Brain Resilience and Aging

تاب آوری مغز

Outline

- Resilience
- Aging Brain
- Neuroplasticity
- Resilience Proxies
- Cognitive Reserve
- Reserve, Maintenance and Compensation
- Cognitive Training
- The Role of Neuroimaging
- Therapeutic Issues

Resilience of the brain

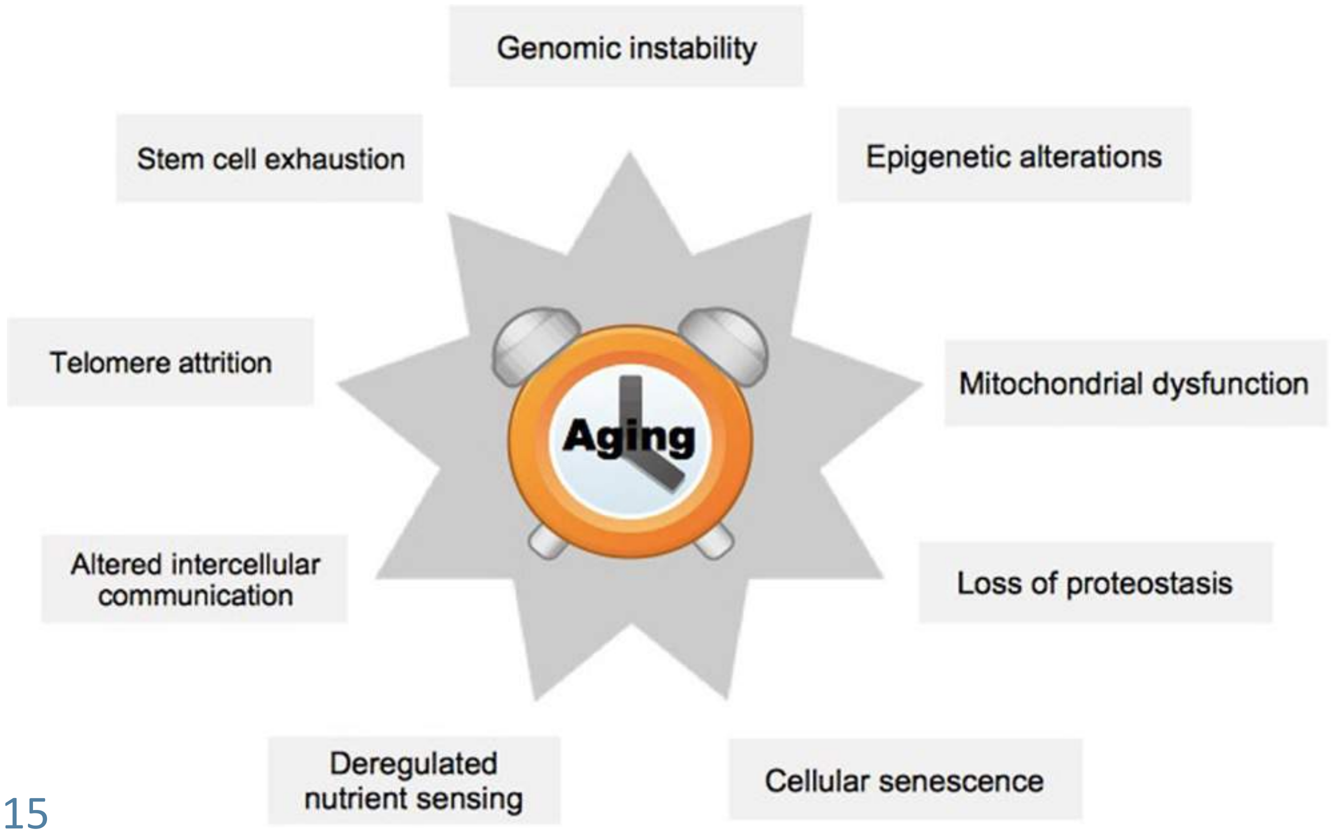
- “Resilience” can be defined as the ability to achieve a successful outcome in the face of adversity.
- Brain as the central organ of stress and adaptation to stress, perceives threatening challenges and determines physiological and behavioral responses.
- The mature, as well as developing brain, has a remarkable ability to show structural and functional plasticity and resilience in response to stressful experiences, by way of neuronal replacement, dendritic remodeling, and synapse turnover.

Aging Brain:
Different Trajectories

Aging brain

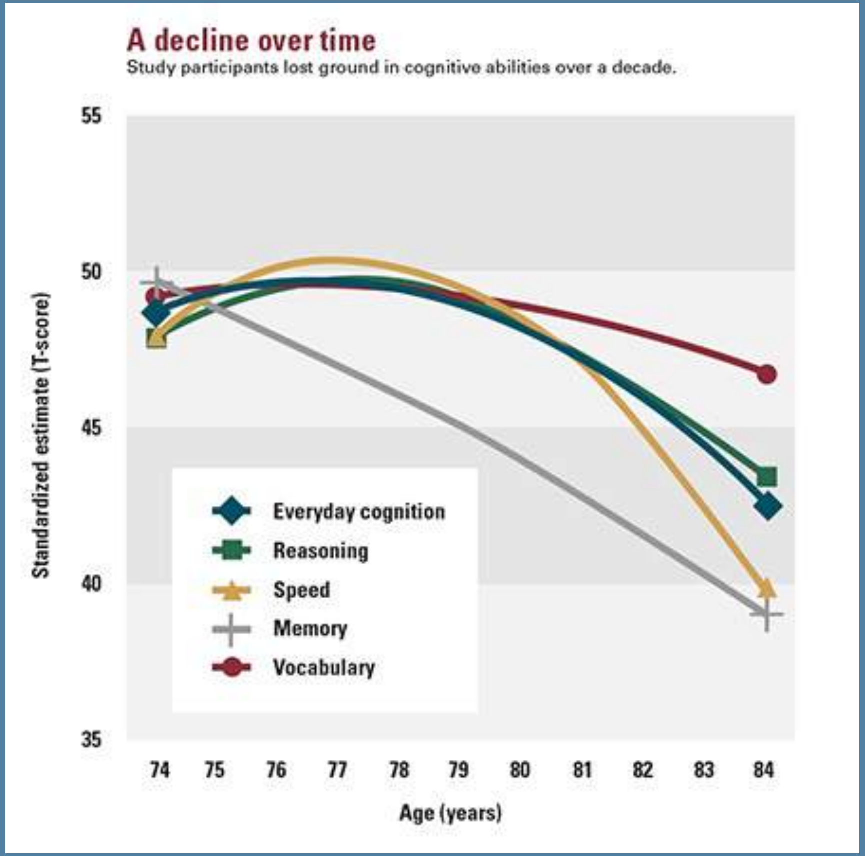
- Ageing affects neurobiological functions at multiple levels:
  - Genes
  - Cellular and molecular functions
  - Brain structure
  - Brain function
- The advent of MRI methods have significantly advanced our understanding of how the brain changes with age at the gross anatomical and functional levels.

Aging brain



Sara Fonseca Costa, 2015

Age-related cognitive decline



Neuroplasticity

Brain Plasticity: History

"Cells that fire together, wire together"

Donald Hebb, 1904-1985

Neuroplasticity: History

- For a long time, it has been assumed that brain plasticity peaks at young age and then gradually decreases as one gets older.
- Up until the middle of the twentieth century, neuroscience dogma emphasized the fixed, irreversible nature of the brain.
- 1960s: researchers at UC Berkeley generated data revealing the dynamic characteristics of mature neural systems.
- 1964: A group of scientists documented the neuroanatomical changes in rats exposed to enriched environments.

