau181. RESULTS: Of the 1255 participants (707 women and 548 men; mean [SD] age, 70.8 [9.9] years), 116 of 173 African American participants (67.1%) and 724 of 1082 non-Hispanic white participants (66.9%) had normal cognition. There were no racial differences in the frequency of cerebral ischemic lesions noted on results of brain magnetic resonance imaging, mean cortical standardized uptake value ratios for Pittsburgh compound B, or for amyloid-β42 concentrations in CSF. However, in individuals with a reported family history of dementia, mean (SE) total hippocampal volumes were lower for African American participants than for white participants (6418.26 [138.97] vs 6990.50 [44.10] mm3). Mean (SE) CSF concentrations of total tau were lower in African American participants than in white participants (293.65 [34.61] vs 443.28 [18.20] pg/mL; $P < .001$), as were mean (SE) concentrations of phosphorylated tau181 (53.18 [4.91] vs 70.73 [2.46] pg/mL; $P < .001$). There was a significant race by APOE ε4 interaction for both CSF total tau and phosphorylated tau181 such that only APOE ε4-positive participants showed the racial differences. CONCLUSIONS AND

RELEVANCE: The results of this study suggest that analyses of molecular biomarkers of Alzheimer disease should adjust for race. The lower CSF concentrations of total tau and phosphorylated tau181 in African American individuals appear to reflect a significant race by APOE ε4 interaction, suggesting a differential effect of this Alzheimer risk variant in African American individuals compared with white individuals.

Mosher, K. I. and T. Wyss-Coray (2014). "Microglial dysfunction in brain aging and Alzheimer's disease." *Biochemical Pharmacology* **88**(5): 594-604.

Microglia, the immune cells of the central nervous system, have long been a subject of study in the Alzheimer's disease (AD) field due to their dramatic responses to the pathophysiology of the disease. With several large-scale genetic studies in the past year implicating microglial molecules in AD, the potential significance of these cells has become more prominent than ever before. As a disease that is tightly linked to aging, it is perhaps not entirely surprising that microglia of the AD brain share some phenotypes with aging microglia. Yet the relative impacts of both conditions on microglia are less frequently considered in concert. Furthermore, microglial "activation" and "neuroinflammation" are commonly analyzed in studies of neurodegeneration but are somewhat ill-defined concepts that in fact encompass multiple cellular processes. In this review, we have enumerated six distinct functions of microglia and discuss the specific effects of both aging and AD. By calling attention to the commonalities of these two states, we hope to inspire new approaches for dissecting microglial mechanisms. (**Keywords**: Aging, Alzheimer's disease, Microglia, Neurodegeneration, Neuroinflammation)

Mueller, K. D., et al. (2018). "Connected speech and language in mild cognitive impairment and Alzheimer's disease: A review of picture description tasks." *Journal of Clinical and Experimental Neuropsychology* **40**(9): 917-939.

Introduction: The neuropsychological profile of people with mild cognitive impairment (MCI) and Alzheimer's disease (AD) dementia includes a history of decline in memory and other cognitive domains, including language. While language impairments have been well described in AD dementia, language features of MCI are less well understood. Connected speech and language analysis is the study of an individual's spoken discourse, usually elicited by a target stimulus, the results of which can facilitate understanding of how language deficits typical of MCI and AD dementia manifest in everyday communication. Among discourse genres, picture description is a constrained task that relies less on episodic memory and more on semantic knowledge and retrieval, within the cognitive demands of a communication context. Understanding the breadth of evidence across the continuum of cognitive decline will help to elucidate the areas of strength and need in terms of using this method as an evaluative tool for both cognitive changes and everyday functional communication. METHOD: We performed an extensive literature search of peer-reviewed journal articles that focused on the use of picture description tasks for evaluating language in persons with MCI or AD dementia. We selected articles based on inclusion and exclusion criteria and described the measures assessed, the psychometric properties that were reported, the findings, and the limitations of the included studies. RESULTS: 36 studies were selected and reviewed. Across all 36 studies, there were 1, 127 patients with AD dementia and 274 with MCI or early cognitive decline. Multiple measures were examined, including those describing semantic content, syntactic complexity, speech fluency, vocal parameters, and pragmatic language. Discriminant validity widely reported and distinct differences in language were observable between adults with dementia and controls; fewer studies were able to distinguish language differences between typically aging adults and those with MCI. DISCUSSION: Our review shows that picture description tasks are useful tools for detecting differences in a wide variety of language and communicative measures. Future research should expand knowledge about subtle changes to language in preclinical AD and Mild Cognitive Impairment (MCI) which may improve the utility of this method as a clinically meaningful screening tool. (**Keywords**: Alzheimer's disease, connected speech, dementia, discourse, language, mild cognitive impairment, picture description, spontaneous speech)

Nagelhus, E. A., et al. (2013). "Glia doctrine: Addressing the role of glial cells in healthy brain ageing." *Mechanisms of Ageing and Development* **134**(10): 449-459.

Glial cells in their plurality pervade the human brain and impact on brain structure and function. A principal component of the emerging glial doctrine is the hypothesis that astrocytes, the most abundant type of glial cells, trigger major molecular processes leading to brain ageing. Astrocyte biology has been examined using molecular, biochemical and structural methods, as well as 3D brain imaging in live animals and humans. Exosomes are extracelluar membrane vesicles that facilitate communication between glia, and have significant potential for biomarker discovery and drug delivery. Polymorphisms in DNA repair genes may indirectly influence the structure and function of membrane proteins expressed in glial cells and predispose specific cell subgroups to degeneration. Physical exercise may reduce or retard age-related brain deterioration by a mechanism involving neuro-glial processes. It is most likely that additional information about the distribution, structure and function of glial cells will yield novel insight into human brain ageing. Systematic studies of glia and their functions are expected to eventually lead to earlier detection of ageing-related brain dysfunction and to interventions that could delay, reduce or prevent brain dysfunction. (**Keywords**: Ageing, Alzheimer's disease, Astrocytes, Brain imaging, Exosomes, Glial cells)

National Research Council et. al. Eds. (2004). *Critical Perspectives on Racial and Ethnic Differences in Health in Late Life*. Washington, DC.: National Academies Press. https://doi.org/10.17226/11086,

In their later years**,** Americans of different racial and ethnic backgrounds are not in equally good--or equally poor--health. There is wide variation, but on average older Whites are healthier than older Blacks and tend to outlive them. But Whites tend to be in poorer health than Hispanics and Asian Americans. This volume documents the differentials and considers possible explanations. Selection processes play a role: selective migration, for instance, or selective survival to advanced ages. Health differentials originate early in life, possibly even before birth, and are affected by events and experiences throughout the life course. Differences in socioeconomic status, risk behavior, social relations, and health care all play a role. Separate chapters consider the contribution of such factors and the biopsychosocial mechanisms that link them to health. This volume provides the empirical evidence for the research agenda provided in the separate report of the Panel on Race, Ethnicity, and Health in Later Life.

Nedergaard, M. (2013). "Garbage truck of the brain." *Science* **340**: 1529-1530.

Essentially all neurodegenerative diseases are associated with misaccumulation of cellular waste products. Of these, misfolded or hyperphosphorylated proteins are among the most difficult for the brain to dispose. For example, tau and β-amyloid can accumulate as stable aggregates that are neurotoxic in conditions such as Alzheimer's disease (1). Intracellular proteasomal degradation and autophagy are considered the principal means for removing proteins in the central nervous system, and the dysfunction of each has been causally associated with neurodegeneration (2). Yet many cytosolic proteins are released into the interstitial space in the brain, suggesting that extracellular disposal routes may also eliminate waste (3).

Nelson, P. T., et al. (2019). "Limbic-predominant age-related TDP-43 encephalopathy (late): Consensus working group report." *Brain* **142**(6): 1503-1527.

We describe a recently recognized disease entity, limbic-predominant age-related TDP-43 encephalopathy (LATE). LATE neuropathological change (LATE-NC) is defined by a stereotypical TDP-43 proteinopathy in older adults, with or without coexisting hippocampal sclerosis pathology. LATE-NC is a common TDP-43 proteinopathy, associated with an amnestic dementia syndrome that mimicked Alzheimer's-type dementia in retrospective autopsy studies. LATE is distinguished from frontotemporal lobar degeneration with TDP-43 pathology based on its epidemiology (LATE generally affects older subjects), and relatively restricted neuroanatomical distribution of TDP-43 proteinopathy. In community-based autopsy cohorts, ~25% of

brains had sufficient burden of LATE-NC to be associated with discernible cognitive impairment. Many subjects with LATE-NC have comorbid brain pathologies, often including amyloid-β plaques and tauopathy. Given that the 'oldest-old' are at greatest risk for LATE-NC, and subjects of advanced age constitute a rapidly growing demographic group in many countries, LATE has an expanding but under-recognized impact on public health. For these reasons, a working group was convened to develop diagnostic criteria for LATE, aiming both to stimulate research and to promote awareness of this pathway to dementia. We report consensus-based recommendations including guidelines for diagnosis and staging of LATE-NC. For routine autopsy workup of LATE-NC, an anatomically-based preliminary staging scheme is proposed with TDP-43 immunohistochemistry on tissue from three brain areas, reflecting a hierarchical pattern of brain involvement: , amygdala, hippocampus, and middle frontal gyrus. LATE-NC appears to affect the medial temporal lobe structures preferentially, but other areas also are impacted. Neuroimaging studies demonstrated that subjects with LATE-NC also had atrophy in the medial temporal lobes, frontal cortex, and other brain regions. Genetic studies have thus far indicated five genes with risk alleles for LATE-NC: GRN, TMEM106B, ABCC9, KCNMB2, and APOE. The discovery of these genetic risk variants indicate that LATE shares pathogenetic mechanisms with both frontotemporal lobar degeneration and Alzheimer's disease, but also suggests disease-specific underlying mechanisms. Large gaps remain in our understanding of LATE. For advances in prevention, diagnosis, and treatment, there is an urgent need for research focused on LATE, including in vitro and animal models. An obstacle to clinical progress is lack of diagnostic tools, such as biofluid or neuroimaging biomarkers, for ante-mortem detection of LATE. Development of a disease biomarker would augment observational studies seeking to further define the risk factors, natural history, and clinical features of LATE, as well as eventual subject recruitment for targeted therapies in clinical trials. (**Keywords**: PET, MRI, FTLD, Epidemiology, SNAP. **Abbreviations** (in the article))

Ngandu, T., et al. (2015). "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." *Lancet* **385**: 2255-2263.

Modifiable vascular and lifestyle-related risk factors have been associated with dementia risk in observational studies. In the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER), a proof-of-concept randomised controlled trial, we aimed to assess a multidomain approach to prevent cognitive decline in at-risk elderly people from the general population. METHODS: In a double-blind randomised controlled trial we enrolled individuals aged 60-77 years recruited from previous national surveys. Inclusion criteria were CAIDE (Cardiovascular Risk Factors, Aging and Dementia) Dementia Risk Score of at least 6 points and cognition at mean level or slightly lower than expected for age. We randomly assigned participants in a 1:1 ratio to a 2 year multidomain intervention (diet, exercise, cognitive training, vascular risk monitoring), or a control group (general health advice). Computer-generated allocation was done in blocks of four (two individuals randomly allocated to each group) at each site. Group allocation was not actively disclosed to participants and outcome assessors were masked to group allocation. The primary outcome was change in cognition as measured through comprehensive neuropsychological test battery (NTB) Z score. Analysis was by modified intention to treat (all participants with at least one post-baseline observation). This trial is registered at ClinicalTrials.gov, number NCT01041989. FINDINGS: Between Sept 7, 2009, and Nov 24, 2011, we screened 2654 individuals and randomly assigned 1260 to the intervention group (n=631) or control group (n=629). 591 (94%) participants in the intervention group and 599 (95%) in the control group had at least one post-baseline assessment and were included in the modified intention-to-treat analysis. Estimated mean change in NTB total Z score at 2 years was 0·20 (SE 0·02, SD 0·51) in the intervention group and 0·16 (0·01, 0·51) in the control group. Between-group difference in the change of NTB total score per year was 0·022 (95% CI 0·002-0·042, p=0·030). 153 (12%) individuals dropped out overall. Adverse events occurred in 46 (7%) participants in the intervention group compared with six (1%) participants in the control group; the most common adverse event was musculoskeletal pain (32 [5%] individuals for intervention vs no individuals for control). INTERPRETATION: Findings from this large, long-term, randomised controlled trial suggest that a multidomain intervention could improve or maintain cognitive functioning in at-risk elderly people from the general population. FUNDING: Academy of Finland, La

Carita Foundation, Alzheimer Association, Alzheimer's Research and Prevention Foundation, Juho Vainio Foundation, Novo Nordisk Foundation, Finnish Social Insurance Institution, Ministry of Education and Culture, Salama bint Hamdan Al Nahyan Foundation, Axa Research Fund, EVO funding for University Hospitals of Kuopio, Oulu, and Turku and for Seinäjoki Central Hospital and Oulu City Hospital, Swedish Research Council, Swedish Research Council for Health, Working Life and Welfare, and af Jochnick Foundation.

Nicholas, M., et al. (1985). "Lexical retrieval in healthy aging." *Cortex* **21**: 595-606.

Lexical retrieval for common nouns and verbs was measured using 2 picture naming tests in 162 healthy female and male subjects aged 30 to 79 years. Responses were scored for correctness, responsivity to cueing, and response type. The ability to name both word types declined with age, especially after age 70 in healthy subjects. More errors were made on object names than action names, especially for older subjects. Subjects of all ages were equally able to utilize phonemic cues. With increasing age subjects produced more circumlocutions and fewer semantic errors. Response type difference need not reflect qualitative differences in lexical retrieval rather, they reflect the quantitatively greater difficulty of the task for healthy older people as compared to younger adults. The naming difficulty for healthy aging, we conclude, is at the label retrieval stage.

Novén, M., et al. (2019). "Cortical thickness of Broca's area and right homologue is related to grammar learning aptitude and pitch discrimination proficiency." *Brain and Language* **188**(2019): 42-47.

Aptitude for and proficiency in acquiring new languages varies in the human population but their neural bases are largely unknown. We investigated the influence of cortical thickness on language learning predictors measured by the LLAMA tests and a pitch-change discrimination test. The LLAMA tests are first language-independent assessments of language learning aptitude for vocabulary, phonetic working memory, sound-symbol correspondence (not used in this study), and grammatical inferencing. Pitch perception proficiency is known to predict aptitude for learning new phonology. Results show a correlation between scores in a grammatical meaning-inferencing aptitude test and cortical thickness of Broca's area ($r(30) = 0.65$, $p = 0.0202$) and other frontal areas ($r(30) = 0.66$, $p = 0.0137$). Further, a correlation was found between proficiency in discriminating pitch-change direction and cortical thickness of the right Broca homologue ($r(30) = 0.57$, $p = 0.0006$). However, no correlations were found for aptitude for vocabulary learning or phonetic working memory. Results contribute to locating cortical regions important for language-learning aptitude. (**Keywords**: Language learning aptitude, Cortical thickness, Broca's area, Inferior frontal gyrus)

Nunez, L., et al. (2019). "Interprofessional collaboration: How audiologists contribute to population health." *The Hearing Journal* **72**(7): 12,13,19.

Audiologists play a vital role in contributing to health care teams to address conditions associated with hearing and/or balance disorders1 including treatment of chronic conditions such as diabetes,2 depression,3 cognitive decline,4 dizziness with falling, and ototoxicity. More than 90 percent of the U.S. annual health care spending is for people with chronic and mental health conditions.5 Chronic diseases (e.g., heart disease, diabetes, Alzheimer's disease) are defined as conditions that last one year or more, require ongoing medical attention, and/or limit activities of daily living (ADL).6 Communication disabilities (hearing, speech, language, and cognitive-communication disorders) are among the most prevalent handicaps in the world.7 Disability percentages increase with age, especially hearing loss. The ability to communicate effectively (speak, listen, and write) affects ADLs, including obtaining the highest quality of health care. Communication disabilities can increase the time, effort, and frustration associated with providing effective care. In addition, communication disabilities can lead to poor adherence to and/or inability to understand treatment recommendations, this, in turn, may affect clinical outcomes or even result in accidental injury or further medical difficulties. Improving population health is a key component of the Institute for Health Improvement (IHI) Triple Aim (or Quadruple Aim). The Quadruple Aim is an approach to optimizing health system performance by improving the health of populations, enhancing the patient experience of care, reducing the per capita cost of health care, and improving the work conditions of health care clinicians

and staff.8 These aims connect interprofessional health care teams, leading to the provision of better health care services that should result in improved health outcomes.9 As such, interprofessional education is based on the concept that health professional students are best trained on the skills, knowledge, and attitudes that promote population health when they learn with, from, and about others from diverse health science fields.10 In 2018, the American Speech-Language-Hearing Association's (ASHA) Audiology Advisory Council was surveyed to examine the role of audiologists in collaboration with other health professionals who serve to improve population health through interprofessional education, collaborative practice, and/or research (i.e., IPECP) endeavors.