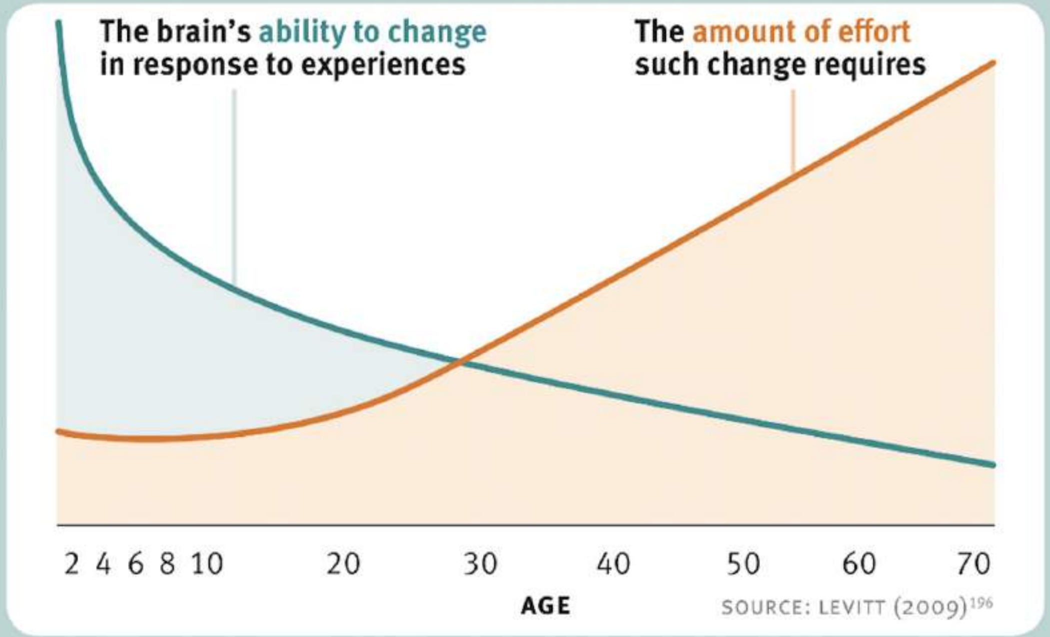
Marian Diamond:
Pioneer in neuroplasticity and enriched environments research

- Marian Diamond most certainly enriched the field of neuroscience, as the notion of neuroplasticity has become a basis of contemporary neuroscience.

- Her research on the brain of Albert Einstein helped fuel the ongoing scientific revolution in understanding the roles of glial cells in the brain.

Marian Diamond, 1926-2017

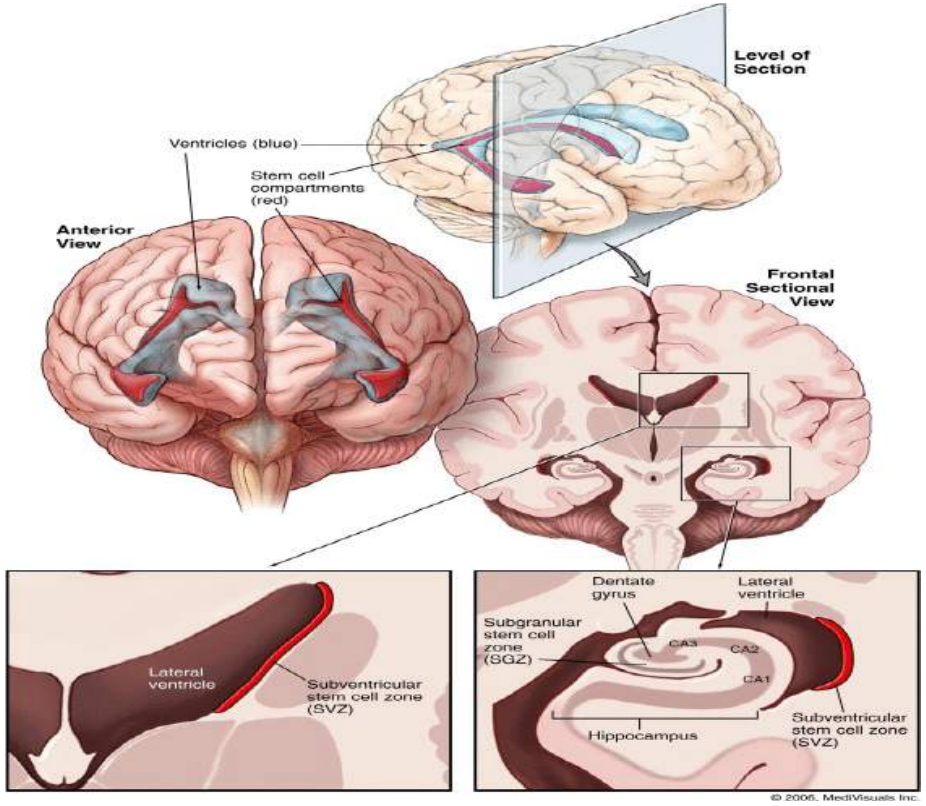
Brain ability to change



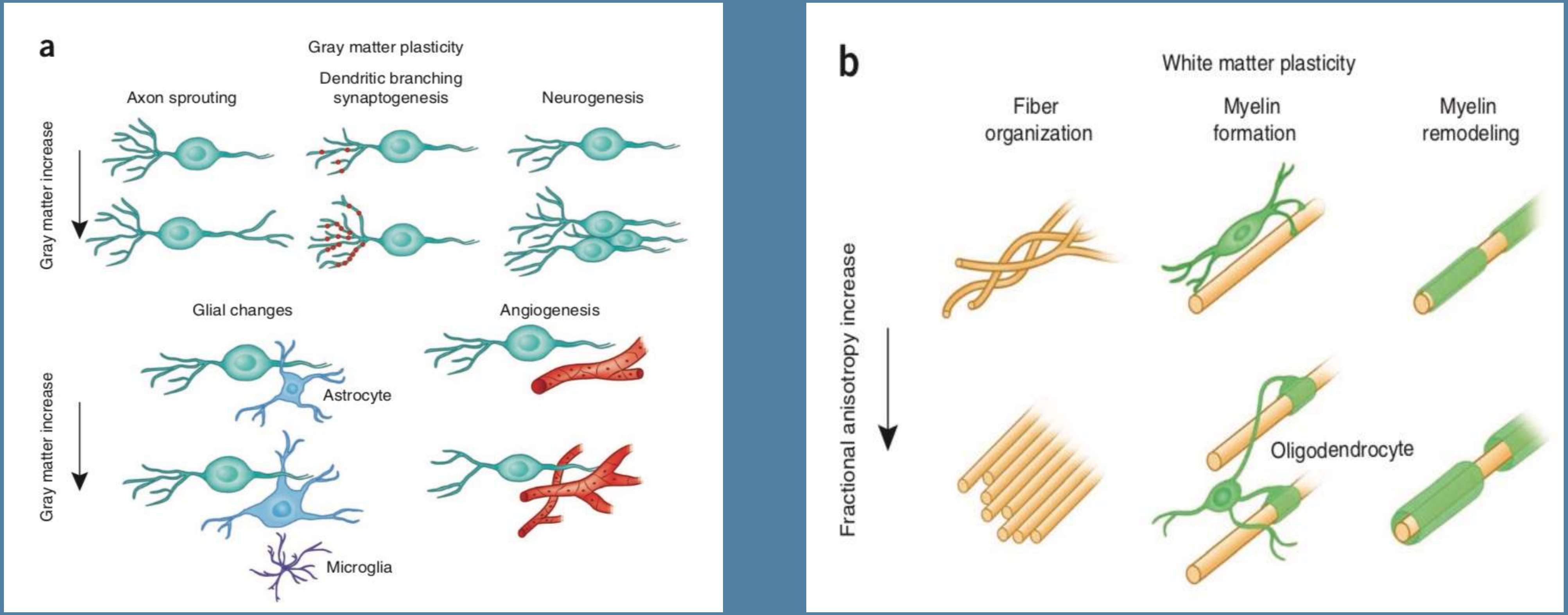
As shown by this conceptual graph, drawn from multiple studies on humans and animals, the brain's plasticity is strongest in the first few years after birth. Thus, it is easier and less costly to form strong brain circuits during the early years than it is to intervene or "fix" them later.

Neurogenesis

- Adult Neurogenesis in the dentate gyrus has gone on to become a huge topic related to effects of stress, exercise, enriched environment, antidepressants, and learning and memory.

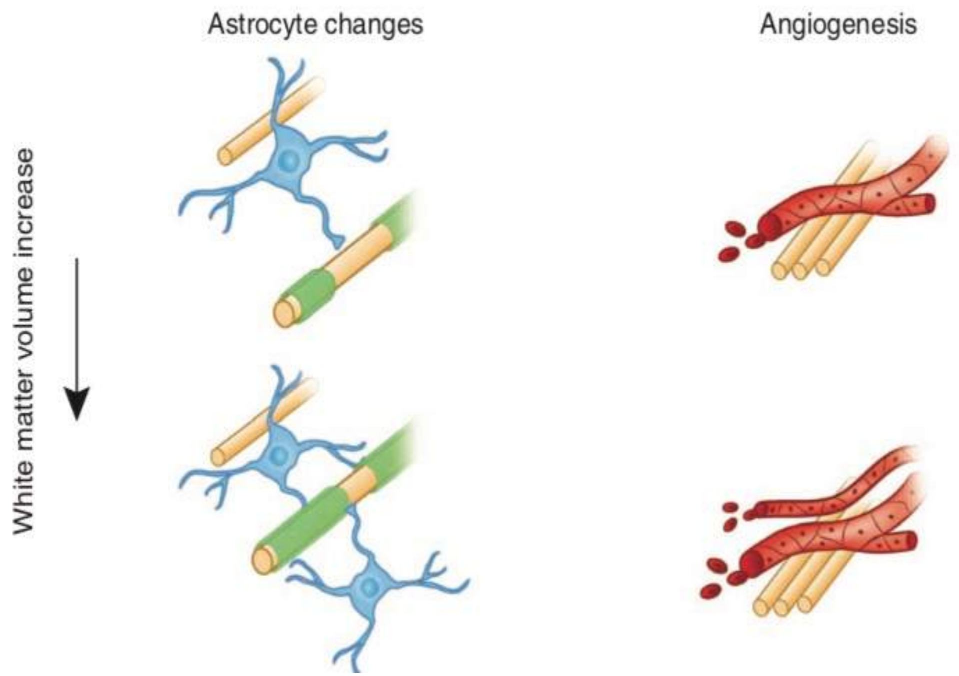


Neuroplasticity in gray and white matter



Astrocytes changes, angiogenesis

- Training studies suggest that experience can alter the vasculature, particularly with regimes that increase physical activity.
- Experiments show that physical exercise increases histologically quantified vascular volume in the cerebral cortex in parallel with improved performance on cognitive tests; **both effects are lost after a 3-month sedentary period.**
- Vascular changes could occur in some contexts even in the absence of neurogenesis.



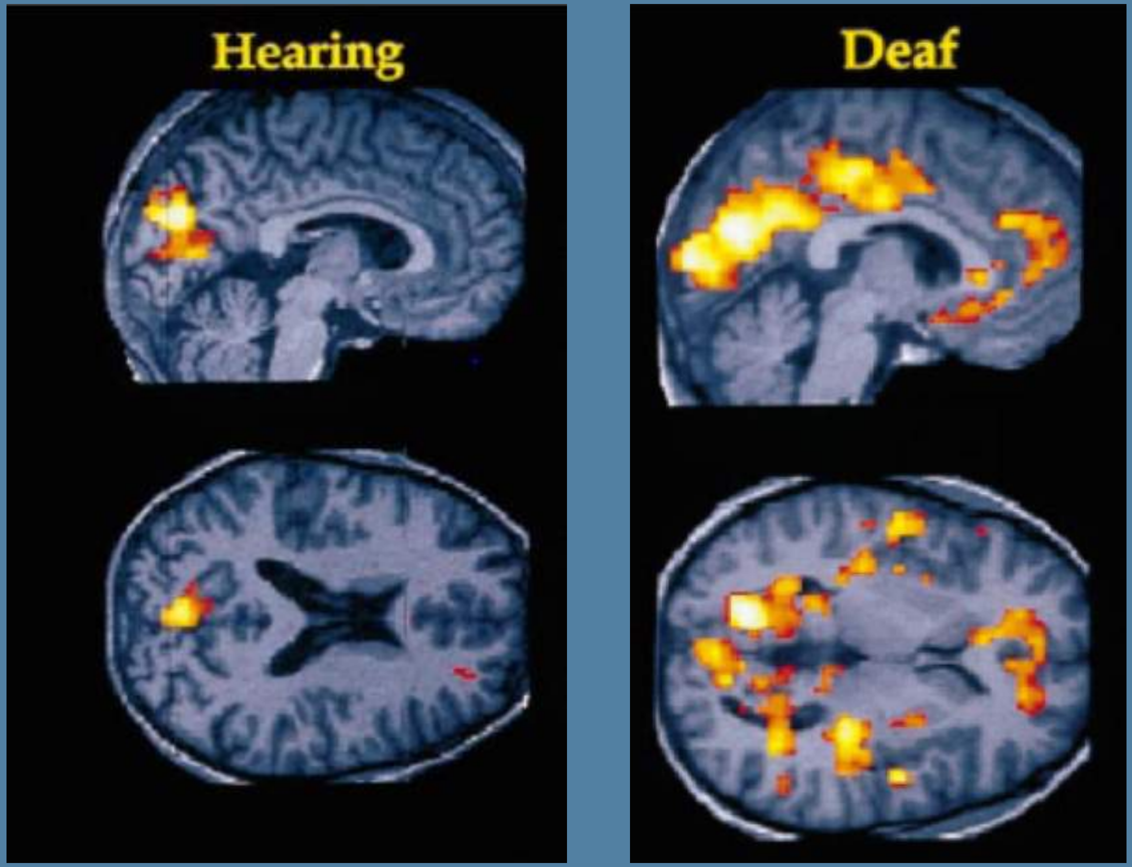
Modulators of neuroplasticity

- Polymorphisms in the Brain-derived Neurotrophic Factor (BDNF) gene are associated with variations in hippocampal volume, memory performance and susceptibility to plasticity-inducing brain stimulation.
- BDNF can regulate development of oligodendrocyte progenitor cells and affect myelination.
- Physical activity and diet modulate common neuroplasticity substrates:
- **Neurotrophic signaling (BDNF)**
- **Neurogenesis**
- **Inflammation**
- **Stress response**
- **Antioxidant defense**

Deafness:
Cross modal neuroplasticity

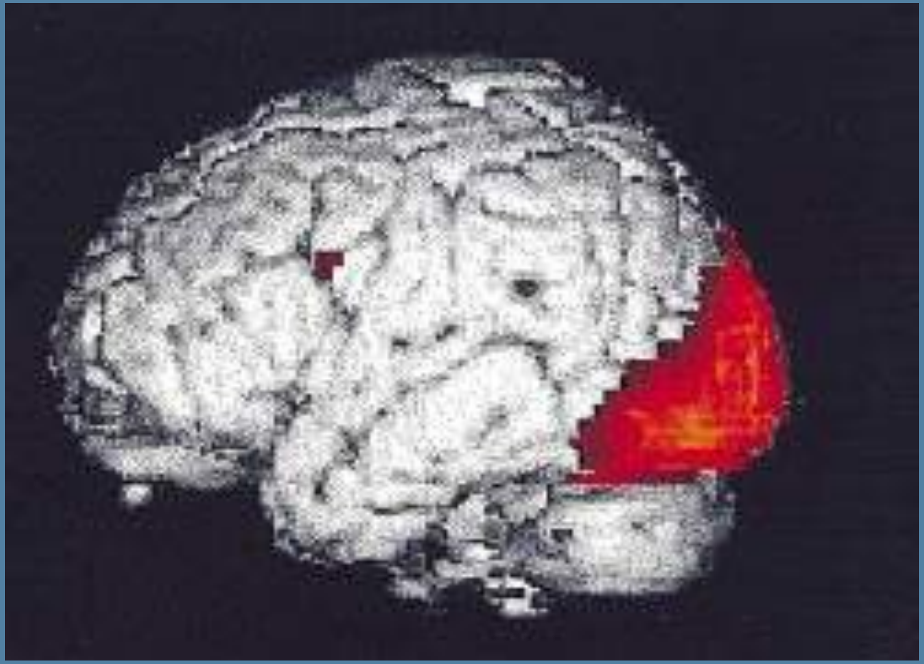
- fMRI Task:

showing a visual moving stimulus

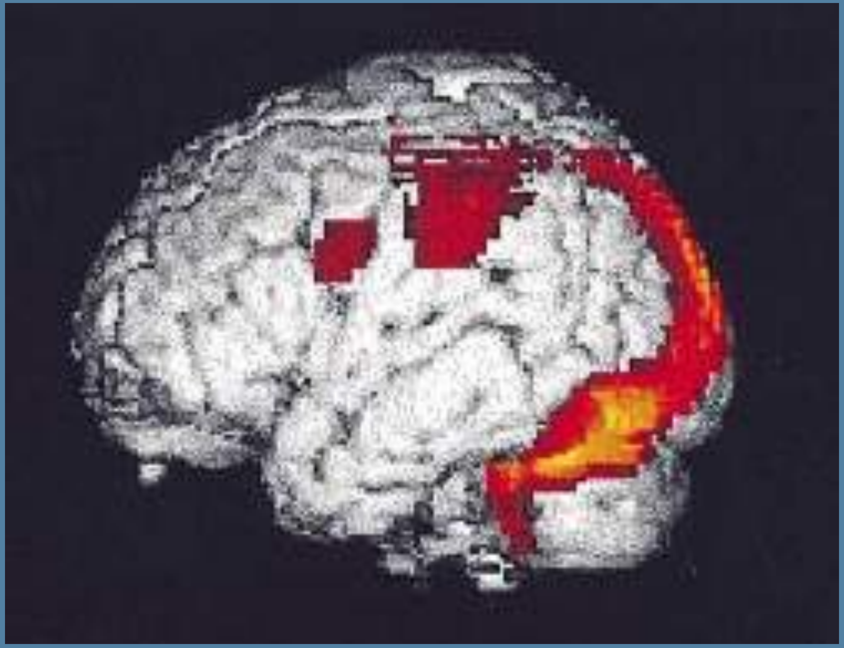


Blindness:
Cross modal neuroplasticity

Letter Reading: sighted



Braille Reading: Blind



Resilience Proxies

Inter-individual variability in cognitive aging

- **There is great individual variability in cognitive aging trajectories.**
- Some older adults show little decline in cognitive ability compared with young adults and are thus termed optimally aging or successful aging , by contrast, others exhibit substantial cognitive decline and may develop dementia.
- The impact of resilience becomes more pronounced at older ages.
- The impact on the life span: The subjects aged 94-98 with increased resilience had a 43.1% higher likelihood of living to be, or becoming a centenarian, than those with lower resilience.

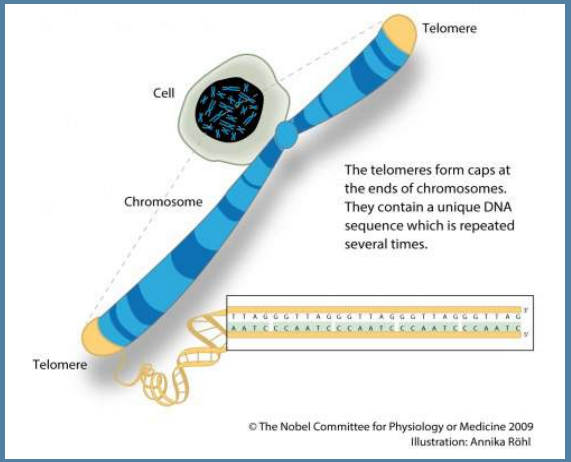
Ageing Research: Methodology

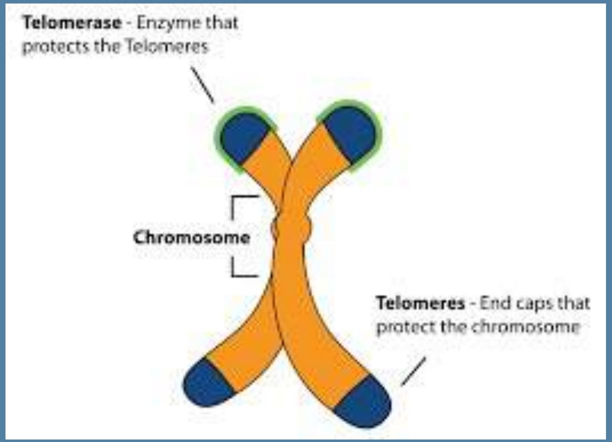
- When investigating individual differences among older adults in Cross-sectional studies, the limitations of this designs should be compared with longitudinal designs.
- Older participants are typically recruited only from the subset of well-educated people who have aged in relatively good health and are free of brain disease, whereas the control young adult samples are more heterogeneous.
- Cross-sectional study designs can also be contaminated by birth cohort effects, including inter-generational IQ increases (Flynn Effect).

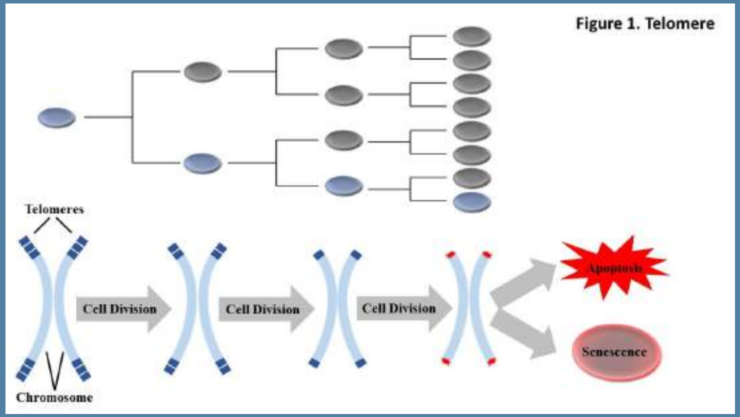
Resilience breakdown

- The aging process
- There are several mechanisms that impairs **maintaining resilience:** Hypothalamic–Pituitary–Adrenal (HPA) axis dysfunction, brain atrophy in regions that are most actively protective against stress, genetic causes, poor nutrition, loss of coping abilities, and the onset of a neurodegenerative disorders.
- Early childhood adversity such as abuse, neglect, or exposure to violence increases pro-inflammatory responses, affects patterns of gene expression regulated by inflammatory signaling, and quickens the process of Telomere shortening.
- Children exposed to maltreatment: smaller volumes of the PFC and the hippocampus, greater activation of the HPA axis and inflammation levels