Nyberg, L., et al. (2012). "Memory aging and brain maintenance." *Trends in Cognitive Sciences* **16**(5): 292-305.

Episodic memory and working memory decline with advancing age. Nevertheless, large-scale population-based studies document well-preserved memory functioning in some older individuals. The influential 'reserve' notion holds that individual differences in brain characteristics or in the manner people process tasks allow some individuals to cope better than others with brain pathology and hence show preserved memory performance. Here, we discuss a complementary concept, that of brain maintenance (or relative lack of brain pathology), and argue that it constitutes the primary determinant of successful memory aging. We discuss evidence for brain maintenance at different levels: cellular, neurochemical, gray- and white-matter integrity, and systems-level activation patterns. Various genetic and lifestyle factors support brain maintenance in aging and interventions may be designed to promote maintenance of brain structure and function in late life.

Nyberg, L., et al. (2010). "Longitudinal evidence for diminished frontal cortex function in aging." *PNAS* **107**(52): 22682–22686.

Cross-sectional estimates of age-related changes in brain structure and function were compared with 6-y longitudinal estimates. The results indicated increased sensitivity of the longitudinal approach as well as qualitative differences. Critically, the cross-sectional analyses were suggestive of age-related frontal overrecruitment, whereas the longitudinal analyses revealed frontal underrecruitment with advancing age. The cross-sectional observation of overrecruitment reflected a select elderly sample. However, when followed over time, this sample showed reduced frontal recruitment. These findings dispute inferences of true age changes on the basis of age differences, hence challenging some contemporary models of neurocognitive aging, and demonstrate age-related decline in frontal brain volume as well as functional response.

Ocampo, A. and J. C. I. Belmonte (2015). "Holding your breath for longevity: A nutrient-sensing protein is important for the health of hematopoietic stem cells during aging." *Science* **347**(6228): 1319-1320.

Aging is a complex process. Progressive molecular changes lead to a decline in the ability of living beings to maintain homeostasis and overcome cellular stress, protein damage, and disease (1). At the organismal level, stem cells play a fundamental role in maintaining tissue integrity, and their functional and proliferative exhaustion is a major cause of aging (2). Hematopoietic stem cells, which reside in the bone marrow and give rise to all blood cell types, are a favored model for studying stem cell aging. However, the exact molecular mechanisms underlying their aging remain unknown. Sirtuins, a family of nutrient-sensing proteins (SIRT1 to SIRT7) that regulate gene expression and protein function in mammalian cells, orchestrate multiple pathways that are associated with age-related processes and longevity. On page 1374 of this issue, Mohrin et al. (3) connect SIRT7 to a metabolic checkpoint that controls aging in hematopoietic stem cells. ... Mohrin et al. seem to bring us a step closer to achieving a healthy longevity. (**This paper is a comment on**: Stem cell aging. A mitochondrial UPR-mediated metabolic checkpoint regulates hematopoietic stem cell aging. [*Science*. 2015])

Onoda, K. and S. Yamaguchi (2013). "Small-worldness and modularity of the resting-state functional brainnetwork decrease with aging." *Neuroscience Letters* **556**: 104-108.

The human brain **is** a complex network that is known to be affected by normal aging. Graph-based

analysis has been used to estimate functional brain network efficiency and effects of normal aging on small-worldness have been reported. This relationship is further investigated here along with network modularity, a statistic reflecting how well a network is organized into modules of densely interconnected nodes. Modularity has previously been observed to vary as a function of working memory capacity, therefore we hypothesized that both small-worldness and modularity would show age-related declines. We found that both small-worldness and modularity were negatively correlated with increasing age but that this decline was relatively slow. (**Keywords**: Aging, Functional network, Modularity, Resting-state, Small-worldness, fMRI)

Öztekin, I., et al. (2012). "Impact of aging on the dynamics of memory retrieval: A time-course analysis." *Journal of Memory and Language* **67**(2): 285-294.

The response-signal speed–accuracy trade-off (SAT) procedure was used to provide an in-depth investigation of the impact of aging on the dynamics of short-term memory retrieval. Young and older adults studied sequentially presented 3-item lists, immediately followed by a recognition probe. Analyses of composite list and serial position SAT functions found no differences in overall accuracy, but indicated slower retrieval speed for older adults. Analysis of false alarms to recent negatives (lures from the previous study list) revealed no differences in the timing or magnitude of early false alarms that are thought to reflect familiarity-based judgments. However, onset and accrual of recollective processing required for resolving interference was slower for older adults. These findings suggest that older adults have a selective impairment on controlled and recollective retrieval operations, and further specify this impairment to arise primarily from delayed onset of cognitive control potentially coupled with reduced availability of recollective information.

Parhizkar, S., et al. (2019). "Loss of TREM2 function increases amyloid seeding but reduces plaque-associated ApoE." *Nature Neuroscience* **22**(2): 191-204.

Coding variants in the triggering receptor expressed on myeloid cells 2 (TREM2) are associated with late-onset Alzheimer's disease (AD). We demonstrate that amyloid plaque seeding is increased in the absence of functional Trem2. Increased seeding is accompanied by decreased microglial clustering around newly seeded plaques and reduced plaque-associated apolipoprotein E (ApoE). Reduced ApoE deposition in plaques is also observed in brains of AD patients carrying TREM2 coding variants. Proteomic analyses and microglia depletion experiments revealed microglia as one origin of plaque-associated ApoE. Longitudinal amyloid small animal positron emission tomography demonstrates accelerated amyloidogenesis in Trem2 loss-of-function mutants at early stages, which progressed at a lower rate with aging. These findings suggest that in the absence of functional Trem2, early amyloidogenesis is accelerated due to reduced phagocytic clearance of amyloid seeds despite reduced plaque-associated ApoE.

Park, D. C. and P. Reuter-Lorenz (2009). "The adaptive brain: Aging." *Annual Review of Psychology* **60**: 173-196.

There are declines with age in speed of processing, working memory, inhibitory function, and long-term memory, as well as decreases in brain structure size and white matter integrity. In the face of these decreases, functional imaging studies have demonstrated, somewhat surprisingly, reliable increases in prefrontal activation. To account for these joint phenomena, we propose the scaffolding theory of aging and cognition (STAC). STAC provides an integrative view of the aging mind, suggesting that pervasive increased frontal activation with age is a marker of an adaptive brain that engages in compensatory scaffolding in response to the challenges posed by declining neural structures and function. Scaffolding is a normal process present across the lifespan that involves use and development of complementary, alternative neural circuits to achieve a particular cognitive goal. Scaffolding is protective of cognitive function in the aging brain, and available evidence suggests that the ability to use this mechanism is strengthened by cognitive engagement, exercise, and low levels of default network engagement. (**Keywords**: default network, dedifferentiation, hippocampus, compensation, cognitive reserve, frontal activation)

Pavlopoulos, E., et al. (2013). "Molecular mechanism for age-related memory loss: The histone-binding protein RbAp48." *Science Translational Medicine* **5**(200): 200ra115.

To distinguish age-related memory loss more explicitly from Alzheimer's disease (AD), we have explored its molecular underpinning in the dentate gyrus (DG), a subregion of the hippocampal formation thought to be targeted by aging. We carried out a gene expression study in human postmortem tissue harvested from both DG and entorhinal cortex (EC), a neighboring subregion unaffected by aging and known to be the site of onset of AD. Using expression in the EC for normalization, we identified 17 genes that manifested reliable age-related changes in the DG. The most significant change was an age-related decline in RbAp48, a histone-binding protein that modifies histone acetylation. To test whether the RbAp48 decline could be responsible for age-related memory loss, we turned to mice and found that, consistent with humans, RbAp48 was less abundant in the DG of old than in young mice. We next generated a transgenic mouse that expressed a dominant-negative inhibitor of RbAp48 in the adult forebrain. Inhibition of RbAp48 in young mice caused hippocampus-dependent memory deficits similar to those associated with aging, as measured by novel object recognition and Morris water maze tests. Functional magnetic resonance imaging studies showed that within the hippocampal formation, dysfunction was selectively observed in the DG, and this corresponded to a regionally selective decrease in histone acetylation. Up-regulation of RbAp48 in the DG of aged wild-type mice ameliorated age-related hippocampus-based memory loss and age-related abnormalities in histone acetylation. Together, these findings show that the DG is a hippocampal subregion targeted by aging, and identify molecular mechanisms of cognitive aging that could serve as valid targets for therapeutic intervention. (**Comment in:** Memory: RBAP48 drives age-related memory loss. [*Annual Review of Psychology* 2013]

Peelle, J. E., et al. (2013). "Age-related vulnerability in the neural systems supporting semantic processing." *Frontiers in Aging Neuroscience* **5**: 1-11(article 46). https://doi.org/10.3389/fnagi.2013.00046.

Our ability to form abstract representations of objects in semantic memory is crucial to language and thought. The utility of this information relies both on the representations of sensory-motor feature knowledge stored in long-term memory and the executive processes required to retrieve, manipulate, and evaluate this semantic knowledge in a task-relevant manner. These complementary components of semantic memory can be differentially impacted by aging. We investigated semantic processing in normal aging using functional magnetic resonance imaging (fMRI). Young and older adults were asked to judge whether two printed object names match on a particular feature (for example, whether a tomato and strawberry have the same color). The task thus required both retrieval of relevant visual feature knowledge of object concepts and evaluating this information. Objects were drawn from either natural kinds or manufactured objects, and were queried on either color or shape in a factorial design. Behaviorally, all subjects performed well, but older adults could be divided into those whose performance matched that of young adults (better performers) and those whose performance was worse (poorer performers). All subjects activated several cortical regions while performing this task, including bilateral inferior and lateral temporal cortex and left frontal and prefrontal cortex. Better performing older adults showed increased overall activity in bilateral premotor cortex and left lateral occipital cortex compared to young adults, and increased activity in these brain regions relative to poorer performing older adults who also showed gray matter atrophy in premotor cortex. These findings highlight the contribution of domain-general executive processing brain regions to semantic memory, and illustrate differences in how these regions are recruited in healthy older adults. (**Keywords:** Aging, Cognitive aging, Compensation, fMRI, Language, Semantic memory)

Pellicciari, M. C., et al. (2009). "Increased cortical plasticity in the elderly: Changes in the somatosensory cortex after paired associative stimulation." *Neuroscience* **163**(1): 266-276.

A fundamental feature of the human cortex is the capability to express plastic changes that seem to be present even during physiological aging. The paired associative stimulation (PAS) protocol is a paradigm capable of inducing neuroplastic changes, possibly by mechanisms related to spike timing-dependent associative neuronal activity, and represents a suitable tool for investigating age-dependent neuroplastic modulations of the primary somatosensory cortex (S1). To examine age dependency of S1 plasticity, the amplitude changes of median nerve

somatosensory evoked potential (SEP) before and after PAS intervention were investigated in young and elderly subjects. The main finding of our study is that low-frequency medial nerve stimulation paired with transcranial magnetic stimulation over the contralateral cortex enhances S1 excitability. Moreover, the S1 long term potentiation-like plasticity changes as a function of aging, with a significant increase of N20-P25 complex in the elderly compared to young subjects. These results are congruent with the hypothesis that some elderly subjects retain a high level of plasticity in specific neuronal circuits. Such plasticity could represent a compensatory mechanism, in terms of functional reserve of somatosensory cortex, used by the aging brain to counterbalance the cortical degeneration associated with aging. (Key words: Age, Somatosensory cortical plasticity, Paired associative stimulation, TMS)

Peng, J., et al. (2015). "Inhibition of telomere recombination by inactivation of KEOPS subunit Cgi121 promotes cell longevity." *PLoS Genetics* **11**(3): e1005071.

DNA double strand break (DSB) is one of the major damages that cause and cellular aging. The homologous recombination (HR)-mediated repair of DSBs plays an essential role in assurance of genome stability and cell longevity. Telomeres resemble DSBs and are competent for HR. Here we show that in budding yeast *Saccharomyces Cerevisiae* telomere recombination elicits genome instability and accelerates cellular aging. Inactivation of KEOPS subunit Cgi121 specifically inhibits telomere recombination, and significantly extends cell longevity in both telomerase-positive and pre-senescing telomerase-negative cells. Deletion of CGI121 in the short-lived yku80(tel) mutant restores lifespan to cgi121Δ level, supporting the function of Cgi121 in telomeric single-stranded DNA generation and thus in promotion of telomere recombination. Strikingly, inhibition of telomere recombination is able to further slow down the aging process in long-lived fob1Δ cells, in which rDNA recombination is restrained. Our study indicates that HR activity at telomeres interferes with telomerase to pose a negative impact on cellular longevity. **(This article has Erratum in Correction:** Inhibition of Telomere Recombination by Inactivation of KEOPS Subunit Cgi121 Promotes Cell Longevity. [*PLoS Genetics* 2015]) (**Author Summary**: Aging is a general biological process among the living organisms which is affected by environmental stimuli but also genetically controlled. Genome instability is one of the aging hallmarks and has long been implicated as one of the main causal factors in aging. DNA double strand breaks (DSBs) are the most deleterious DNA damages that cause genome instability. To counteract DNA damage of DSBs and maintain high level of genome integrity, cells have evolved powerful repair systems such as homologous recombination (HR). HR is crucial for DNA repair and genome integrity maintenance, and is generally believed to be essential for assurance of cell longevity. Telomeres, the physical ends of eukaryotic linear chromosomes, are preferentially elongated by telomerase, a specialized reverse transcriptase, in most cases. However, due to the resemblance of telomeres to DSBs, HR cannot be eliminated but rather readily takes place on telomeres, even in the presence of telomerase. Here we show that HR at yeast telomeres elicits genome instability and accelerates cellular aging. Inactivation of the evolutionarily conserved KEOPS complex subunit Cgi121 specifically inhibits telomere HR and results in extremely long lifespan, indicating a dark side of HR in longevity regulation.)

Pereira, A. C., et al. (2007). "An in vivo correlate of exercise-induced neurogenesis in the adult dentate gyrus." *Proceedings of the National Academy of Sciences* **104**(13): 5638-5643.

With continued debate over the functional significance of adult neurogenesis, identifying an in vivo correlate of neurogenesis has become an important goal. Here we rely on the coupling between neurogenesis and angiogenesis and test whether MRI measurements of cerebral blood volume (CBV) provide an imaging correlate of neurogenesis. First, we used an MRI approach to generate CBV maps over time in the hippocampal formation of exercising mice. Among all hippocampal subregions, exercise was found to have a primary effect on dentate gyrus CBV, the only subregion that supports adult neurogenesis. Moreover, exercise-induced increases in dentate gyrus CBV were found to correlate with postmortem measurements of neurogenesis. Second, using similar MRI technologies, we generated CBV maps over time in the hippocampal formation of exercising humans. As in mice, exercise was found to have a primary effect on dentate gyrus CBV, and the CBV changes were found to selectively correlate with cardiopulmonary and cognitive function. Taken together, these findings show that dentate gyrus

CBV provides an imaging correlate of exercise-induced neurogenesis and that exercise differentially targets the dentate gyrus, a hippocampal subregion important for memory and implicated in cognitive aging.

Persson, J., et al. (2006). "Altered brain white matter integrity in healthy carriers of the APOEε4 allele: A risk for AD?" *Neurology* **66**(7): 1029-1033.

Previous research has shown that polymorphisms of apolipoprotein E (APOE) represent genetic risk factors for dementia and for cognitive impairment in the elderly. The neural mechanisms by which these genetic variations influence behavioral performance or clinical severity are not well understood. Methods: The authors used diffusion tensor imaging to investigate ultra structural properties in brain white matter to detect pathologic processes that modify tissue integrity. Sixty participants were included in the study of which 30 were homozygous for the APOEε3 allele, 10 were homozygous for the APOEε4 allele, and 20 had the APOEε34 allele combination. All individuals were non-demented, and the groups were matched on demographic variables and cognitive performance. Results: The results showed a decline in fractional anisotropy, a marker for white matter integrity, in the posterior corpus callosum of ε4 carriers compared to non-carriers. Additional sites of altered white matter integrity included the medial temporal lobe. Conclusions: Although the mechanism underlying vulnerability of white matter tracts in APOEε4 carriers is still unknown, these findings suggest that increased genetic risk for developing Alzheimer disease is associated with changes in microscopic white matter integrity well before the onset of dementia.

Pluvinage, J. V., et al. (2019). "CD22 blockade restores homeostatic microglial phagocytosis in ageing brains." *Nature* **568**(7751): 187-192.