Resilience and genes: Telomere shortening







The timeline of early life experiences on cognitive reserve and Alzheimer's

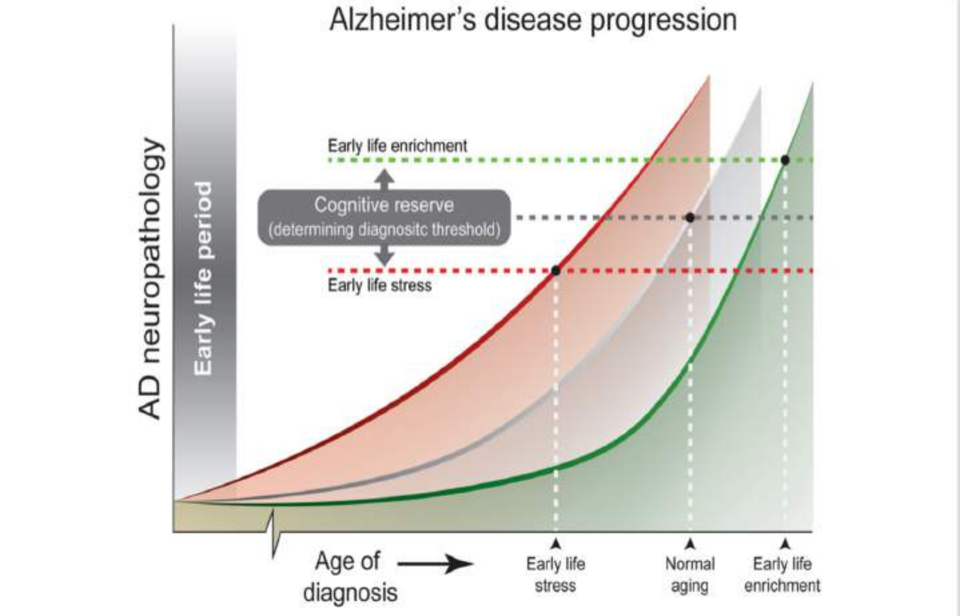
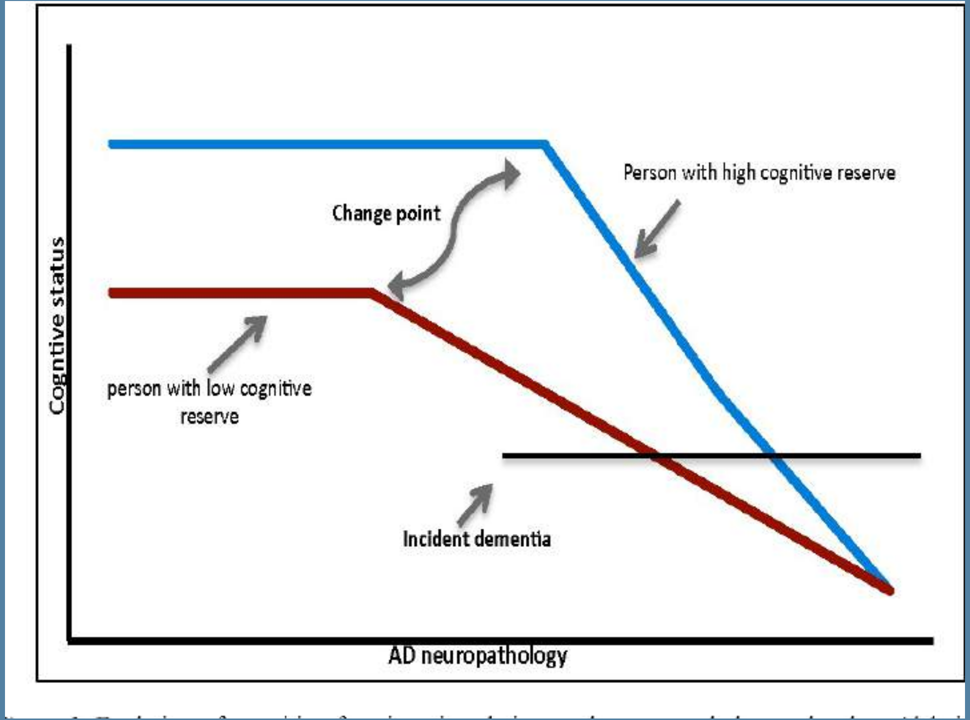


Fig. 1 Proposed timelines illustrating how early life experiences can alter brain and cognitive reserve and impact development of AD neuropathology. Early life period determines rate at which AD neuropathology develops, with early life stress (red) accelerating disease progression, while early life enrichment (green) decreases disease progression. In addition, cognitive reserve of the brain is modulated by early life experiences, thereby determining at what pathological stage the clinical diagnosis of dementia is established. AD: Alzheimer's disease



Resilience: Male vs. female

- Sex differences in stress responses are found at all ages, and are related to gonadal hormone changes that occur throughout development and maturation, and sex chromosome genes.
- Females:
- Decreased quality of health throughout life due to an increased vulnerability to stress
- Lose hippocampal volume more rapidly than men in older age, despite living longer lives
- Generally experience worse health throughout life than men
- Increased lifespan may be due to the rate at which telomeres shorten

Stress: The role on neuroplasticity

- **Hypothalamic- Pituitary-Adrenal** (HPA) axis: Stress induces alterations in this axis and glutamate neurotransmission as well as impaired neurotrophic and neuroprotective signaling.
- **Neuroplasticity:** Stress can divert its protective influence to instead become harmful and reduce the neurogenesis.
- **Hippocampus:** Repeated stress can lead to atrophy and death of neurons.
- **Prefrontal Cortex (PFC):** Vulnerable to the stress in particular.
- **Amygdala:** Dendrites in the basolateral part grow and become more branched and, as a result, there is increased anxiety.
- **The whole body:** Reciprocal communication between the brain and the body : neuroendocrine, autonomic and immune systems and metabolic mechanisms

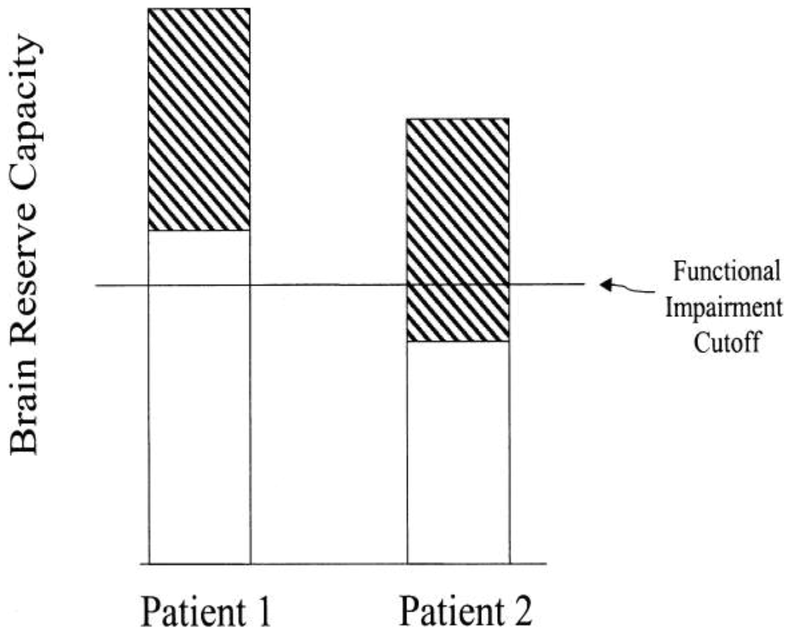
Cognitive Reserve

Cognitive Reserve (CR)

- The cognitive performance of two people with relatively similar brain health is not necessarily more similar than the cognitive performance of two people with appreciably different levels of brain health.
- A third variable was needed to adequately account for the relationship between brain structure/metabolism and cognitive performance: **Cognitive Reserve**
- Resilience is a more general term referring to multiple reserve-related processes.

Cognitive Reserve (CR)

- The term CR refers to the adaptability of cognitive processes that helps to explain differential susceptibility of cognitive abilities or day-to-day function to brain aging, pathology, or insult.
- It can be influenced by the interaction of innate (e.g., in utero, or genetically determined) individual differences and lifetime exposures such as early-life general cognitive ability (e.g., intelligence), education, occupational complexity, physical exercise, leisure activities, or social engagement.



Cognitive Reserve (CR)

- It was first formulated as concept in:

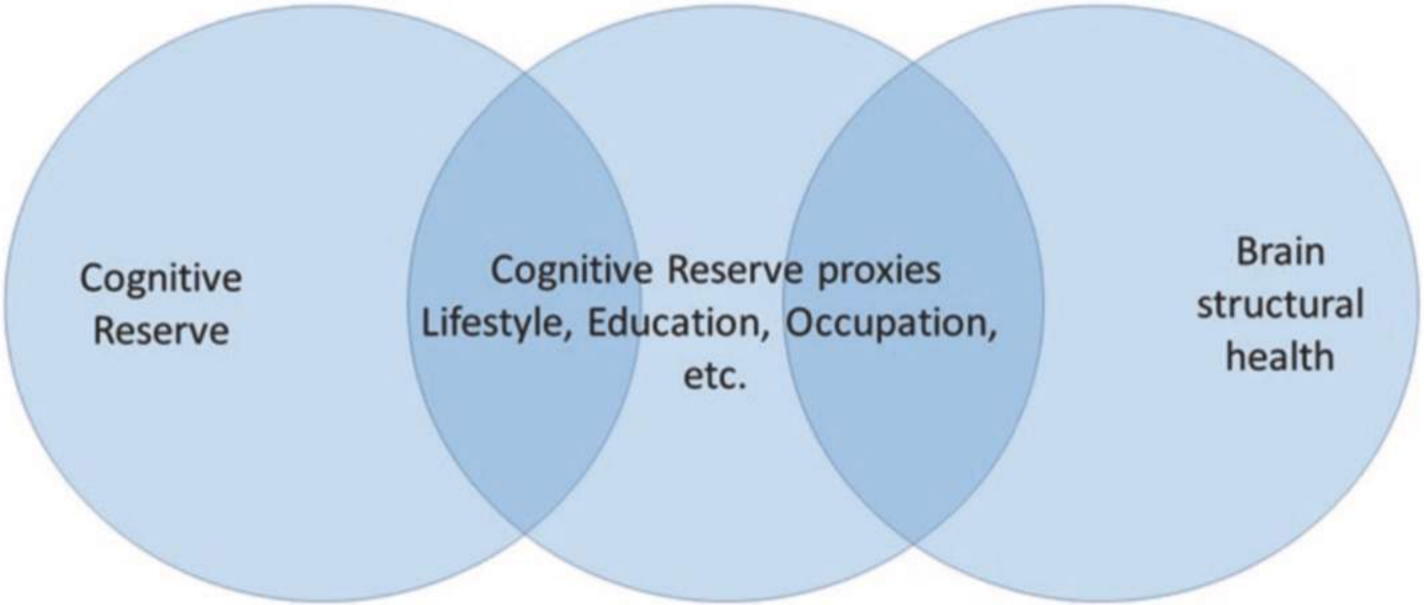
(1) Autopsy data of person appearing cognitively normal at death showed varying degrees of Alzheimer-like pathology.