Microglia maintain homeostasis in the central nervous system through phagocytic clearance of protein aggregates and cellular debris. This function deteriorates during ageing and neurodegenerative disease, concomitant with cognitive decline. However, the mechanisms of impaired microglial homeostatic function and the cognitive effects of restoring this function remain unknown. We combined CRISPR–Cas9 knockout screens with RNA sequencing analysis to discover age-related genetic modifiers of microglial phagocytosis. These screens identified CD22, a canonical B cell receptor, as a negative regulator of phagocytosis that is upregulated on aged microglia. CD22 mediates the anti-phagocytic effect of α2,6-linked sialic acid, and inhibition of CD22 promotes the clearance of myelin debris, amyloid-β oligomers and α-synuclein fibrils in vivo. Long-term central nervous system delivery of an antibody that blocks CD22 function reprograms microglia towards a homeostatic transcriptional state and improves cognitive function in aged mice. These findings elucidate a mechanism of age-related microglial impairment and a strategy to restore homeostasis in the ageing brain.

Postle, B. R. and S. Corkin (1998). "Impaired word-stem completion priming but intact perceptual identification priming with novel words: Evidence from the amnesic patient H.M." *Neuropsychologia* **36**(5): 421-440.

We hypothesized that word-stem completion (WSC) priming and perceptual identification (PI) priming, two types of repetition priming, rely on different cognitive and neural mechanisms: WSC priming on a modification mechanism that influences lexical retrieval, and PI priming on plasticity in pre-lexical perceptual systems. We compared the priming performance of the amnesic patient H.M. with words that came into common usage after the onset of his amnesia, and thus were novel to him (post-1965 words), and with familiar (pre-1953) words. We also tested age- and education-matched normal control subjects (NCS) and a patient with anterograde amnesia of recent onset (P.N.). The modification hypothesis predicted that H.M. would fail to show WSC priming with post-1965 words because pre-existing lexical representations of the test stimuli would be necessary for priming to occur. H.M.'s WSC priming score in the post-1965 condition did not differ from 0, and was inferior to the performance of NCS and of P.N. In contrast, H.M. displayed normal WSC priming in the pre-1953 condition. H.M. also showed robust and equivalent levels of PI priming in both conditions. A final experiment demonstrated preserved post-1965 word PI priming in H.M. when his baseline performance was matched with his post-1965 WSC priming baseline score. Our results challenge models that assume that most kinds of verbal repetition

priming rely on the same or similar perceptual mechanisms.

Price, J. L., et al. (1991). "Distribution of tangles, plaques and related immunohistochemical markers in healthy aging and Alzheimer's disease." *Neurobiology of Aging* **12**: 295-312.

Neurofibrillary tangles and senile plaques, together with cells immunoreactive for the Alz-50 antibody (A50-ir cells) or for an antibody against paired helical filaments (PHF-ir cells), and amyloid deposits stained with antibodies against β-(or A4)-amyloid, have been mapped throughout the ventral forebrains of 25 old people. The cognitive status of each individual was assessed and a “Clinical Dementia Rating” (CDR) assigned, either before death in the Memory and Aging Project of Washington University, or by a postmortem interview, with an appropriate collateral source. The cases studied included 13 nondemented cases (CDR = 0), six very mildly to mildly demented cases (CDR = 0/0.5 to 1) and six more severely demented cases (CDR = 2 to 3). Because even the very mildly demented brains showed substantial pathological change, emphasis was placed on examining the nondemented cases for the earliest changes that could be associated with Alzheimer's disease. Different distributions were found for tangles and plaques. Tangles (and A50-ir and PHF-ir cells) were present in all of the brains examined. In the younger nondemented cases (aged 54 to 63) there were a few affected cells in the anterior olfactory nucleus and the parahippocampal gyrus. In older nondemented cases (aged 73–89) more tangles were found in the same areas, and also in hippocampal field CA1. The very mildly demented cases had many more tangles, but their distribution was similar. Only in the severely demented cases were large numbers of tangles present in the neocortex. In contrast, no plaques (or β-amyloid immunoreactivity) were found in any of the younger nondemented cases or in four of the eight older nondemented cases. In three older nondemented cases there were a few primitive plaques, which were restricted to localized regions of the neocortex (e.g., a portion of the inferior temporal cortex). In one nondemented case and all of the very mildly to mildly demented cases there were very large numbers of mostly primitive plaques, particularly in the neocortex. With greater severity of dementia there is a shift from primitive to mature plaques. These results were interpreted to imply that the first development of tangles and plaques occurs in different parts of the brain. Tangles appear during aging in the anterior olfactory nucleus, the parahippocampal gyrus and the hippocampus, but are rare in the neocortex except in demented brains. Conversely plaques may develop first in the neocortex. Unlike tangles, plaques are not a consistent feature of aging, at least up to age 80. (**Keywords**: Aging, Alzheimer's disease, Paired helical filaments, Alz-50, Amyloid, Neurofibrillary tangles, Senile plaques, Anterior olfactory nucleus, Parahippocampal gyrus, Hippocampal field CA1)

Prichep, L. S. (2007). "Quantitative EEG and electromagnetic brain imaging in aging and in the evolution of dementia." *Annals of the New York Academy of Sciences* **1097**(1): 156-167.

Electroencephalographic (EEG) changes with normal aging have long been reported. Departures from age-expected changes have been observed in mild cognitive impairment and dementia, the magnitude of which correlates with the degree of cognitive impairment. Such abnormalities include increased delta and theta activity, decreased mean frequency, and changes in coherence. Similar findings have been reported using magnetoencephalography (MEG) at rest and during performance of mental tasks. Electrophysical features have also been shown to be predictive of future decline in mild cognitive impairment (MCI) and Alzheimer's disease (AD). We have recently reported results from initial quantitative electroencephalography (QEEG) evaluations of normal elderly subjects (with only subjective reports of memory loss), predicting future cognitive decline or conversion to dementia, with high prediction accuracy (approximately 95%). In this report, source localization algorithms were used to identify the mathematically most probable underlying generators of abnormal features of the scalp-recorded EEG from these patients with differential outcomes. Using this QEEG method, abnormalities in brain regions identified in studies of AD using MEG, MRI, and positron emission tomography (PET) imaging were found in the premorbid recordings of those subjects go on to decline or convert to dementia.

Profant, O., et al. (2014). "Diffusion tensor imaging and MR morphometry of the central auditory pathway and auditory cortex in aging." *Neuroscience* **260**: 87-97.

Age-related hearing loss (presbycusis) is caused mainly by the hypofunction of the inner ear, but recent findings point also toward a central component of presbycusis. We used MR morphometry and diffusion tensor imaging (DTI) with a 3T MR system with the aim to study the state of the central auditory system in a group of elderly subjects (>65years) with mild presbycusis, in a group of elderly subjects with expressed presbycusis and in young controls. Cortical reconstruction, volumetric segmentation and auditory pathway tractography were performed. Three parameters were evaluated by morphometry: the volume of the gray matter, the surface area of the gyrus and the thickness of the cortex. In all experimental groups the surface area and gray matter volume were larger on the left side in Heschl's gyrus and planum temporale and slightly larger in the gyrus frontalis superior, whereas they were larger on the right side in the primary visual cortex. Almost all of the measured parameters were significantly smaller in the elderly subjects in Heschl's gyrus, planum temporale and gyrus frontalis superior. Aging did not change the side asymmetry (laterality) of the gyri. In the central part of the auditory pathway above the inferior colliculus, a trend toward an effect of aging was present in the axial vector of the diffusion (L1) variable of DTI, with increased values observed in elderly subjects. A trend toward a decrease of L1 on the left side, which was more pronounced in the elderly groups, was observed. The effect of hearing loss was present in subjects with expressed presbycusis as a trend toward an increase of the radial vectors (L2L3) in the white matter under Heschl's gyrus. These results suggest that in addition to peripheral changes, changes in the central part of the auditory system in elderly subjects are also present however, the extent of hearing loss does not play a significant role in the central changes. (**Abbreviations**: AC auditory cortex, AP auditory pathway above IC, DTI, diffusion tensor imaging, EP, elderly subjects with expressed presbycusis; FA, fractional anisotropy; GFS, gyrus frontalis superior; GM, gray matter; HG, Heschl's gyrus; IC, inferior colliculus; MD, mean diffusivity; MP, elderly subjects with mild presbycusis; PT, planum temporale; ROI, region of interest; SNHL, sensorineural hearing loss; V1, visual cortex; WM, white matter; WM_HG, white matter under Heschl's gyrus; YC, young subjects with physiologic hearing/young controls) (**Keywords**: Presbycusis; Aging; Auditory cortex; Auditory pathway; MR morphometry; Diffusion tensor imaging)

Prusiner, S. B. (1987). "Prions and neurodegenerative diseases." *New England Journal of Medicine* **317**(25): 1571-1581.

CREUTZFELDT–JAKOB disease (CJD), kuru, and the Gerstmann–Sträussler syndrome are human neurodegenerative diseases that can be transmitted experimentally to animals. In 1920, Creutzfeldt described a progressive dementing illness in a 22-year-old woman. The following year, Jakob described four older patients with a clinically similar presentation and course.1 During the ensuing four decades, numerous cases of CJD were described clinically and pathologically. Although most cases of CJD present with a progressive dementia characterized initially by loss of memory, diminished intellect, and poor judgment, a few cases present as progressive cerebellar syndromes, with diminished coordination, tremor, and ataxia. Patients with the ataxic form CJD eventually beome profoundly demented. ... On the basis of these studies, the term "prion" was introduced in order to distinguish the class of particles causing scrapie from those responsible for viral illness.7 "Prion" has an operational definition -- i.e. "small proteinaceous infectious particles which resis inactivation by precedures that modify mucleic acids." 7

Prusiner, S. B. (1998). "Prions." *Proceedings of the National Academy of Sciences of the United States of America* **95**(23): 13363-13383.

Prions are unprecedented infectious pathogens that cause a group of invariably fatal neurodegenerative diseases by an entirely novel mechanism. Prion diseases may present as genetic, infectious, or sporadic disorders, all of which involve modification of the prion protein (PrP). Bovine spongiform encephalopathy (BSE), scrapie of sheep, and Creutzfeldt-Jakob disease (CJD) of humans are among the most notable prion diseases. Prions are transmissible particles that are devoid of nucleic acid and seem to be composed exclusively of a modified protein (PrPSc). The normal, cellular PrP (PrPC) is converted into PrPSc through a posttranslational process during which it acquires a high beta-sheet content. The species of a particular prion is encoded by the sequence of the chromosomal PrP gene of the mammals in which it last replicated. In contrast to pathogens carrying a nucleic acid genome, prions appear to encipher strain-specific properties in the tertiary structure of PrPSc. Transgenetic

studies argue that PrPSc acts as a template upon which PrPC is refolded into a nascent PrPSc molecule through a process facilitated by another protein. Miniprions generated in transgenic mice expressing PrP, in which nearly half of the residues were deleted, exhibit unique biological properties and should facilitate structural studies of PrPSc. While knowledge about prions has profound implications for studies of the structural plasticity of proteins, investigations of prion diseases suggest that new strategies for the prevention and treatment of these disorders may also find application in the more common degenerative diseases.

Pugh, K. G. and L. A. Lipsitz (2002). "Microvascular frontal-subcortical syndrome of aging." *Neurobiology of Aging* **23**: 421-431.

Many features of aging suggest dysfunction in both frontal and subcortical regions. Connections between the two areas form a series of pathways that critically influence various aspects of cognition, motor control, affect, and as recently discovered, normal urinary function. Age-related changes in the structure and integrity of these circuits may be associated with cognitive impairment, mood disorders, loss of balance, falls, and urinary dysfunction. In addition, cardiovascular risk factors in elderly people are associated with the development of cerebral microangiopathic changes in both the periventricular white matter and basal ganglia. These lesions are common, usually unsuspected, and were previously believed to be clinically innocuous. However, increasing evidence supports a role for these lesions as a cause for both dysfunction in frontal-subcortical systems, and many clinical features of aging that account for substantial disability. Because this form of cerebrovascular disease is potentially preventable, interventions that address risk factors for the development of cerebral microangiopathy may go a long way in preventing disability for the next generation of elderly persons. (**Keywords**: Subcortical, Aging, Cerebrovascular disease, White matter, Leukoaraiosis)

Quentin, R. and L. G. Cohen (2019). "Reversing working memory decline in the elderly." *Nature Neuroscience* **22**: 686-688.

Noninvasive delivery of alternating electrical currents to temporal and prefrontal brain regions improves working memory and reverses age-related changes in brain dynamics in the elderly, report Reinhart and Nguyen in this issue of Nature Neuroscience. They also report a similar effect in young adults with poor working memory performance. (**This paper is a comment** on "Working memory revived in older adults by synchronizing rhythmic brain circuits" [*Nature Neuroscience* 2019]

Radvansky, G. A. (1999). "Aging, memory, and comprehension." *Current Directions in Psychological Science* **8**(2): 49-53. https://doi.org/10.1111/1467-8721.00012

There are changes in the ability to comprehend and remember information with aging. In general, older adults perform more poorly than younger adults at tasks that require knowledge of the information that was actually encountered. However, they can perform as well as or better than younger adults at tasks involving more global levels of understanding, such as in the use of information in a situation model. This increased emphasis on situation models may serve to compensate for deficits at lower levels of processing and may be achieved through more focused selection of situation-defining information, increased dependence on schemas, and a broader generation and use of inferences.

Raichlen, D. A. and G. E. Alexander (2017). "Adaptive capacity: An evolutionary neuroscience model linking exercise, cognition, and brain health." *Trends in Neurosciences* **40**(7): 408-421.

Recent work has shown that exercise can significantly improve brain structure and function in adults, especially during aging. We currently lack a comprehensive theoretical model to explain why exercise can lead to improved brain function. Taking an evolutionary neuroscience approach suggests that physiological systems,

including the brain, respond to activity-related stress by expanding capacity, and that reductions in capacity represent an energy-minimizing strategy in response to inactivity. From an evolutionary neuroscience perspective, physical activity stresses brain function because of the cognitively demanding foraging context in which our ancestors engaged in aerobic physical activity. The ACM links evolutionary theory with cognitive neuroscience to show that cognitively demanding exercise is beneficial to brain structure and function, and that we can take advantage of this adaptation to help prevent declines due to aging and to developing neurological disease. The field of cognitive neuroscience was transformed by the discovery that exercise induces neurogenesis in the adult brain, with the potential to improve brain health and stave off the effects of neurodegenerative disease. However, the basic mechanisms underlying exercise-brain connections are not well understood. We use an evolutionary neuroscience approach to develop the adaptive capacity model (ACM), detailing how and why physical activity improves brain function based on an energy-minimizing strategy. Building on studies showing a combined benefit of exercise and cognitive challenge to enhance neuroplasticity, our ACM addresses two fundamental questions: (i) what are the proximate and ultimate mechanisms underlying age-related brain atrophy, and (ii) how do lifestyle changes influence the trajectory of healthy and pathological aging?

Rajah, M. N. and A. R. McIntosh (2008). "Age-related differences in brain activity during verbal recency memory." *Brain Research* **1199**: 111-125.

In the current event-related fMRI study young and older adults underwent fMRI scanning while performing recognition, recency and reverse alphabetizing tasks. The reverse alphabetizing task served as a control for executive processes, such as working memory manipulation and monitoring (Henson, R.N., Shallice, T., et al., 1999. Right prefrontal cortex and episodic memory retrieval: a functional MRI test of the monitoring hypothesis. Brain 122 (Pt 7), 1367-1381 Dobbins, I.G., Schnyer, D.M., et al., 2004a. Cortical activity reductions during repetition priming can result from rapid response learning. Nature 428 (6980), 316-319 Rajah, M.N., McIntosh, A.R., 2006. Dissociating prefrontal contributions during a recency memory task. Neuropsychologia 44 (3), 350-364). Multivariate spatio-temporal partial least squares (ST-PLS) analysis was used to identify task-related similarities and differences in regional activity in young versus older adults. The behavioural results indicated that older adults performed disproportionately worse on recency, but not recognition memory, compared to young adults. The fMRI results show the older adults activated right parahippocampal, right parietal, left precuneus and right prefrontal regions to a greater degree during both recognition and recency retrieval, compared to young adults. Brain-behaviour correlation analysis showed that increased activity in right parahippocampal and parietal cortex was related to poorer retrieval performance in older adults, but was related to improved recency accuracy and reverse alphabetizing accuracy in young adults, respectively. In contrast, the age-related increase in right prefrontal and left precuneus activity was related to improved recognition, but not recency, performance in older adults. In young adults, activity in these regions was not strongly related to retrieval performance. These results suggest that older adults exhibited deficits in medial temporal and parietal function during retrieval, which was functionally compensated for by increased recruitment of prefrontal and precuneus regions. This functional compensation was sufficient for maintaining recognition but not recency retrieval in older adults. (**Keywords**: fMRI, Aging, Prefrontal cortex, Episodic memory, Recency memory)

Rajan, R. and K. E. Cainer (2008). "Ageing without hearing loss or cognitive impairment causes a decrease in speech intelligibility only in informational maskers." *Neuroscience* **154**(2): 784-795.

In most everyday settings, speech is heard in the presence of competing sounds and understanding speech requires skills in auditory streaming and segregation, followed by identification and recognition, of the attended signals. Ageing leads to difficulties in understanding speech in noisy backgrounds. In addition to age-related changes in hearing-related factors, cognitive factors also play a role but it is unclear to what extent these are generalized or modality-specific cognitive factors. We examined how ageing in normal-hearing decade age cohorts from 20 to 69 years affected discrimination of open-set speech in background noise. We used two types of sentences of similar structural and linguistic characteristics but different masking levels (i.e. differences in signal-to-noise ratios required for detection of sentences in a standard masker) so as to vary sentence demand, and

two background maskers (one causing purely energetic masking effects and the other causing energetic and informational masking) to vary load conditions. There was a decline in performance (measured as speech reception thresholds for perception of sentences in noise) in the oldest cohort for both types of sentences, but only in the presence of the more demanding informational masker. We interpret these results to indicate a modality-specific decline in cognitive processing, likely a decrease in the ability to use acoustic and phonetic cues efficiently to segregate speech from background noise, in subjects aged >60.

Ramsay, C. B., et al. (1999). "Verb naming in normal aging." *Applied Neuropsychology* **6**(2): 57-67.

Few studies have examined verb naming in normal aging, although decline in the ability to name nouns has been well documented. In this study, we examined longitudinal performance on the Action Naming Test (ANT), a confrontation naming test for verbs. The purpose of this study was to confirm the verb naming deficit associated with aging, which was previously seen only in cross-sectional studies, and to provide additional normative data on verb naming ability that may prove useful to studies on verb naming in populations with brain dysfunction. Sixty-six healthy men and women aged 30 to 79 were each tested with the ANT 3 times over a 7-year span. ANT performance showed a significant decline over time for all participants except the youngest group. Longitudinal methodology supports the conclusion that this finding of a decline in verb naming ability arises from true age-related changes and not from cohort differences. (**Keyword:** Verb naming, Aging, Actionaming)

Ranasinghe, K. G., et al. (2017). "Abnormal vocal behavior predicts executive and memory deficits in Alzheimer's disease." *Neurobiology of Aging* **52**: 71-80.

Speakers respond automatically and rapidly to compensate for brief perturbations of pitch in their auditory feedback. The specific adjustments in vocal output require integration of brain regions involved in speech-motor-control in order to detect the sensory-feedback error and implement the motor correction. Cortical regions involved in the pitch reflex phenomenon are highly vulnerable targets of network disruption in Alzheimer's disease (AD). We examined the pitch reflex in AD patients (n = 19) compared to an age-matched control group (n = 16). We measured the degree of behavioral compensation (peak compensation) and the extent of the adaptive response (pitch-response persistence). Healthy-controls reached a peak compensation of 18.7 +/- 0.8 cents, and demonstrated a sustained compensation at 8.9 +/- 0.69 cents. AD patients, in contrast, demonstrated a significantly elevated peak compensation (22.4 +/- 1.2 cents, $p < 0.05$), and a reduced sustained response (pitch-response persistence, 4.5 +/- 0.88 cents, $p < 0.001$). The degree of increased peak compensation predicted executive dysfunction, while the degree of impaired pitch-response persistence predicted memory dysfunction, in AD patients. The current study demonstrates pitch reflex as a sensitive behavioral index of impaired prefrontal modulation of sensorimotor integration, and compromised plasticity mechanisms of memory, in AD. (**Keywords**: Alzheimer's disease, Pitch perturbation, Network disruption, Executive dysfunction, Prefrontal modulation, Sensorimotor integration)

Ranasinghe, K. G., et al. (2019). "Neural correlates of abnormal auditory feedback processing during speech production in Alzheimer's disease." *Scientific Reports* **9**(1): 5686 (p.5681-5612).

Accurate integration of sensory inputs and motor commands is essential to achieve successful behavioral goals. **A robust model of sensorimotor integration** is the pitch perturbation response, in which speakers respond rapidly to shifts of the pitch in their auditory feedback. In a previous study, we demonstrated abnormal sensorimotor integration in patients with Alzheimer's disease (AD) with an abnormally enhanced behavioral response to pitch perturbation. Here we examine the neural correlates of the abnormal pitch perturbation response in AD patients, using magnetoencephalographic imaging. The participants phonated the vowel /α/ while a real-time signal processor briefly perturbed the pitch (100 cents, 400 ms) of their auditory feedback. We examined the high-gamma band (65–150 Hz) responses during this task. AD patients showed significantly reduced left prefrontal activity during the early phase of perturbation and increased right middle temporal activity during the later phase of perturbation, compared to controls. Activity in these brain regions significantly correlated with the

behavioral response. These results demonstrate that impaired prefrontal modulation of speech-motor-control network and additional recruitment of right temporal regions are significant mediators of aberrant sensorimotor integration in patients with AD. The abnormal neural integration mechanisms signify the contribution of cortical network dysfunction to cognitive and behavioral deficits in AD.

Raz, N., et al. (2005). "Regional brain changes in aging healthy adults: General trends, individual differences and modifiers." *Cerebral Cortex* **15**: 1676--1689.

Brain aging research relies mostly on cross-sectional studies, which infer true changes from age differences. We present longitudinal measures of five-year change in the regional brain volumes in . Average and individual differences in volume changes and the effects of age, sex and hypertension were assessed with latent difference score modeling. The caudate, the cerebellum, the hippocampus and the association cortices shrunk substantially. There was minimal change in the entorhinal and none in the primary visual cortex. Longitudinal measures of shrinkage exceeded cross-sectional estimates. All regions except the inferior parietal lobule showed individual differences in change. Shrinkage of the cerebellum decreased from young to middle adulthood, and increased from middle adulthood to old age. Shrinkage of the hippocampus, the entorhinal cortices, the inferior temporal cortex and the prefrontal white matter increased with age. Moreover, shrinkage in the hippocampus and the cerebellum accelerated with age. In the hippocampus, both linear and quadratic trends in incremental age-related shrinkage were limited to the hypertensive participants. Individual differences in shrinkage correlated across some regions, suggesting common causes. No sex differences in age trends except for the caudate were observed. We found no evidence of neuroprotective effects of larger brain size or educational attainment. (**Keywords**: Cortex, Hippocampus, Hypertension, Latent change models, White matter. **Topic:** Aging, Hypertension, Adult, Educational status, Entorhinal cortex, Follow-up, Hippocampus, Brain, Cerebellum, Temporal lobe, Older adult, White matter, Brain volume, Primary visual cortex)

Reinhart, R. M. G. and J. A. Nguyen (2019). "Working memory revived in older adults by synchronizing rhythmic brain circuits." *Nature Neuroscience* **22**: 820-827.

Understanding normal brain aging and developing methods to maintain or improve cognition in older adults are major goals of fundamental and translational neuroscience. Here we show a core feature of cognitive decline-working-memory deficits-emerges from disconnected local and long-range circuits instantiated by theta-gamma phase-amplitude coupling in temporal cortex and theta phase synchronization across frontotemporal cortex. We developed a noninvasive stimulation procedure for modulating long-range theta interactions in adults aged 60-76 years. After 25 min of stimulation, frequency-tuned to individual brain network dynamics, we observed a preferential increase in neural synchronization patterns and the return of sender-receiver relationships of information flow within and between frontotemporal regions. The end result was rapid improvement in working-memory performance that outlasted a 50 min post-stimulation period. The results provide insight into the physiological foundations of age-related cognitive impairment and contribute to groundwork for future non-pharmacological interventions targeting aspects of cognitive decline. (**See also Comment in "**Reversing working memory decline in the elderly" [*Nature Neuroscience* 2019])

Reuter-Lorenz, P. A. and D. C. Park (2014). "How does it STAC up? Revisiting the scaffolding theory of aging and cognition." *Neuropsychology Review* **24**: 355-370.

"The Scaffolding Theory of Aging and Cognition (STAC)", proposed in 2009, is a conceptual model of cognitive aging that integrated evidence from structural and functional neuroimaging to explain how the combined effects of adverse and compensatory neural processes produce varying levels of cognitive function. The model made clear and testable predictions about how different brain variables, both structural and functional, were related to cognitive function, focusing on the core construct of compensatory scaffolding. The present paper provides a revised model that integrates new evidence about the aging brain that has emerged since STAC was published 5 years ago. Unlike the original STAC model, STAC-r incorporates life-course factors that serve to enhance or

deplete neural resources, thereby influencing the developmental course of brain structure and function, as well as cognition, over time. Life-course factors also influence compensatory processes that are engaged to meet cognitive challenge, and to ameliorate the adverse effects of structural and functional decline. The revised model is discussed in relation to recent lifespan and longitudinal data as well as emerging evidence about the effects of training interventions. STAC-r goes beyond the previous model by combining a life-span approach with a life-course approach to understand and predict cognitive status and rate of cognitive change over time.

Reyes, P. A., et al. (2019). "Networks disrupted in linguistic variants of frontotemporal dementia." *Frontiers in Neurology* **10**: Published online. https://doi.org/10.3389/fneur.2019.00903

The non-fluent/agrammatic variant of primary progressive aphasia (nfvPPA) and semantic variant (svPPA) of frontotemporal dementia (FTD) are neurodegenerative diseases. Previous works have shown alterations of fractional anisotropy (FA) and mean diffusivity (MD) from diffusion tensor images (DTIs). This manuscript is aimed at using DTI images to build a global tractography and to identify atrophy patterns of white matter in each variant. Twenty patients with svPPA, 20 patients with nfvPPA, 26 patients with behavioral variant of FTD (bvFTD) and, 33 controls were included. An analysis based on the connectivity of structural networks showed changes in FA and MD in svPPA and nfvPPA with respect to bvFTD. Much damage in the internal networks of the left temporal lobe was found in svPPA patients; in contrast, patients with nfvPPA showed atrophy in networks from the basal ganglia to motor and premotor areas. Those findings support the dual stream model of speech and language.

Riek, R. and D. S. Eisenberg (2016). "The activities of amyloids from a structural perspective." *Nature* **539**: 227-235.

The aggregation of proteins into structures known as amyloids is observed in many neurodegenerative diseases, including Alzheimer's disease. Amyloids are composed of pairs of tightly interacting, many stranded and repetitive intermolecular β-sheets, which form the cross-β-sheet structure. This structure enables amyloids to grow by recruitment of the same protein and its repetition can transform a weak biological activity into a potent one through cooperativity and avidity. Amyloids therefore have the potential to self-replicate and can adapt to the environment, yielding cell-to-cell transmissibility, prion infectivity and toxicity.

Robinson, K. M., et al. (1996). "Category-specific difficulty with naming verbs in Alzheimer's disease." *Neurology* **47**: 178-182.

We studied 20 patients with Alzheimer's disease (AD) on a picture-naming task consisting of frequency-matched pairs of nouns and verbs that were homophonic and homographic (e.g., paint). Intragroup comparisons revealed that verb naming is significantly more difficult for patients with AD than noun naming. An error analysis demonstrated that patients with AD produce significantly more semantic and descriptive errors for verbs than nouns. We correlated verb naming and noun naming with measures of grammatical comprehension, lexical retrieval, and visuoperceptual processing, but there were no selective effects for verbs compared with nouns. Differences in the mental representation of concepts underlying verbs and nouns may account, in part, for the relative difficulty naming with verbs in AD.

Royle, P., et al. (2019). "Aging and language: Maintenance of morphological representations in older adults." *Frontiers in Communication* **4**(16): https://doi.org/10.3389/fcomm.2019.00016

Studies employing primed lexical decision tasks have revealed morphological facilitation effects in children and young adults. It is unknown if this effect is preserved or diminished in older adults. In fact, only few studies have investigated age-related changes in morphological processing and results are inconsistent across studies. To address this issue, we investigated inflection morphology compared to orthographic and semantic processing in young and older adults. Twenty-six adults aged 60–85 and 22 younger adults aged 19–28 participated. We probed verb recognition using a sandwich-masked primed lexical decision paradigm. We investigated lexical decision using different prime presentation times (PPTs) (33, 66, and 150 ms), and prime

types with priming conditions involving orthographic (e.g., cassis—CASSE 'blackcurrant—break'), regular inflection morphological (cassait—CASSE 'broke—break'), and semantic primes (brise—CASSE 'break—break') and their controls, while measuring response accuracy and reaction times. Response accuracy analyses revealed that older participants performed at ceiling on the lexical decision task, and that accuracy levels were higher compared to young adults. Reaction-time data revealed effects of age group, priming condition, and an interaction of age group and morphological priming, but no PPT effects. Both young and older adults presented a significant facilitation effect (reduced reaction times) in the orthographic and morphological priming conditions. No semantic effects were observed in either group. Younger adults also showed a significantly stronger morphological priming effect, while older adults showed no difference between orthographic and morphological priming when comparing priming magnitudes. These findings suggest (1) that regular inflectional morphological processing benefits lexical access in younger French adults, confirming studies in other languages, and (2) that this advantage is reduced at older ages.

Salthouse, T. A., et al. (1998). "Relation of task switching to speed, age, and fluid intelligence." *Psychology and Aging* **13**(3): 445-461.

Two studies were conducted to investigate whether a meaningful task-switching construct could be identified and, if so, to determine how it was related to measures of higher order cognition and to adult age. Both studies revealed that measures of task switching were moderately correlated across different combinations of tasks and that a switching construct could be distinguished from a construct reflecting processing speed. The results of the 2nd study revealed that although the task-switching construct was related to age and to measures of episodic memory, inductive reasoning, and spatial visualization, most of the relations between the switching construct and both age and other measures of cognition were shared with other variables.

Santello, M., et al. (2019). "Astrocyte function from information processing to cognition and cognitive impairment." *Nature Neuroscience* **22**: 154–166.

Astrocytes serve important roles that affect recruitment and function of neurons at the local and network levels. Here we review the contributions of astrocyte signaling to synaptic plasticity, neuronal network oscillations, and memory function. The roles played by astrocytes are not fully understood, but astrocytes seem to contribute to memory consolidation and seem to mediate the effects of vigilance and arousal on memory performance. Understanding the role of astrocytes in cognitive processes may also advance our understanding of how these processes go awry in pathological conditions. Indeed, abnormal astrocytic signaling can cause or contribute to synaptic and network imbalances, leading to cognitive impairment. We discuss evidence for this from animal models of Alzheimer's disease and multiple sclerosis and from animal studies of sleep deprivation and drug abuse and addiction. Understanding the emerging roles of astrocytes in cognitive function and dysfunction will open up a large array of new therapeutic opportunities.

Schneider-Garces, N. J., et al. (2010). "Span, crunch, and beyond: Working memory capacity and the aging brain." *Journal of Cognitive Neuroscience* **22**(4): 655-669.

Neuroimaging data emphasize that older adults often show greater extent of brain activation than younger adults for similar objective levels of difficulty. A possible interpretation of this finding is that older adults need to recruit neuronal resources at lower loads than younger adults, leaving no resources for higher loads, and thus leading to performance decrements [Compensation- Related Utilization Of Neural Circuits Hypothesis; e.g., Reuter- Lorenz, P. A., & Cappell, K. A. Neurocognitive aging and the compensation hypothesis. *Current Directions in Psychological Science*, 17, 177-182, 2008]. The Compensation-Related Utilization of Neural Circuits Hypothesis [CRUNCH] leads to the prediction that activation differences between younger and older adults should disappear when task difficulty is made subjectively comparable. In a Sternberg memory search task, this can be achieved by assessing brain activity as a function of load relative to the individual 's memory span,

which declines with age. Specifically, we hypothesized a nonlinear relationship between load and both performance and brain activity and predicted that asymptotes in the brain activation function should correlate with performance asymptotes (corresponding to working memory span). The results suggest that age differences in brain activation can be largely attributed to individual variations in working memory span. Interestingly, the brain activation data show a sigmoid relationship with load. Results are discussed in terms of Cowan's [Cowan, N. The magical number 4 in short-term memory: A reconsideration of mental storage capacity. *Behavioral and Brain Sciences*, 24, 87-114, 2001] model of working memory and theories of impaired inhibitory processes in aging.

Schwämmle, V. (2005). "Simulation for competition of languages with an ageing sexual population." *International Journal of Modern Physics* C: *Computational Physics and Physical Computation* **16**(10):1519-1526.