(2) When matched for disease severity of clinical presentations, PET scans revealed worse metabolic deficits in parieto-temporal areas for patients with higher premorbid educational and occupational attainment.

- Systematic review on the life-course factors which protect older individuals from expressing cognitive decline despite the presence of brain pathology.
- **Education has a protective effect on general cognition in the face of multiple brain burden measures.**

Cognitive Reserve (CR)

- Genetic
- Intelligence
- Education
- Bilingualism
- Physical activity
- Occupation
- Leisure activities



- **The Venn diagram:** CR proxies consist of two parts: (1) a part that correlates with brain structure and points to to build and maintain a healthy brain and (2) cognitive reserve, which is independent of brain structure.

Reserve: Brain vs. Cognitive

Brain Reserve	Cognitive Reserve
Hardware, Neurobiological substrate of Reserve	Software, Function of Reserve
Fixed, Passive	Dynamic, Active
Measurement by structural Neuroimaging	Measurement by functional Neuroimaging

Cognitive reserve measurement:

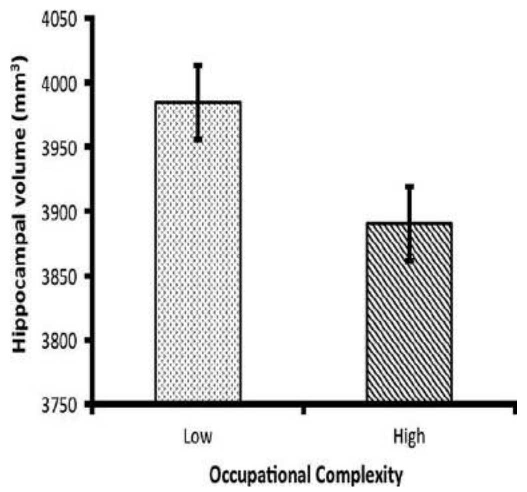
- **Efficiency** can be defined as the degree to which a given ask-related brain network must become activated to do a given task.
- An individual with greater efficiency will show less task-related activation at a given level of task demand.
- Higher CR might be associated with either greater efficiency or capacity.
- **Capacity**
- **Flexibility**

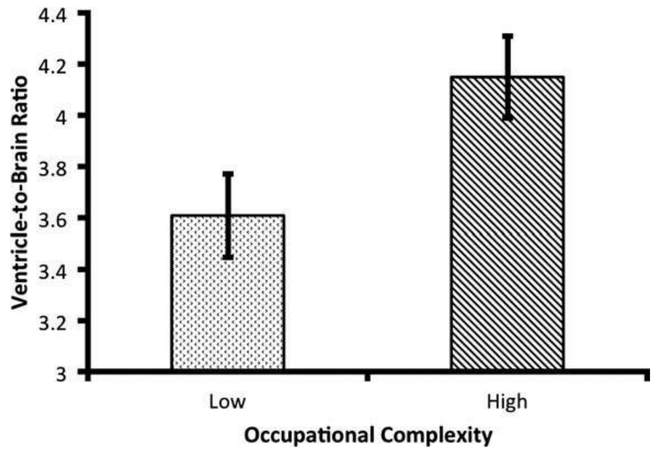
Cognitive reserve measurement:

- **Capacity** can be defined as the maximum degree to which a task-related brain network can be activated to keep performing a task in the face of increasing demands.
- The maximum capacity varies across individuals.
- **Flexibility:** an individual with higher CR may have more varied solution strategies available.
- Flexibility might be reflected by the ability to utilize alternate networks during task performance that result in more successful performance.

Occupational complexity

- Occupational complexity (OCC) was assessed using three complexity ratings (work with data, people, and things) in 323 subjects at risk for Alzheimer's.
- Greater OCC was associated with decreased hippocampal volume and increased whole-brain atrophy when matched for cognitive function.
- Occupational complexity may confer resilience to the adverse effects of neuropathology on cognition.
- Significant impact of working with people: indicating that social components of occupation may have the greatest relevance to CR.





London taxi drivers

- Structural MRIs of the brains of humans with extensive navigation experience, licensed London taxi drivers were analyzed.
- The posterior hippocampi of taxi drivers were significantly larger relative to those of control subjects.
- Hippocampal volume correlated with the amount of time spent as a taxi driver.

Central London

Musicians

- Musicians consistently show greater gray matter volume and cortical thickness in auditory cortices; they also show differences in motor regions and in white matter organization of the spinothalamic tract.
- The effects generally increase as a function of years of musical practice, again supporting an experience-dependent explanation.
- A solution to these problems comes from longitudinal studies.
- Causality?

Neuroplasticity following learning Juggling

- **Juggling training:** One of the first longitudinal MRI studies used to demonstrate increased gray matter density in the visual motion area bilaterally (in occipitoparietal regions) when people learn to juggle over a 3-month period,
- The changes are apparent after as little as 7 days of training.
- Such experience-dependent macrostructural changes are not restricted to gray matter but can also in white matter, was detected by fractional anisotropy.

Reserve, Maintenance and Compensation

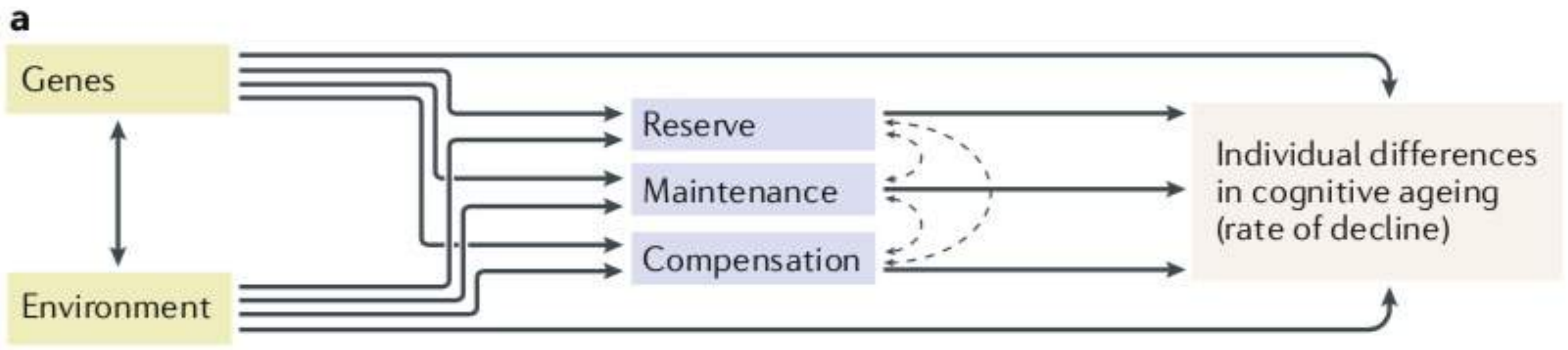
Reserve, Maintenance and Compensation

- **Reserve:** The accumulation of brain resources during the lifespan.