Recently, individual-based models originally **used for** biological purposes revealed interesting insights into processes of the competition of languages. Within this new field of population dynamics a model considering sexual populations with aging is presented. The agents are situated on a lattice and each one speaks one of two languages or both. The stability and quantitative structure of an interface between two regions, initially speaking different languages, is studied. We find that individuals speaking both languages do not prefer any of these regions and have a different age structure than individuals speaking only one language. (**Keywords**: Language; Ageing; Numerical model; Interface)

Schwämmle, V. (2006). "Phase transition in a sexual age-structured model of learning foreign languages." *International Journal of Modern Physics C: Computational Physics & Physical Computation* **17**(1): 103-111.

The understanding of language competition helps us to predict extinction and survival of languages spoken by minorities. A simple agent-based model of a sexual population, based on the Penna model, is built in order to find out under which circumstances one language dominates other ones. This model considers that only young people learn foreign languages. The simulations show a first order phase transition of the ratio between the number of speakers of different languages with the mutation rate as control parameter.

Seinfeld, S., et al. (2013). "Effects of music learning and piano practice on cognitive function, mood and quality of life in older adults." *Frontiers in Psychology* **4**: Article 810.

Reading music and playing a musical instrument is a complex activity that comprises motor and multisensory (auditory, visual, and somatosensory) integration in a unique way. Music has also a well-known impact on the emotional state, while it can be a motivating activity. For those reasons, musical training has become a useful framework to study brain plasticity. Our aim was to study the specific effects of musical training vs. the effects of other leisure activities in elderly people. With that purpose we evaluated the impact of piano training on cognitive function, mood and quality of life (QOL) in older adults. A group of participants that received piano lessons and did daily training for 4-month (n = 13) was compared to an age-matched control group (n = 16) that participated in other types of leisure activities (physical exercise, computer lessons, painting lessons, among other). An exhaustive assessment that included neuropsychological tests as well as mood and QOL questionnaires was carried out before starting the piano program and immediately after finishing (4 months later) in the two groups. We found a significant improvement on the piano training group on the Stroop test that measures executive function, inhibitory control and divided attention. Furthermore, a trend indicating an enhancement of visual scanning and motor ability was also found (Trial Making Test part A). Finally, in our study piano lessons decreased depression, induced positive mood states, and improved the psychological and physical QOL of the elderly. Our results suggest that playing piano and learning to read music can be a useful intervention in older adults to promote cognitive reserve (CR) and improve subjective well-being. (**Keywords**: Aging, Brain plasticity, Cognitive function, Elderly, Music, Piano, Quality of life, Training)

Shafto, M. A. and L. K. Tyler (2014). "Language in the aging brain: The network dynamics of cognitive decline and preservation." *Science* **346**(6209): 583-587.

Language is a crucial and complex lifelong faculty, underpinned by dynamic interactions within and between specialized brain networks. Whereas normal aging impairs specific aspects of language production, most core language processes are robust to brain aging. We review recent behavioral and neuroimaging evidence showing that language systems remain largely stable across the life span and that both younger and older adults depend on dynamic neural responses to linguistic demands. Although some aspects of network dynamics change with age, there is no consistent evidence that core language processes are underpinned by different neural networks in younger and older adults.

Shine, J. M., et al (2019). "Human cognition involves the dynamic integration of neural activity and neuromodulatory systems." *Nature Neuroscience* **22**: 289–296.

The human brain integrates diverse cognitive processes into a coherent whole, shifting fluidly as a function of changing environmental demands. Despite recent progress, the neurobiological mechanisms responsible for this dynamic system-level integration remain poorly understood. Here we investigated the spatial, dynamic, and molecular signatures of system-wide neural activity across a range of cognitive tasks. We found that neuronal activity converged onto a low-dimensional manifold that facilitates the execution of diverse task states. Flow within this attractor space was associated with dissociable cognitive functions, unique patterns of network-level topology, and individual differences in fluid intelligence. The axes of the low-dimensional neurocognitive architecture aligned with regional differences in the density of neuromodulatory receptors, which in turn relate to distinct signatures of network controllability estimated from the structural connectome. These results advance our understanding of functional brain organization by emphasizing the interface between neural activity, neuromodulatory systems, and cognitive function. (**Erratum in** "Publisher Correction: Human cognition involves the dynamic integration of neural activity and neuromodulatory systems" [*Nature Neuroscience* 2019])

Sia, G. M., et al. (2013). "The human language–associated gene SRPX2 regulates synapse formation and vocalization in mice." *Science* **342**: 987-991.

Synapse formation in the developing brain depends on the coordinated activity of synaptogenic proteins, some of which have been implicated in a number of neurodevelopmental disorders. Here, we show that the sushi repeat-containing protein X-linked 2 (SRPX2) gene encodes a protein that promotes synaptogenesis in the cerebral cortex. In humans, SRPX2 is an epilepsy- and language-associated gene that is a target of the foxhead box protein P2 (FoxP2) transcription factor. We also show that FoxP2 modulates synapse formation through regulating SRPX2 levels and that SRPX2 reduction impairs development of ultrasonic vocalization in mice. Our results suggest FoxP2 modulates the development of neural circuits through regulating synaptogenesis and that SRPX2 is a synaptogenic factor that plays a role in the pathogenesis of language disorders. (Comment in: Neuroscience. Synapses, language, and being human. [*Science* 2013])

Siegel, J. m. (2003). "Why we sleep: The reasons that we sleep are gradually becoming less enigmatic." *Scientific American*. November (2003) 92-97.

Overview: Researchers are still debating the function of REM and non-REM sleep and why we need both, but new findings suggest several reasonable hypotheses. 1) One is that reduced activity during non-REM sleep may give many brain cells a chance to repair themselves. 2) Another is that interrupted release of neurotransmitters called monoamines during REM sleep may allow the brain's receptors for those chemicals to recover and regain full sensitivity, which helps with regulation of mood and learning. 3) The intense neuronal activity of REM sleep in early life may allow the brain to develop properly.

Sinclair, D., et al. (2019). *Lifespan: The Revolutionary Science of Why We Age--And Why We Don't Have To*. London: Thorsons.

Ever since I can remember, I have wanted to understand **why we grow old**. But finding the source of a complex biological process is like searching for the spring at the source of a river: it's not easy. On my quest, I've

wound my way left and right and had days when I wanted to give up. But I've persevered. Along the way, I have seen a lot of tributaries, but I've also found what may be the spring. **In the coming pages**, I will present a new idea about why aging evolved and how it fits into what I call the **Information Theory of Aging**. I will also tell you why I have come to see aging as a disease—the most common disease—one that not only can but should be aggressively treated. **That's part I. In part II**, I will introduce you to the steps that can be taken right now—and new therapies in development—that may slow, stop, or reverse aging, bringing an end to aging as we know it. And yes, I fully recognize the implications of the words "bringing an end to aging as we know it," so, **in part III,** I will acknowledge the many possible futures these actions could create and propose a path to a future that we can look forward to, a world in which the way we can get to an increased lifespan is through an ever-rising healthspan, the portion of our lives spent without disease or disability. ... There's also a difference between extending life and prolonging vitality. We're capable of both, but simply keeping people alive—decades after their lives have become defined by pain, disease, frailty, and immobility—is no virtue. **Prolonged vitality—meaning not just more years of life but more active, healthy, and happy ones**—is coming. It is coming sooner than most people expect ... One hundred and twenty years might be not an outlier but an expectation, so much so that **we won't even call it longevity; we will simply call it "life,"** and we will look back with sadness on the time in our history in which it was not so.**(from the "Introduction" by the author)**

Skeide, M. A., et al. (2017). "Learning to read alters cortico-subcortical cross-talk in the visual system of illiterates." *Science Advances* **3**(5): e1602612.

Learning to read is known to result in a reorganization of the developing cerebral cortex. In this longitudinal resting-state functional magnetic resonance imaging study in illiterate adults, we show that only 6 months of literacy training can lead to neuroplastic changes in the mature brain. We observed that literacy-induced neuroplasticity is not confined to the cortex but increases the functional connectivity between the occipital lobe and subcortical areas in the midbrain and the thalamus. Individual rates of connectivity increase were significantly related to the individual decoding skill gains. These findings crucially complement current neurobiological concepts of normal and impaired literacy acquisition. (**Keywords**: Reading, Illiterates, Dyslexia, Resting-state fMRI, Functional connectivity, Visual system, Superior colliculus, Pulvinar nucleus)

Smith, A. and L. Goffman (1998). "Stability and patterning of speech movement sequences in children and adults" *Journal of Speech, Language, and Hearing Research* **41**: 18-30.

Children (aged 4 and 7 years) and young adults produced a six-syllable utterance 15 times. The displacement of the lower lip was recorded with an Optotrak system and analyzed in a number of ways. First, using a procedure recently developed in our laboratory, displacement records from the 15 repetitions were amplitude- and time-normalized, and the spatiotemporal index (the STI) was computed. The STI reflects the degree to which repeated performance of a task produces movement trajectories that converge on a single pattern. Children produced less stable movement trajectories, as reflected in higher values on the STI. In a second analysis, standard measurements of amplitude and peak velocity were made for two opening and two closing lip movements. These measures suggested that, relative to the size of their oral structures, children have large movement ranges in speech. Also, children tend to move with a lower peak velocity. This large-amplitude, low-velocity movement style may reflect different underlying control processes. Finally, another analysis focused on open-close movement sequences associated with two words of the utterance. A pattern-recognition algorithm applied to the normalized waveforms from the open-close sequences revealed that children and adults produced equally distinctive movement trajectories for the two syllables. Taken together, these preliminary results suggest that nonlinear and nonuniform changes occur in components of the **SPEECH MOTOR SYSTEM** during development. (**Keywords**: Speech motor control, Development, Kinematics, Articulation, Physiology)

Snowdon, D. (2001). *Aging with Grace, the Nun Study and the Science of Old Age*. London, Fourth Estate.

This text presents the story of an ongoing, long-term study of a large group of Catholic nuns who have

given Dr David Snowdon access to their medical and archival records and participate each year in comprehensive mental and physical examinations designed to measure the long-term effects of aging. They have also agreed to donate their brains upon death. So far there are 250 brains in the bank making it the world's largest of its kind. Dr Snowdon is one of the world's leading experts on Alzheimer's disease and director of the "Nun Study", a research project involving 678 Catholic sisters ranging in age from 75 to 104 and which has been running for the past 15 years. We get to know many of the nuns personally, and through them discover some of the ground-breaking work which the "Nun Study" has achieved. (Synosis on amazon website, https://www.amazon.co.uk/Aging-Grace-science-Longer-Healthier/dp/1841152919) "we found that the later the age at natural menopause, the older the age at death. Every one year in age at natural menopause was associated with a half-year increase in life expectancy." (Snowden 2001: 27) Table of Contents: https://www.amazon.com/Aging-Grace-Teaches-Healthier-Meaningful/dp/0553380923#reader_0553380923)

Sörman, D. E., et al. (2019). "Different features of bilingualism in relation to executive functioning." *Frontiers in Psychology* **10**: Article 269.

The notion that the long-term practice of managing two languages is beneficial for the executive control system is an ongoing debate. Criticism have been raised that studies demonstrating a bilingual advantage often suffer from small sample sizes, and do not control for fluid intelligence as a possible confound. Taking those suggested factors into account, focusing on older bilingual age groups and investigating the potential effects of linguistic distances, this study aimed to improve the interpretations of the bilinguals' advantages. Measures of inhibition (Flanker, Stroop, Simon task) and switching (Number-letter, Color-Shape, Local-global task) were collected in participants in the ages 50-75 years (n = 193). Despite a large study sample, results did not support any beneficial effects related to improve processing costs in executive functioning. Sub-analyses of the two different language groups (Swedish-Finnish / Swedish-English) intended to investigate the effect of linguistic distances did not change this outcome. Future studies exploring the potential long-term term effects of bilingualism would benefit from identifying tests of cognitive control with greater ecological validity and include other measures of cognitive functioning. Language learning interventions may also be a promising tool for future research. (**Keywords**: Bilingualism, Cognitive control, Executive functioning. Inhibition, Linguistic distance, Middle age, Old age, Switching)

Squire, L. R. and E. R. Kandel (2009). *Memory: From Mind to Molecules*. 2nd edition. Greenwood Village, Colo.: Roberts & Company.

"Combining insights from both cognitive neuroscience and molecular biology, Memory presents the basics of memory--from molecules and cells to brain systems and cognition. What is memory and where in the brain is it stored? How is memory storage accomplished? This book touches on these questions and more" (Provided by publisher). Contents: From mind to molecules -- Modifiable synapses for nondeclarative memory -- Molecules for short-term memory -- Declarative memory -- Brain systems for declarative memory -- A synaptic storage mechanism for declarative memory -- From short-term memory to long-term memory -- Priming, perceptual learning, and emotional learning -- Memory for skills, habits, and conditioning -- Memory and the biological basis of individuality. (from Library of Hong Kong Polytechnic University, https://www.lib.polyu.edu.hk/)

Steiner, E., et al. (2019). "A fresh look at adult neurogenesis." *Nature Medicine* **25**: 542-543.

Improved protocols for the visualization of immature neurons in the human brain provide evidence for generation of neurons in the adult hippocampus and uncover reduced neurogenesis in Alzheimer’s disease. (**Comment on:** Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease. [*Nature Medicine* 2019])

Stern, Y. (2002). "What is cognitive reserve? Theory and research application of the reserve concept." *Journal of*

the International Neuropsychological Society **8**: 448-460.

The idea of reserve against brain damage stems from the repeated observation that there does not appear to be a direct relationship between the degree of brain pathology or brain damage and the clinical manifestation of that damage. This paper attempts to develop a coherent theoretical account of reserve. One convenient subdivision of reserve models revolves around whether they envision reserve as a passive process, such as in brain reserve or threshold, or see the brain as actively attempting to cope with or compensate for pathology, as in cognitive reserve. Cognitive reserve may be based on more efficient utilization of brain networks or of enhanced ability to recruit alternate brain networks as needed. A distinction is suggested between reserve, the ability to optimize or maximize normal performance, and compensation, an attempt to maximize performance in the face of brain damage by using brain structures or networks not engaged when the brain is not damaged. Epidemiologic and imaging data that help to develop and support the concept of reserve are presented.

Stimpson, N. J., et al. (2018). "Joggin' the noggin: Towards a physiological understanding of exercise-induced cognitive benefits." *Neuroscience and Biobehavioral Reviews* **88**: 177-186.

This narrative review examines literature pertaining to possible physiological explanations for observed cognitive benefits stemming from improvements to cardiovascular fitness following chronic aerobic exercise. Studies regarding exercise and cardiovascular fitness, angiogenesis, neuroinflammation in relation to IGF-1 signalling, regulation of neurotrophins, neurogenesis and plasticity, cognitive training, are briefly described. We propose that current evidence points towards a mechanism by which cardiovascular fitness improvements act to promote long-term angiogenesis and cerebral circulation. This important adaptation allows for increased delivery and upregulation of neurotrophins along with supporting factors to the brain, particularly to the hippocampal neurogenic niche, following acute exercise bouts. We propose a sequential timeline and approximate time scale for this mechanism, describing how these stages generate increased support for neurogenesis and brain plasticity in combination with cognitive training to provide long-term cognitive benefits and protection against age-related cognitive decline. Influences from age, gender and other variables are considered, and methodological factors that could be utilised in future studies to further clarify the proposed model are discussed. (**Keywords**: physical activity, physical exercise, cognitive training, cognitive enhancement, angiogenesis, neurogenesis, neurotrophins, brain-derived neurotrophic factor)

Su, X., et al. (2014). "Prevalence and predictors of mild cognitive impairment in Xi'an: A community-based study among the elders." *PLoS ONE* **9**(1): e83217.

Mild cognitive impairment (MCI) is an intermediate stage between normal cognitive function and dementia among aging individuals. This study was designed to estimate the prevalence of MCI and explore the possible risk factors including gender disparities among community-dwelling older individuals. The study was conducted in Xi'an, China. This is a cross-sectional study. A total of 815 individuals, 60 years and older were selected by stratified random cluster sampling. Cognitive function was measured using the mini-mental status examination (MMSE), the Chinese version of the Dementia Rating Scales (CDRS) was used to apply the diagnostic of non-dementia, and activities of daily living (ADL) and instrumental activities of daily living (IADL) systems were used to functional status. The association between sociodemographic characteristics, lifestyle, history of chronic diseases and MCI were evaluated separately for men and women using the Pearson chi(2)-test and binary logistic regression. Of the 815 community-dwelling individuals, 145 were found to have MCI. Overall, the prevalence of MCI was 18.5%, with a prevalence of 19.6% in women (105/535), and 15.3% (40/261) in men. The results of the binary logistical regression analysis indicated that age and history of stroke were associated with MCI in men. For women, the risk factors were lower level of educational and lack of religious attendance. Results suggested that the factors capable of influencing MCI differed profoundly between older men and older women. For this reason, different preventative measures should be adopted to delay or reverse cognitive impairment among community-dwelling older men and women.

Takashima, H. (2010). "Shrinkage of the mental lexicon of kanji in an elderly Japanese woman: The effect of a 10-year passage of time." *Journal of Cross-Cultural Gerontology* **25**(1): 105-115.

This investigation addressed the questions at what rate and how an elderly Japanese woman, AA, lost kanji nouns between the ages of 83 years and 93 years. Results from a kanji naming task given twice with a 10-year interval showed that (1) on average, the size of AA's mental lexicon of kanji shrank at a rate of approximately 1% per year and (2) while ease of acquisition had the highest correlation with naming performance followed by kanji frequency, age of acquisition, and visual complexity in this order, a logistic regression analysis identified ease of acquisition and age of acquisition as potent independent variables. Results of error analysis indicated that visual encoding errors were most prevalent. The decline in AA's mental lexicon is discussed in light of the rates of declines in object naming ability reported in previous studies. The concept of ease of acquisition and the dissociation between AA's general mental state and lexicon of kanji are also discussed.

Tao, L., et al. (2011). "The efficiency of attentional networks in early and late bilinguals: The role of age of acquisition." *Frontiers in Psychology* **2**: 1-19. https://doi.org/10.3389/fpsyg.2011.00123

Previous studies have demonstrated a bilingual advantage in the efficiency of executive attention. A question remains, however, about the impact of the age of L2 acquisition and relative balance of the two languages on the enhancement of executive functions in bilinguals, and whether this is modulated by the similarity of the bilingual's two languages. The present study explores these issues by comparing the efficiency of attentional networks amongst three groups of young adults living in Australia: English monolinguals and early and late Chinese–English bilinguals. We also address the impact of bilingualism on hemispheric lateralization of cognitive functions, which is of interest since a recent study on early bilinguals revealed reduced hemispheric asymmetry in attentional functioning. In the present study, participants performed a modified version of the lateralized attention network test. Both early and late bilinguals were found to have more efficient executive network than monolinguals. The late bilinguals, who were also reported to be more balanced in the proficiency and usage of their two languages, showed the greatest advantage in **conflict resolution**, whereas early bilinguals seemed to show enhanced **monitoring processes**. These group differences were observed when controlling for non-verbal intelligence and socioeconomic status. Such results suggest that specific factors of language experience may differentially influence the mechanisms of **cognitive control**. Since the bilinguals had distinct language sets, it seems that the influence of bilingualism on executive functions is present regardless of the similarity between the two languages. As for hemispheric lateralization, although the results were not clear-cut, they suggest the reduced lateralization in early bilinguals. (**Keywords**: Bilingualism, Age of L2 Acquisition, Attentional networks, Attention network test, Lateralization)

Taylor, J. P., et al. (2016). "Decoding ALS: From genes to mechanism." *Nature* **539**: 197.

Amyotrophic lateral sclerosis (ALS) is a progressive and uniformly fatal neurodegenerative disease. A plethora of genetic factors have been identified that drive the degeneration of motor neurons in ALS, increase susceptibility to the disease or influence the rate of its progression. Emerging themes include dysfunction in RNA metabolism and protein homeostasis, with specific defects in nucleocytoplasmic trafficking, the induction of stress at the endoplasmic reticulum and impaired dynamics of ribonucleoprotein bodies such as RNA granules that assemble through liquid-liquid phase separation. Extraordinary progress in understanding the biology of ALS provides new reasons for optimism that meaningful therapies will be identified.

Tays, W. J., et al. (2011). "Age-related differences during simple working memory decisions: ERP indices of early recognition and compensation failure." *Brain Research* **1393**(0): 62-72.

Imaging data has identified frontal cortical activation in older adults during simple recognition tasks that relates positively with performance and could, therefore, be considered compensatory. However, in a previous electrophysiological study involving a Sternberg task with proactive interference manipulations, we observed a

frontal positive scalp potential between 400 and 500 ms that was unique to older adults and predictive of poorer performance. These results led us to ask whether unique frontal activation in older adults serves a compensatory role only during relatively simple tasks when stimulus familiarity provides an unambiguous basis for response selection. In the current study, we tested this hypothesis by having younger and older adults complete a verbal Sternberg task without interference manipulations. In younger adults, we observed an early posterior negativity (90–120 ms) that predicted performance accuracy. Older adults failed to show this early negativity but did produce the expected frontal positivity. However, the frontal positivity was again associated with poorer performance. These data support the view that younger adults are able to bias early target discrimination to benefit response selection whereas older adults rely on later controlled processes that are not always effective in buffering against normative age-related decline. (**Keywords**: Cognitive aging, Event-related potential, Early visual processing, Cognitive decline, Executive function, Incidental memory)

Tyler, L. K., et al. (2010). "Preserving syntactic processing across the adult life span: The modulation of the frontotemporal language system in the context of age-related atrophy." *Cerebral Cortex* **20**(2): 352-364.

Although widespread neural atrophy is an inevitable consequence of normal aging, not all cognitive abilities decline as we age. For example, spoken language comprehension tends to be preserved, despite atrophy in neural regions involved in language function. Here, we combined measures of behavior, functional activation, and gray matter (GM) change in a younger (19-34 years) and older group (49-86 years) of participants to identify the mechanisms leading to preserved language comprehension across the adult life span. We focused primarily on syntactic functions because these are strongly left lateralized, providing the potential for contralateral recruitment. In a functional magnetic resonance imaging study, we used a word-monitoring task to minimize working memory demands, manipulating the availability of semantics and syntax to ask whether syntax is preserved in aging because of the functional recruitment of other brain regions, which successfully compensate for neural atrophy. Performance in the older group was preserved despite GM loss. This preservation was related to increased activity in right hemisphere frontotemporal regions, which was associated with age-related atrophy in the left hemisphere frontotemporal network activated in the young. We argue that preserved syntactic processing across the life span is due to the shift from a primarily left hemisphere frontotemporal system to a bilateral functional language network.

Ullman, M. T. (2001). "A neurocognitive perspective on language: The declarative/procedural model." *Nature Reviews Neuroscience* **2**: 717-726.

What are the psychological, computational and neural underpinnings of language? Are these neurocognitive correlates dedicated to language? Do different parts of language depend on distinct neurocognitive systems? Here I address these and other issues that are crucial for our understanding of two fundamental language capacities: the memorization of words in the mental lexicon, and the rule-governed combination of words by the mental grammar. According to the declarative/procedural model, the mental lexicon depends on declarative memory and is rooted in the temporal lobe, whereas the mental grammar involves procedural memory and is rooted in the frontal cortex and basal ganglia. I argue that the declarative/procedural model provides a new framework for the study of lexicon and grammar.

Unsworth, N., et al. (2015). "Is playing video games related to cognitive abilities?" *Psychological Science* **26** (6): 759-774.

The relations between video-game experience and cognitive abilities were examined in the current study. In two experiments, subjects performed a number of working memory, fluid intelligence, and attention-control measures and filled out a questionnaire about their video-game experience. In Experiment 1, an extreme-groups analysis indicated that experienced video-game players outperformed nonplayers on several cognitive-ability measures. However, in Experiments 1 and 2, when analyses examined the full range of subjects at both the task

level and the latent-construct level, nearly all of the relations between video-game experience and cognitive abilities were near zero. These results cast doubt on recent claims that playing video games leads to enhanced cognitive abilities. Statistical and methodological issues with prior studies of video-game experience are discussed along with recommendations for future studies. (**Keywords**: cognitive ability; individual differences)

Vallesi, A., et al. (2009). "Age-related differences in processing irrelevant information: Evidence from event-related potentials." *Neuropsychologia* **47**(2): 577-586.

Ignoring irrelevant information becomes more difficult with increasing age. The present cross-sectional study addressed this issue by investigating age-related differences in the ability to withhold a response to non-target stimuli. Fourteen young (20-34 years) and 14 elderly (60-80 years) participants performed two go/nogo tasks (simple vs. complex). In the simple task the subjects responded to red O and blue X (target go stimuli) while withholding responses to the blue O and red X (conflict nogo stimuli) and to numbers of either color (irrelevant nogo stimuli). In the complex version, 4 vowels and 4 consonants were used instead of O and X. Accuracy, response times (RTs) and event-related potentials (ERPs) were recorded. Both young and elderly groups made more commission errors to conflict nogo stimuli (mean 5% and 8% in the simple and complex tasks, respectively, age differences not significant) than to irrelevant nogo stimuli (mean<1%), indicating difficulty in withholding a response when a pertinent stimulus feature (letter identity) was shared with the go stimuli. In addition to later RTs to go stimuli and later P3 waves for the conflicting stimuli than the young group, elderly participants showed a very prominent left posterior P2 and a large pre-central P3 to the irrelevant nogo stimuli. These findings suggest that elderly have difficulty in ignoring irrelevant nogo stimuli even when they are easily distinguishable from the go stimuli. (**Keywords**: Go/nogo, Aging, Irrelevant stimuli, Cognitive interference, Event-related Potentials)

Van Lancker Sidtis, D. (2012). "Formulaic language and language disorders." *Annual Review of Applied Linguistics* **32**: 62-80. https://doi.org/10.1017/S0267190512000104

The importance of formulaic language is recognized by many branches of the language sciences. Second language learners acquire a language using a maturationally advanced neurological substrate, leading to a profile of formulaic language use and knowledge that differs from that of the prepuberty learner. Unlike the considerable interest in formulaic language seen in second language learning, attention paid to this theme in clinical communicative disorders has been limited. Historically, verbal expressions preserved in severe nonfluent aphasia, including counting, interjections, and memorized phrases, have been referred to as automatic speech. Closer examination of all forms of aphasic speech reveals a high proportion of formulaic expressions, while speech samples from persons with right hemisphere and subcortical damage show a significant impoverishment. These findings are supported by studies of persons with Alzheimer's disease, who have intact subcortical nuclei and abnormally high proportions of formulaic expressions, and Parkinson's disease, which is characterized by dysfunctional subcortical systems and impoverished formulaic language. Preliminary studies of schizophrenic speech also reveal a paucity of formulaic language. A dissociation between knowledge and use of the expressions is found in some of these populations. Observations in clinical adult subjects lead to a profile of cerebral function underlying production of novel and formulaic language, known as the dual processing model. Whereas the left hemisphere modulates newly created language, production of formulaic language is dependent on a right hemisphere/subcortical circuit. Implications of the dual process model for evaluation and treatment of language disorders are discussed.

Vaughn, K. A., et al. (2019). "Parietal lobe volume distinguishes attentional control in bilinguals and monolinguals: A structural MRI study." *Brain and Cognition* **134**: 103-109.

Research suggests that bilingualism is associated with increases in parietal gray matter volume (GMV). These parietal GMV increases are a source of variability that may help explain the reported bilingual/monolingual differences in attentional control. The current study examined how parietal GMV variability and a participant's

language background predicted Simon task performance. GMV measures were extracted from the bilateral angular and supramarginal gyri from participants' MRI scans using Freesurfer image analysis suite. Contrary to expectations, bilinguals did not outperform monolinguals on the Simon task. In fact, bilinguals had slower response times across all conditions of the task (incongruent, congruent, and neutral) than monolinguals. In addition, GMV in the right supramarginal gyrus was negatively associated with response times for congruent trials for bilinguals, and positively associated with these response times for monolinguals. The difference in the relationships between parietal GMV and task performance suggests that bilinguals rely on spatial attention to complete the Simon task, while monolinguals may rely on verbal attention. These results help to connect bilingual advantages in tasks requiring spatial attention (e.g., attentional control) with bilingual disadvantages in tasks requiring verbal attention (e.g., verbal fluency). (**Keywords**: Attention, Bilingual, Gray matter volume, Inferior parietal lobule)

Vernes, S. C. D. P., et al. (2008). "A functional genetic link between distinct developmental language disorders." *The New England Journal of Medicine* **359**(22): 2337-2345.

Rare mutations affecting the FOXP2 transcription factor cause a monogenic speech and language disorder. We hypothesized that neural pathways downstream of FOXP2 influence more common phenotypes, such as specific language impairment. We performed genomic screening for regions bound by FOXP2 using chromatin immunoprecipitation, which led us to focus on one particular gene that was a strong candidate for involvement in language impairments. We then tested for associations between single-nucleotide polymorphisms (SNPs) in this gene and language deficits in a well-characterized set of 184 families affected with specific language impairment. We found that FOXP2 binds to and dramatically down-regulates CNTNAP2, a gene that encodes a neurexin and is expressed in the developing human cortex. On analyzing CNTNAP2 polymorphisms in children with typical specific language impairment, we detected significant quantitative associations with nonsense-word repetition, a heritable behavioral marker of this disorder (peak association, P=5.0×10−5 at SNP rs17236239). Intriguingly, this region coincides with one associated with language delays in children with autism. The FOXP2–CNTNAP2 pathway provides a mechanistic link between clinically distinct syndromes involving disrupted language.

Vlahou, E. L., et al. (2014). "Resting-state slow wave power, healthy aging and cognitive performance." *Scientific Reports* **4**(1): 5101.

Cognitive functions and spontaneous neural activity show significant changes over the life-span, but the interrelations between age, cognition and resting-state brain oscillations are not well understood. Here, we assessed performance on the Trail Making Test and resting-state magnetoencephalographic (MEG) recordings from 53 healthy adults (18–89 years old) to investigate associations between age-dependent changes in spontaneous oscillatory activity and cognitive performance. Results show that healthy aging is accompanied by a marked and linear decrease of resting-state activity in the slow frequency range (0.5–6.5 Hz). The effects of slow wave power on cognitive performance were expressed as interactions with age: For older (>54 years), but not younger participants, enhanced delta and theta power in temporal and central regions was positively associated with perceptual speed and executive functioning. Consistent with previous work, these findings substantiate further the important role of slow wave oscillations in neurocognitive function during healthy aging.

Walhovd, K. B., et al. (2011). "Consistent neuroanatomical age-related volume differences across multiple samples." *Neurobiology of Aging* **32**: 916-932. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4040218/pdf/nihms4119683.pdf

Magnetic resonance imaging (MRI) **is** the principal method for studying structural age-related brain changes in vivo. However, previous research has yielded inconsistent results, precluding understanding of structural changes of the aging brain. This inconsistency is due to methodological differences and/or different aging patterns across samples. To overcome these problems, we tested age effects on 17 different neuroanatomical

structures and total brain volume across five samples, of which one was split to further investigate consistency (883 participants). Widespread age-related volume differences were seen consistently across samples. In four of the five samples, all structures, except the brainstem, showed age-related volume differences. The strongest and most consistent effects were found for cerebral cortex, pallidum, putamen and accumbens volume. Total brain volume, cerebral white matter, caudate, hippocampus and the ventricles consistently showed non-linear age functions. Healthy aging appears associated with more widespread and consistent age-related neuroanatomical volume differences than previously believed. (**Keywords**: MRI morphometry, Age, Cortex, White matter, Cerebellum, Ventricles, Hippocampus, Amygdala, Thalamus, Basal ganglia)

Walker, M. P. (2017). *Why We Sleep: Unlocking the Power of Sleep and Dreams*. (First Scribner hardcover edition) New York: Scribner, an imprint of Simon & Schuster, Inc. https://www.lib.polyu.edu.hk/

Table of Contents: **Part 1.** This thing called sleep (--To sleep ... --Caffeine, jet lag, and melatonin: losing and gaining control of your sleep rhythm, --Defining and generating sleep: time dilation and what we learned from a baby in 1952, -- Ape beds, dinosaurs, and napping with half a brain: who sleeps, how do we sleep, and how much?）**Part 2**. Why should you sleep? （--Your mother and Shakespeare knew: the benefits of sleep for the brain, --Too extreme for the Guinness Book of World Records: sleep deprivation and the brain, --Cancer, heart attacks, and a shorter life: sleep deprivation and the body) **Part 3**. How and why we dream (--Routinely psychotic: REM-sleep dreaming, --Dreaming as overnight therapy, --Dream creativity and dream control) **Part 4.** From sleeping pills to society transformed (--Things that go bump in the night: sleep disorders and death caused by no sleep, -- iPads, factory whistles, and nightcaps: what's stopping you from sleeping? --Hurting and helping your sleep: pills vs. therapy, -- Sleep and society: what medicine and education are doing wrong; what Google and NASA are doing right, --A new vision for sleep in the twenty-first century) **Conclusion**: To sleep or not to sleep. **Appendix**: Twelve tips for healthy sleep. (Schlow Centre Region Library. 2020. https://search.schlowlibrary.org/Record/413760/TOC) **The first sleep book by** a leading scientific expert - Professor Matthew Walker, director of UC Berkeley's Sleep and Neuroimaging Lab - reveals his groundbreaking exploration of sleep, explaining how we can harness its transformative power to change our lives for the better. Sleep is one of the most important but least understood aspects of our life, wellness, and longevity. Until very recently, science had no answer to the question of why we sleep, or what good it served, or why we suffer such devastating health consequences when we don't sleep. Compared to the other basic drives in life - eating, drinking, and reproducing - the purpose of sleep remained elusive. But an explosion of scientific discoveries in the last 20 years has shed new light on this fundamental aspect of our lives. Now, preeminent neuroscientist and sleep expert Matthew Walker gives us a new understanding of the vital importance of sleep and dreaming. Among so many other things, within the brain, sleep enriches our ability to learn, memorize, and make logical decisions. It recalibrates our emotions, restocks our immune system, fine-tunes our metabolism, and regulates our appetite. Dreaming mollifies painful memories and creates a virtual reality space in which the brain melds past and present knowledge to inspire creativity. Walker answers important questions about sleep: How do caffeine and alcohol affect sleep? What really happens during REM sleep? Why do our sleep patterns change across a lifetime? How do common sleep aids affect us, and can they do long-term damage? Charting cutting-edge scientific breakthroughs and synthesizing decades of research and clinical practice, Walker explains how we can harness sleep to improve learning, mood, and energy levels; regulate hormones; prevent cancer, Alzheimer's, and diabetes; slow the effects of aging; increase longevity; enhance the education and lifespan of our children, and boost the efficiency, success, and productivity of our businesses. Clear-eyed, fascinating, and immensely accessible, Why We Sleep is the crucial account on sleep that will forever change listeners' minds on the subject. (From publisher's summery at https://www.audible.com/pd/Why-We-Sleep-Audiobook/B0752ZQR33?source_code=ROWGB13108101800NA&gclid=EAIaIQobChMI88ucvpPH6AIVT6aWCh3Q0wgwEAAYASAAEgIWPPD_BwE)