  It is about how much you have.
- **Maintenance:** The preservation of these resources via constant recovery and repair.
  It is about how well you keep it.
- **Compensation:** The deployment of these resources in response to task demands.
  It is about when and how you use it.

Reserve, Maintenance and Compensation

- **Reserve** is essentially an increased supply of neural resources created as a result of experiences, whereas neural **compensation** is the ability to draw more effectively and efficiently on networks.
- It is not enough to accumulate reserve and maintain it; it is also necessary to deploy these resources during task performance in response to task demands to engage in compensation.



Reserve

- **Accumulation of neural resources:** occurs before the brain is affected by age-related processes and to take place over a period of years.
- Due to genetic and/or environmental factors, of neural resources that relieves the effects of neural decline caused by ageing or age-related diseases.
- **Reserve substrates:**

1. **Neural Capacity**
2. **Neural Efficiency**

Reserve substrates: Neural capacity

- **Neural Capacity:** The total amount of neural resources available for cognition:
- The gray matter volume of a brain region
- The white matter quality of a fiber tract that mediate cognitive processes.
- The function of a region, as measured by functional neuroimaging
- Operation of a brain network, as assessed by functional connectivity methods

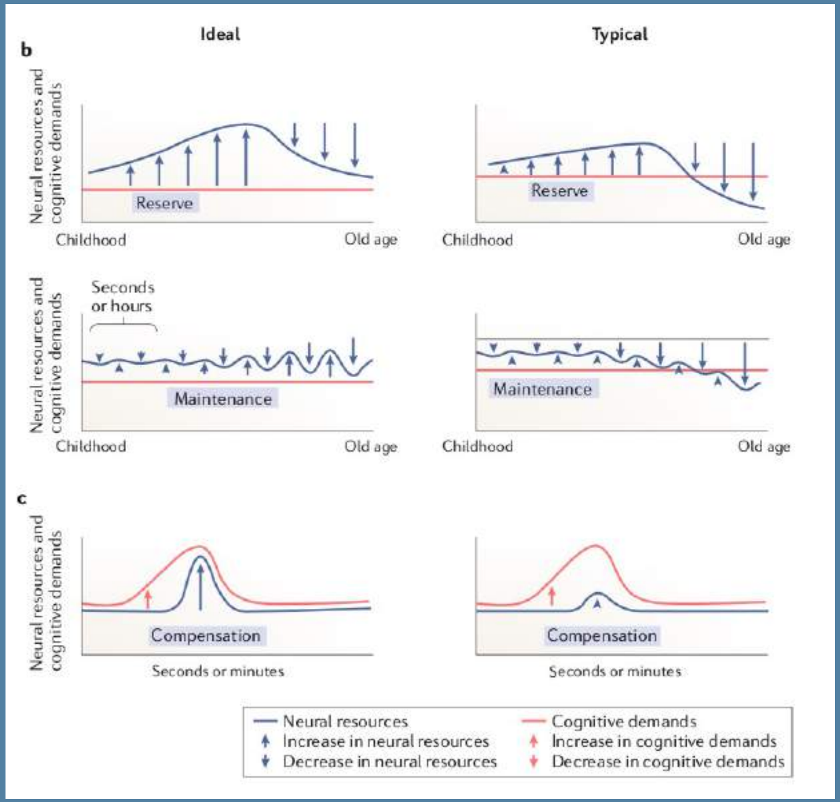
Reserve substrates: Neural efficiency

- **Neural Efficiency:** The use of less neural resources (development of expertise):
  - In a particular domain through training, which in turn is often associated with reduced regional brain activity.
  - Associated with the presence of richer and more differentiated conceptual representations, which can attenuate age-related decline in the domain of expertise.
- The burden of age-related neuronal decline – at some level - may becomes great enough to overcome the protective mechanisms of reserve, resulting in rapid cognitive decline.

Reserve and education

- **The best example of a factor that promotes reserve is education,** which improves neural resources during childhood and young adulthood (possibly by enhancing synaptic density) and attenuates age-related cognitive decline in later adulthood.
- The beneficial effect of education on cognitive performance might also be mediated partly by its effects on a range of other outcomes that have also served as **proxy measures of reserve, including health, stress, profession and lifestyle.**
- In the ideal case, accumulated reserve is enough against age-related neural decline; however, in a more typical case, it only attenuates this decline.

Reserve, Maintenance and Compensation: Ideal vs. Typical



Reserve measurement

- Using functional neuroimaging to investigate reserve, it is possible to distinguish between the across-individual activity differences that are related to reserve or compensation.
- Reserve is linked to more effective use of cerebral networks.
- Greater cognitive reserve, as measured using IQ and education–occupation as proxies, is associated with lower brain activity in a variety of brain regions (including the superior temporal and superior parietal cortices) during cognitive processing.

Maintenance mechanism

- Preservation of neural resources, which require repair of the brain in response to the impact of damage at the cellular and molecular levels.
- The efficacy of maintenance depends both on the magnitude of decline and the efficacy of repair.
- The mechanisms: both genetic and environmental (diet, exercise and cognitive and social engagement) origins.
- The basic mechanisms include both neural components (such as neurogenesis) and non-neural components (such as vascular changes).

Reserve & Maintenance: mechanisms of action

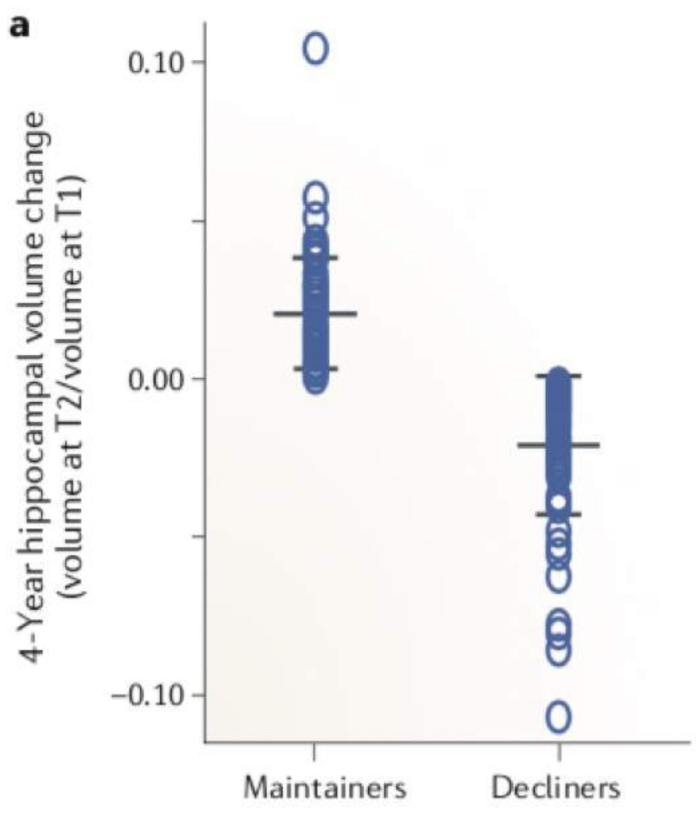
Reserve	Maintenance
Augmenting resources beyond their current level	Returning them to their former higher level
Influence on neural capacity and neural efficiency	Mechanisms of repair and plasticity
More environmental	More biological
Increase in neural resource in childhood	Increase in neural resource in the old age

The link: Exercise and WM integrity

- it is possible that individuals who exercise regularly maintain white matter integrity better than they maintain other aspects of the brain.
- Different individuals in terms of:
- Forms of maintenance
- Extent of maintenance
- Structures of the brain (the gray matter or white matter)
- Neurotransmitter systems
- Brain regions (hippocampus or the prefrontal cortex)