Wang Shiyuan (William S-Y. Wang) (2018). "Yuyan he shengming shicheng 语言和生命时程 Language and life timelines ." *Zhengda Zhongwe Xuebao* 政大中文学报(30): 5-36. http://ctma.nccu.edu.tw/chibulletin/app/paper.php?action=show_content&Sn=248

比起其它灵长类，人类寿命除了明显较长外，还多了一个有助学习的「童年期」，两者皆是文化演化的产物。大脑在我们诞生後的头两年内有爆炸性成长，重量增长叁倍，以吸收外在世界以及周遭文化的大量讯息。语言是一套既独立又彼此相关的繁複技巧，在不同时程内习得，能够达到不同的熟练度，习得结果存在大量的个别差异。学说任何语言都须习得一整套的感知敏感度，才能辨别该语言里重要的语音区别，还得要协调及精细控制几百条与呼吸、发声和发音有关的肌肉。虽然越早开始越能轻松学会说新语言所需的运动技能，但语言的认知成分，而非其运动成分，可以在年纪很大了才掌握，如词彙和语法。语言和行为的许多其它方面的不同时程，都在基因与环境的互动下有其源头，若干的遗传性病变是在幼儿期或人生的迟暮之年才浮现。儘管许多人能健康安享晚年，有些人却饱受不同型态的神经退化折磨，如阿兹海默症。随著世界渐趋高龄化，语言失调的挑战在规模上快速增长，病徵也渐趋多样複杂。希望未来的研究更应考量构成人类社会的生物多样性和文化多样性。 Compared with other primates, humans have an extended lifespan and are blessed with the additional stage of " childhood " for learning, both of which are products of cultural evolution. Our brains grow at an explosive rate during our first two years, tripling its weight at birth, soaking up an astonishing amount of information about the physical world as well as the culture into which we are born. Language is a complex set of independent but interrelated skills, acquired at different timelines to different degrees of proficiency, with a great deal of variation across individuals. Speaking any language well requires the acquisition of a full set of perceptual sensitivities to the phonetic distinctions significant for that language. It also requires the coordination and fine control of several hundred muscles for respiration, phonation, and articulation. Although the motor skills for speaking a new language come much more easily to the young, the cognitive components of language, not its motoric components, can be mastered quite late in life, such as its vocabulary and grammar. The various timelines for language and many other aspects of behavior have their sources in the interaction of genes with environment. Several genetic pathologies surface either in infancy, or in the sunset years. While many of us live out the newly available years in good health, some suffer from various types of neuro-degeneration, and foremost among these is a severe form of dementia called the Alzheimer's disease. The challenge of language disorders has mushroomed in size and become manifold more complex with the world aging so fast. Hopefully due consideration in this area of research will be given to the biological and cultural diversity that comprise our entire humanity.

Wei, C., et al. (2018). "Wuyixing chidai de linchuang tedian 语义性痴呆的临床特点" (Study on the clinical features of patients with semantic dementia)." *Zhongguo Shenjing Jingshen Jibing Zazhi* 中国神经精神疾病杂志 *(*Chinese journal of nervous and mental diseases*)* **44**(8): 449-452.

目的通过分析5例语义性痴呆(semantic dementia,SD)患者的临床资料,结合文献报道,探究SD患者临床特点。方法对于我院收诊5例语义性痴呆患者一般临床信息、病史查体、神经心理及神经影像学检查结果进行回顾性分析及相关文献回顾。结果 患者平均发病年龄为63.8岁,神经心理检查均显示有不同程度认知功能障碍MMSE 7~28分,MOCA 2~15分，4例患者均有命名能力下降,命名正确率为4%~31%; 1例患者出现精神行为异常NPI 18分，患者日常生活能力损害较轻ADL 22~31分。患者头MRI均显示双侧不对称性颞叶皮层萎缩,其中4例以左侧为重。结论 语义性痴呆患者日常生活能力保留较好,偏重左侧萎缩，SD语言障碍较为突出，偏重右侧萎缩，SD更容易出现精神行为症状。 （关键词：语义性痴呆； 神经心理测验； 影像） To explore the clinical features through analyzing the clinical data of 5 patients with semantic dementia(SD) and reviewing the literatures. Methods We retrospectively analyzed the history, general data, neuropsychological assessment and imaging data of 5 patients with semantic dementia at our hospital and reviewed the literature on SD research. Result: The average age of onset was 63.8 in five SD patients. The psychological examinations showed the cognitive dysfunction to certain degrees. The scores of MMSE and MOCA were between 7 and 28 and between 2 and15, respectively. Four cases had a decline in naming test and the correct rate was 4% ~31%. One case presented behavioral and psychological symptoms and NPI score was 18. The patient’s daily living ability showed a relatively slight damage and the scores of ADL were between 22 and 31. Brain MRI showed atrophy in the left temporal lobe in 4 patients and in the right side in 1 patient. Conclusions The patients with SD well preserve the daily life ability. SD patients with left temporal lobe atrophy tend to have language problems,while those with right temporal lobe atrophy are more likely to develop behavior disorders. （**Keywords**: Semantic dementia； Neuropsychological test； Image)

Weiss, M. W. and I. Peretz (2019). "Ability to process musical pitch is unrelated to the memory advantage for vocal music." *Brain and Cognition* **129**: 35-39.

Listeners remember vocal melodies better than instrumental melodies, but the origins of the effect are unclear. One explanation for the 'voice advantage' is that general perceptual mechanisms enhance processing of conspecific signals. An alternative possibility is that the voice, by virtue of its expressiveness in pitch, simply provides more musical information to the listener. Individuals with congenital amusia provide a unique opportunity to disentangle the effects of conspecific status and vocal expressiveness because they cannot readily process subtleties in musical pitch. Forty-one participants whose musical pitch discrimination ability ranged from congenitally amusic to typical were tested. Participants heard vocal and instrumental melodies during an exposure phase, and heard the same melodies intermixed with timbre-matched foils in a recognition phase. Memory was better for vocal than instrumental melodies, but the magnitude of the advantage was unrelated to musical pitch discrimination or memory overall. The voice enhances melodic memory regardless of music perception ability, ruling out the role of pitch expressiveness in the voice advantage. More importantly, listeners across a wide range of musical ability can benefit from the privileged status of the voice. (**Keywords**: Amusia, Pitch, Recognition memory, Timbre, Voice)

Wierenga, C. E., et al. (2008). "Age-related changes in word retrieval: Role of bilateral frontal and subcortical networks." *Neurobiology of Aging* **29**(3): 436-451.

Healthy older adults frequently report word-finding difficulties, yet the underlying cause of these problems is not well understood. This study examined whether age-related changes in word retrieval are related to changes in areas of the frontal lobes thought to subserve word retrieval or changes in areas of the inferior temporal lobes thought to be involved in semantic knowledge. Twenty younger and 20 older healthy adults named aloud photographs during event-related fMRI. Results showed that in the face of equivalent naming accuracy, older adults activated a larger frontal network than younger adults during word retrieval, but there were no activity differences between groups in the fusiform gyrus, suggesting that the substrates for word retrieval but not for semantic knowledge change with aging. Additionally, correlations between BOLD response and naming accuracy and response latency were found in several frontal and subcortical regions in older adults. Findings are discussed in the context of possible compensatory mechanisms invoked to maintain performance in healthy aging, and suggest that increased involvement of the right hemisphere is not universally beneficial to performance. (**Keywords**: Aging; Language; fMRI; Word retrieval; Confrontation naming; Compensation)

Williams, G. C. (1957). "Pleiotropy, natural selection, and the evolution of senescence." *Evolution* **11**(4):398-411.

Senescence is a widespread phenomenon, but it has been largely neglected by non-medical biologists. This neglect may be attributed to a number of causes. One is that the process seldom present itself to students of natural populations, since recognizably senile individuals are not often found in the wild. Another, perhaps, is an emotional difficulty associated with aging, a situation that was hardly helped by the early clinical association of senescence with sex hormones. Another is the existence of theories that have gained tacit acceptance, despite their conceptual obsolescence and poverty of factual support. The most injurious of these is the identification of senescence with the "wearing out" that is shown by human artifacts.

Williamson, D. J. G., et al. (1998). "Object and action naming in Alzheimer's disease." *Cortex* **34**(4): 601-610.

We administered measures of object naming and action naming to matched groups of ten patients with Alzheimer's disease (AD) and ten normal control subjects. AD patients were impaired in both object and action naming, with object naming impaired to a significantly greater extent than action naming. This difference remained after controlling for the effects of word frequency. We propose that the pattern of pathological changes in AD impairs both conceptual and lexical retrieval systems for objects but only conceptual systems for actions. The similar patterns of error during the two tasks suggest quantitative rather than qualitative differences in the breakdown of the two abilities. (**Keywords**: Naming; Alzheimer disease)

Wilson, R. S., et al. (2015). "Early life instruction in foreign language and music and incidence of mild cognitive impairment." *Neuropsychology* **29**(2): 292-302.

To test the hypothesis that foreign language and music instruction in early life are associated with lower incidence of mild cognitive impairment (MCI) and slower rate of cognitive decline in old age. METHOD: At enrollment in a longitudinal cohort study, 964 older persons without cognitive impairment estimated years of foreign language and music instruction by age 18. Annually thereafter they completed clinical evaluations that included cognitive testing and clinical classification of MCI. RESULTS: There were 264 persons with no foreign language instruction, 576 with 1-4 years, and 124 with > 4 years; 346 persons with no music instruction, 360 with 1-4 years, and 258 with > 4 years. During a mean of 5.8 years of observation, 396 participants (41.1%) developed MCI. In a proportional hazards model adjusted for age, sex, and education, higher levels (> 4 years) of foreign language (hazard ratio [HR] = 0.687, 95% confidence interval [CI] [0.482, 0.961]) and music (HR = 0.708, 95% CI [0.539, 0.930]) instruction by the age of 18 were each associated with reduced risk of MCI. The association persisted after adjustment for other early life indicators of an enriched cognitive environment, and it was stronger for nonamnestic than amnestic MCI. Both foreign language and music instruction were associated with higher initial level of cognitive function, but neither instruction measure was associated with cognitive decline. CONCLUSIONS: Higher levels of foreign language and music instruction during childhood and adolescence are associated in old age with lower risk of developing MCI but not with rate of cognitive decline.

Witelson, S. f. and W. Pallie (1973). "Left hemisphere specialization for language in the newborn: Neuroanatomical evidence of asymmetry." *Brain* **96**: 641-646. Fulltext article: https://doi.org/10.1093/brain/96.3.641

Functional asymmetry of the two cerebral hemispheres in man has been accepted for over a century. In contrast, until recently no anatomical asymmetries were found associated with the functional differences, although the assumption remained that perhaps some subtle structural asymmetry might exist related to the functional differentiation (Mountcastle, 1962). Recently Geschwind and Levitsky (1968) reported a gross left-right morphological asymmetry, observable by naked eye inspection, in the posterior region of the superior surface of the temporal lobe (planurn temporale) which is part of the classical area of Wernicke known to be of significance for language function. In 65 per cent of their sample of adult brains, linear measurement of this region was greater on the left side. They suggested that the anatomical difference is of sufficient magnitude to be compatible with the functional asymmetry of the two hemispheres in mediating language. It is not known at what time in ontogenetic development this anatomical asymmetry is first present. Such information would be relevant for the issue of the origin of the adult pattern of hemispheric functional asymmetry. It has been clearly shown that speech functions are lateralized in the left hemisphere in most adults regardless of hand preference (Branch, Milner and Rasmussen, 1964; Zangwill, 1967). The question remains whether this nonrandom pattern of hemispheric functional asymmetry results from biological pre-programming or environmental factors such as language learning or preferential hand usage. Information as to the onset of the anatomical asymmetry would also be important for any theory about the role of innate biological factors underlying language acquisition. Recent behavioural studies in which infants as young as 4 weeks of age were observed to discriminate acoustic differences, specifically those across phonemic boundaries which are relevant for linguistic classifications and which are universal across cultures (Eimas, Siqueland, Jusczyk and Vigorito, 1971; Trehub and Rabinovitch, 1972), suggest that aspects of speech perception may be biologically pre-programmed at an unexpectedly early age. **The purpose of the present study** was to examine the human temporal lobe for evidence of anatomical asymmetry in the neonatal period, when no learning related to language or unimanual hand preference has occurred. The specific hypothesis investigated was whether the area of the superior surface of the temporal lobe known to mediate language in the adult is larger in the left than in the right hemisphere in the human neonate.

Wu, Y., et al. (2013). "The effects of tai chi exercise on cognitive function in older adults: A meta-analysis." *Journal of Sport and Health Science* **2**: 193-203. https://doi.org/10.1016/j.jshs.2013.09.001

Cognitive impairment is prevalent among older adults and results in degraded quality of life for older adults. As the population ages, this may cause a huge burden to society. Research has demonstrated that physical

exercise is beneficial to cognitive function. The purpose of this meta-analysis was to critically assess the effect of Tai Chi exercise on global cognitive, executive, and memory functions in older adults. Methods: After a thorough electronic search and selection, eight studies were included in this meta-analysis with two cross-sectional and six intervention studies. Nine variables included in this meta-analysis were: mini mental status examination (MMSE), Alzheimer's disease assessment scale-cognitive subscale (ADAS-cog), trailmaking test part A (TMA), trailmaking test part B (TMB), digit span test forward (DSF), digit span test backward (DSB), visual span test backward (VSB), verbal fluency test (VFT), and word delay recall test (WDR). The effect sizes and forest plots of these nine variables were generated. Results: Four (MMSE, DSB, VSB, and VFT) out of nine variables were significantly improved after Tai Chi exercise with the effect sizes ranged from 0.20 to 0.46 (small to medium). MMSE represented global cognitive function, and DSB, VSB, and VFT represented memory function. Conclusion: Tai Chi as a mind-body exercise has the positive effects on global cognitive and memory functions, and more consistent positive effects were found on memory function, especially verbal working memory. (**Keywords**: Cognitive impairment, Executive function, Global cognitive function, Intellectual experience, Memory function Mind-body exercise)

Wulff, D. U., et al. (2019). "New perspectives on the aging lexicon." *Trends in Cognitive Sciences* **23**(8):686-698.

The field of cognitive aging has seen considerable advances in describing the linguistic and semantic changes that happen during the adult life span to uncover the structure of the mental lexicon (i.e., the mental repository of lexical and conceptual representations). Nevertheless, there is still debate concerning the sources of these changes, including the role of environmental exposure and several cognitive mechanisms associated with learning, representation, and retrieval of information. We review the current status of research in this field and outline a framework that promises to assess the contribution of both ecological and psychological aspects to the aging lexicon.

Wyss-Coray, T. (2016). "Ageing, neurodegeneration and brain rejuvenation**."** *Nature* **539**: 180.

Although systemic diseases take the biggest toll on human health and well-being, increasingly, a failing brain is the arbiter of a death preceded by a gradual loss of the essence of being. Ageing, which is fundamental to neurodegeneration and dementia, affects every organ in the body and seems to be encoded partly in a blood-based signature. Indeed, factors in the circulation have been shown to modulate ageing and to rejuvenate numerous organs, including the brain. The discovery of such factors, the identification of their origins and a deeper understanding of their functions is ushering in a new era in ageing and dementia research.

Xia, R., et al. (2019). "The effect of traditional Chinese mind-body exercise (*Baduanjin*) and brisk walking on the dorsal attention network in older adults with mild cognitive impairment." *Frontiers in Psychology* **10**(2075): Article 2075.

A growing number of studies have shown that mind-body exercise is beneficial to cognitive function, especially memory, in elderly MCI patients. However, few studies have explored the effect of mind-body exercise on the attention of MCI population. We recruited 69 participants and divided them equally into *Baduanjin*, brisk walking (BWK) exercise or usual physical activity (UAP) control groups. The two exercise groups performed 60 min of exercise three times per week for 24 weeks. All subjects underwent whole-brain functional MRI and assessment of attentional abilities, including selective, divided, and sustained attention, and processing speed at baseline and after 24 weeks. The results show that: *Baduanjin* exercise significantly increased the selective attention of MCI patients, and Dorsal attention network (DAN) of *Baduanjin* exercise group exhibited functional connectivity decreased in right rolandic operculum (ROL. R), right middle temporal gyrus (MTG. R), right supramarginal inferior parietal, angular gyri (IPL. R), right precuneus (PCUN. R), and right fusiform gyrus (FFG. R) regions compared with the other two groups. The BWK exercise group had obviously functional connectivity increased in IPL. R and decreased in the MTG. R region compared to that in the UAP group. But no significant

association between the changes of functional connectivity of DAN and the change of attentional ability test was observed. Thus, our data indicated *Baduanjin* exercise may be a potential beneficial intervention to improve the attention of the elderly with MCI. Further study with more samples is necessary to elucidate its imaging mechanism. (**Keywords**: *Baduanjin*; Brisk walking; Dorsal attention network; Mild cognitive impairment; Mind-body exercise)

Xie, L., et al. (2013). "Sleep drives metabolite clearance from the adult brain." *Science* **342**(6156): 373-377. https://doi.org/10.1126/science.1241224

The conservation of sleep across all animal species suggests that sleep serves a vital function. We here report that sleep has a critical function in ensuring metabolic homeostasis. Using real-time assessments of tetramethylammonium diffusion and two-photon imaging in live mice, we show that natural sleep or anesthesia are associated with a 60% increase in the interstitial space, resulting in a striking increase in convective exchange of cerebrospinal fluid with interstitial fluid. In turn, convective fluxes of interstitial fluid increased the rate of β-amyloid clearance during sleep. Thus, the restorative function of sleep may be a consequence of the enhanced removal of potentially neurotoxic waste products that accumulate in the awake central nervous system.

Zhang, G., et al. (2013). "Hypothalamic programming of systemic ageing involving IKKβ/NF-κB and GnRH." *Nature* **497**: 211-216.

Ageing is a result of gradual and overall functional deteriorations across the body; however, it is unknown whether an individual tissue primarily works to mediate the ageing progress and control lifespan. Here we show that the hypothalamus is important for the development of whole-body ageing in mice, and that the underlying basis involves hypothalamic immunity mediated by IκB kinase-β (IKK-β), nuclear factor κB (NF-κB) and related microglia-neuron immune crosstalk. Several interventional models were developed showing that ageing retardation and lifespan extension are achieved in mice by preventing ageing-related hypothalamic or brain IKK-β and NF-κB activation. Mechanistic studies further revealed that IKK-β and NF-kB inhibit gonadotropin-releasing hormone (GnRH) to mediate ageing-related hypothalamic GnRH decline, and GnRH treatment amends ageing-impaired neurogenesis and decelerates ageing. In conclusion, the hypothalamus has a programmatic role in ageing development via immune-neuroendocrine integration, and immune inhibition or GnRH restoration in the hypothalamus/brain represent two potential strategies for optimizing lifespan and combating ageing-related health problems. (**Comment in Physiology**: Inflammation links ageing to the brain. [*Nature* 2013], Hypothalamic inflammation and GnRH in aging development. [*Cell Cycle* 2013], Can inflammation regulate systemic aging? [*Experimental Gerontology* 2015])

Zhang, P., et al. (2019). "Senolytic therapy alleviates aβ-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model." *Nature Neuroscience* **22**: 719-728.

Neuritic plaques, a pathological hallmark in Alzheimer's disease (AD) brains, comprise extracellular aggregates of amyloid-beta (Aβ) peptide and degenerating neurites that accumulate autolysosomes. We found that, in the brains of patients with AD and in AD mouse models, Aβ plaque-associated Olig2- and NG2-expressing oligodendrocyte progenitor cells (OPCs), but not astrocytes, microglia, or oligodendrocytes, exhibit a senescence-like phenotype characterized by the upregulation of p21/CDKN1A, p16/INK4/CDKN2A proteins, and senescence-associated β-galactosidase activity. Molecular interrogation of the Aβ plaque environment revealed elevated levels of transcripts encoding proteins involved in OPC function, replicative senescence, and inflammation. Direct exposure of cultured OPCs to aggregating Aβ triggered cell senescence. Senolytic treatment of AD mice selectively removed senescent cells from the plaque environment, reduced neuroinflammation, lessened Aβ load, and ameliorated cognitive deficits. Our findings suggest a role for Aβ-induced OPC cell senescence in neuroinflammation and cognitive deficits in AD, and a potential therapeutic benefit of senolytic treatments. (**Comment in** "Senescent glia spell trouble in Alzheimer's disease." [see Nat Neurosci. 2019]

Zhang, R. (2018). "Jiyu wos (web of science) de laonian ren yuyanhua yanjiu keshihua fenxi 基于wos 的老年人语言老化研究可视化分析 (2002—2016 年)" (Visualized analysis of deterioration in older people's language abilities based on wos (2002—2016)). *Laoling Kexue Yanjiu* 老龄科学研究 (Scientific research on aging) **6**(4): 3-13.

以 2002- 2016年 Web of Science 数据库中收录的306 篇老年人语言老化研究文献为数据来源，运用CiteSpace 可视化技术，绘制语言老化研究的科学知识图谱。并通过文献聚类，从宏观上梳理语言老化研究的核心领域。通过软件生成的关键文献和高突发性文献，对语言老化研究热点及其演变路径进行分析。（关键词：CiteSpace；语言老化；可视化分析） Based on 306 literatures on deterioration in older People's language abilities included in Web of Science between 2002 and 2016 and using the visualization software CiteSpace, this paper mapped out a knowledge graph showing studies on deterioration in older people's language abilities. The paper also identified key areas of research through literature clustering. Then key and high mutation literatures generated by the software were used to analyze research hotspots and its evolution path. （**Keywords**: CiteSpace, Deterioration in older people's language abilities, Visualized analysis)

Zhang, Y.-J, et al (2019). "Heterochromatin anomalies and double-stranded RNA accumulation underlie *C9orf72* poly(PR) toxicity." *Science* **363**(6428): eaav2606.

How hexanucleotide GGGGCC (G4C2) repeat expansions in C9orf72 cause frontotemporal dementia (FTD) and amyotrophic lateral sclerosis (ALS) is not understood. We developed a mouse model engineered to express poly(PR), a proline-arginine (PR) dipeptide repeat protein synthesized from expanded G4C2 repeats. The expression of green fluorescent protein-conjugated (PR)50 (a 50-repeat PR protein) throughout the mouse brain yielded progressive brain atrophy, neuron loss, loss of poly(PR)-positive cells, and gliosis, culminating in motor and memory impairments. We found that poly(PR) bound DNA localized to heterochromatin, and caused heterochromatin protein 1α (HP1α) liquid-phase disruptions, decreases in HP1α expression, abnormal histone methylation, and nuclear lamina invaginations. These aberrations of histone methylation, lamins, and HP1α, which regulate heterochromatin structure and gene expression, were accompanied by repetitive element expression and double-stranded RNA accumulation. Thus, we uncovered mechanisms by which poly(PR) may contribute to the pathogenesis of C9orf72-associated FTD and ALS.

Zheng, D., et al. (2014). "Executive dysfunction and gray matter atrophy in amnestic mild cognitive impairment." *Neurobiology of Aging* **35**: 548-555.

Recent studies have shown that impairment in executive function (EF) is common in patients with amnestic mild cognitive impairment (aMCI). However, the neuroanatomic basis of executive impairment in patients with aMCI remains unclear. In this study, multiple regression voxel-based morphometry analyses were used to examine the relationship between regional gray matter volumes and EF performance in 50 patients with aMCI and 48 healthy age-matched controls. The core EF components (response inhibition, working memory and task switching, based on the EF model of Miyake et al) were accessed with computerized tasks. Atrophic brain areas related to decreases in the three EF components in patients with aMCI were located in the frontal and temporal cortices. Within the frontal cortex, the brain region related to response inhibition was identified in the right inferior frontal gyrus. Brain regions related to working memory were located in the left anterior cingulate gyrus, left premotor cortex, and right inferior frontal gyrus, and brain regions related to task shifting were distributed in the bilateral frontal cortex. Atrophy in the right inferior frontal gyrus was most closely associated with a decrease in all three EF components in patients with aMCI. Our data, from the perspective of brain morphology, contribute to a better understanding of the role of these brain areas in the neural network of EF. (**Keywords**: Mild cognitive impairment, Executive function, Magnetic resonance imaging, Inhibition, Working memory)

Zhou, R., et al. (2019). "Recognition of the amyloid precursor protein by human γ-secretase." *Science* **363**(6428): eaaw0930.

Cleavage of amyloid precursor protein (APP) by the intramembrane protease γ-secretase is linked to

Alzheimer's disease. We report an atomic structure of human γ-secretase in complex with a transmembrane APP fragment at 2.6-Å resolution. The transmembrane helix (TM) of APP closely interacts with five surrounding TMs of PS1 (the catalytic subunit of γ-secretase). A hybrid β-sheet, which is formed by a β-strand from APP and two β-strands from PS1, guides γ-secretase to the scissile peptide bond of APP between its TM and β-strand. Residues at the interface between PS1 and APP are heavily targeted by recurring mutations from AD patients. This structure, together with that of γ-secretase bound to Notch, reveal contrasting features of substrate binding, which may be exploited toward design of substrate-specific inhibitors. (**Comment in** Pathology-linked protease caught in action. *Science*. 2019 Feb 15, 363(6428):690-691. https://doi.org/10.1126/science.aaw5547)

Zhou, W., et al. (2019). "Loss of function of NCOR1 and NCOR2 impairs memory through a novel GABAergic hypothalamus–CA3 projection." *Nature Neuroscience* **22**: 205–217. Nuclear receptor corepressor 1 (NCOR1) and NCOR2 (also known as SMRT) regulate gene expression by activating histone deacetylase 3 [HDAC3] through their deacetylase activation domain (DAD). We show that mice with DAD knock-in mutations have memory deficits, reduced anxiety levels, and reduced social interactions. Mice with NCOR1 and NORC2 depletion specifically in GABAergic neurons (NS-V mice) recapitulated the memory deficits and had reduced GABAA receptor subunit α2 (GABRA2) expression in lateral hypothalamus GABAergic (LHGABA) neurons. This was associated with LHGABA neuron hyperexcitability and impaired hippocampal long-term potentiation, through a monosynaptic LHGABA to CA3GABA projection. Optogenetic activation of this projection caused memory deficits, whereas targeted manipulation of LHGABA or CA3GABA neuron activity reversed memory deficits in NS-V mice. We describe de novo variants in NCOR1, NCOR2 or HDAC3 in patients with intellectual disability or neurodevelopmental disorders. These findings identify a hypothalamus-hippocampus projection that may link endocrine signals with synaptic plasticity through NCOR-mediated regulation of GABA signaling. (**Erratum in Author Correction**: Loss of function of NCOR1 and NCOR2 impairs memory through a novel GABAergic hypothalamus-CA3 projection. [*Nature Neuroscience* 2019])

Zhu, Y., et al. (2019). "Prevalence of dementia in the people's republic of China from 1985 to 2015: A systematic review and meta-regression analysis." *BMC Public Health* **19**(1): 578. In China, the most populous developing country in the world, dementia represents a serious challenge. We performed a large-scale systematic review and meta-regression analysis to elucidate the prevalence of dementia and its subtypes and to identify potential factors underlying the differences between articles. METHODS: A comprehensive literature search was conducted in the following databases to identify studies published up to December 2015: Cochrane Library, CBMDISK, Chongqing VIP, CNKI, PubMed and EMBASE. All statistic analyses (including subtype and meta-regression analyses) were performed with R version 3.3.3. RESULTS: In total, 51 surveys were selected. The pooled prevalence rates of dementia and its main subtypes, namely, Alzheimer's disease (AD) and vascular dementia (VAD), for the population aged 55 years and older were 4.03, 2.44 and 1.09%, respectively. The outcomes showed that the meta-regression analysis was affected by the publication year, sample size, region and diagnostic criteria. CONCLUSIONS: Our analysis provided reliable estimates of the prevalence of dementia/ AD/ VD over the past 30 years, which may be affected by education level, and diagnostic criteria. The prevalence of AD/VAD was higher in northern than in southern China, which warrants further study.

Zhuang, J., et al. (2018). "Language processing in age-related macular degeneration associated with unique functional connectivity signatures in the right hemisphere." *Neurobiology of Aging* **63**: 65-74.

Age-related macular degeneration (AMD) is a retinal disease associated with significant vision loss among older adults. Previous large-scale behavioral studies indicate that people with AMD are at increased risk of cognitive deficits in language processing, particularly in verbal fluency tasks. The neural underpinnings of any relationship between AMD and higher cognitive functions, such as language processing, remain unclear. This study aims to address this issue using independent component analysis of spontaneous brain activity at rest. In 2 components associated with visual processing, we observed weaker functional connectivity in the primary visual

cortex and lateral occipital cortex in AMD patients compared with healthy controls, indicating that AMD might lead to differences in the neural representation of vision. In a component related to language processing, we found that increasing connectivity within the right inferior frontal gyrus was associated with better verbal fluency performance across all older adults, and the verbal fluency effect was greater in AMD patients than controls in both right inferior frontal gyrus and right posterior temporal regions. As the behavioral performance of our patients is as good as that of controls, these findings suggest that preservation of verbal fluency performance in AMD patients might be achieved through higher contribution from right hemisphere regions in bilateral language networks. If that is the case, there may be an opportunity to promote cognitive resilience among seniors with AMD or other forms of late-life vision loss. (**Keywords**: Age-related macular degeneration, Cognitive preservation, Functional connectivity, Language processing)

Zingeser, L. B. and R. S. Berndt (1990). "Retrieval of nouns and verbs in agrammatism and anomia." *Brain and Language* **39**(1): 14-32.

The ability of five agrammatic and five anomic aphasic patients to produce nouns and verbs was assessed in four tasks. Target words were form class unambiguous, frequency and length matched nouns and verbs, elicited as single words in picture naming and naming-to-definition tasks. The same unambiguous verbs were targets in an action description task. Narrative speech was obtained from each patient using a story elicitation procedure. Agrammatic aphasics produced significantly fewer verbs than nouns, relative to other groups, in all tasks. Anomic aphasics reliably produced more verbs than nouns in naming to definition. These results replicate previous findings for Italian-speaking patient groups, and for several individual cases. In addition, these results extend the relative verb deficit among agrammatic patients to connected speech tasks. Results are interpreted in light of current models of lexical and sentence production.

Zou, Y., Ka, Steven and William S-Y. Wang (2017). "Dementia in the Chinese population and the potential of musical treatment." *Experimental Linguistics* **6**: 1-18.

In terms of the targeting population, research of cognitive performance tends to cluster much more towards the younger end of the lifespan, where scholars put much emphasis on how cognitive abilities develop rather than decline. The Chinese population has been contributing the largest proportion of people with dementia more than any other regions in the world, and such situation will get even severer in the near future as reported by Ferri et al (2006) and Rodriguez et al (2008). In this regard, a more thorough investigation into the dementia problem in the Chinese population is in urgent need. Among all the cognitive screening tools for dementia, MMSE (Mini–mental State Examination) and MoCA (Montreal Cognitive Assessment) are the most heavily-adapted ones, yet in their Mandarin and HK-Cantonese versions, there are not a few linguistic bias which should be paid sufficient attention to. Another flourishing study area brought along by the dementia issue is musical treatment. The unique power of music as both cognitive reserve & healing tools has not only been reported in anecdotals but also manifested by increasingly more empirical evidence (Baird & Samson, 2015). Scholars has just begun to unlock this mysterious power and are expecting a new boom for the musical treatment in dementia. The aim of this study is three-fold: 1) to provide meta-analyses of dementia prevalence and its major risk factors (such as age, gender, and educational background, etc.) in the Chinese population 2) to point out the problem of culture bias when adapting various screening tools for dementia in the Chinese population 3) to probe into the power of music as both cognitive reserve and healing device in dementia, with special attention to the uniqueness of Chinese music and the potential direction for music treatment tailored for the Chinese population.