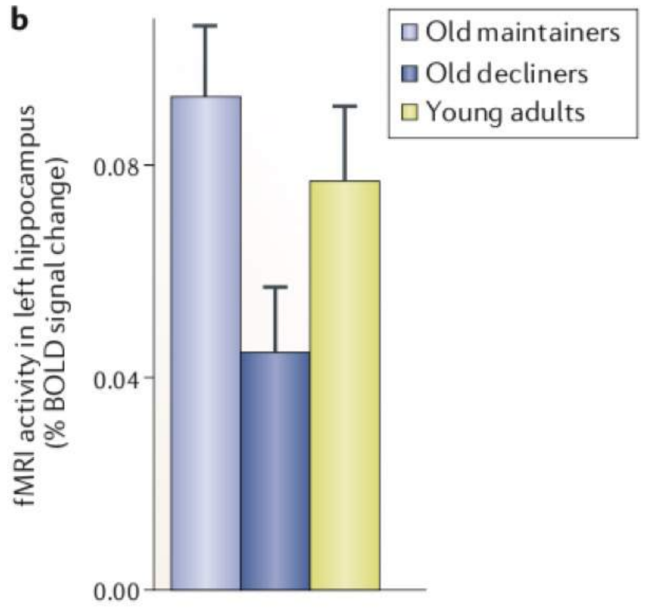
Maintenance: Clinical decline and neuroimaging

- A longitudinal structural MRI study found that individuals aged 65 years or older who exhibited little or no episodic memory decline over a 4-year period **(‘maintainers’)** showed less hippocampal atrophy during the same period than individuals with substantial memory decline **(‘decliners’).**



Maintenance: maintainers vs. decliners

- Hippocampal activity during an episodic memory task was significantly higher in **('maintainers')** over the previous two decades than in **('decliners').**
- Old maintainers showed no significant episodic memory decline over a period of two decades compared with young adults with a mean age of 35.3 years) displayed levels of hippocampal activity comparable to those of young adults.
- Because hippocampal activity was not measured at initial testing (20 years prior), it is unclear whether the maintainers exhibited higher hippocampal activity than decliners at the start of the experiment.



BOLD, Blood-oxygen-level-dependent

Compensation

- The term compensation is to describe a situation in which brain activity or functional connectivity is greater or more widespread in the elderly.
- Compensation is linked to variations in cognitive demands and can occur rapidly, in a matter of seconds.
- **Individual differences reflecting compensation**, differ according to the nature of the cognitive challenge.
- Highly educated individuals may show different activation patterns because their greater reserve allows them to deploy more effective compensatory processes.

Compensation: supply-demand gap

- The increased activation in older adults is directly or indirectly related to some insufficiency or gap between available neural resources and task demands (the supply–demand gap).
- This gap may be due to an age-related reduction in neural resources (e.g. brain atrophy, reduced blood flow, neurotransmitter deficits or reduced neural specificity), to an increase in task demands, or to both.
- This gap is primarily due to the age-related decline in neural resources.
- Beneficial effect on cognitive performance

Compensation:
Three different mechanisms

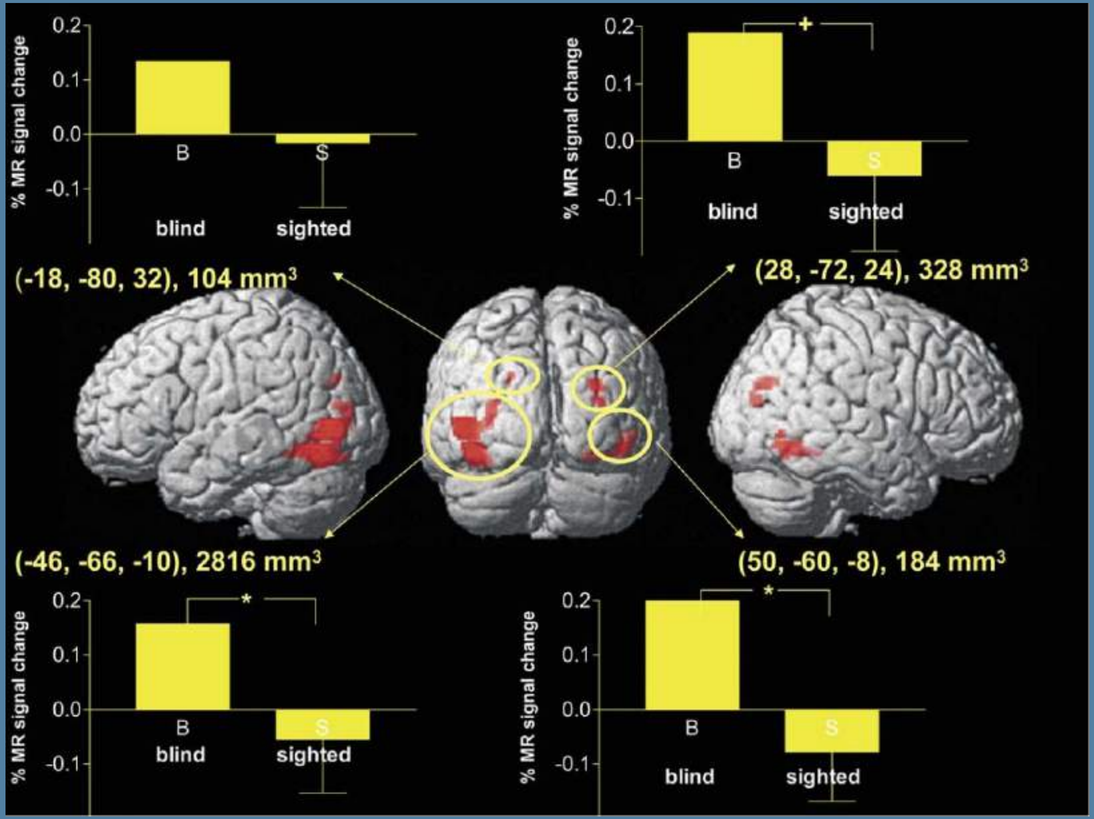
- Upregulation
- Selection
- Recruitment of additional processes

Compensation by Upregulation

- By <u>boosting</u> a neural process in response to task demands.
- The same processes while the primary difference between the ages would be <u>quantitative</u>.
- Older adults would engage the process to a greater extent than younger adults.
- Young adults may also upregulate activity in response to increased task demands but that the demand threshold for such upregulation may be higher in young adults than it is for older adults.

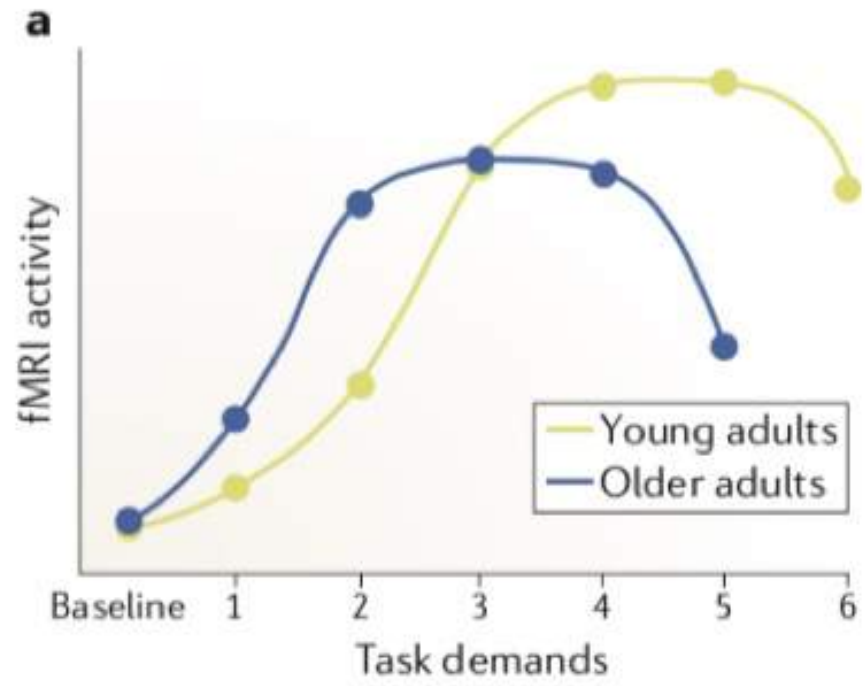
Reserve: Upregulation

- **Feeling with the mind's eye:**
- Contribution of visual cortex to tactile perception
- Tactile discrimination activates the visual cortex of the recently blind naive to Braille: a functional magnetic resonance imaging study in humans



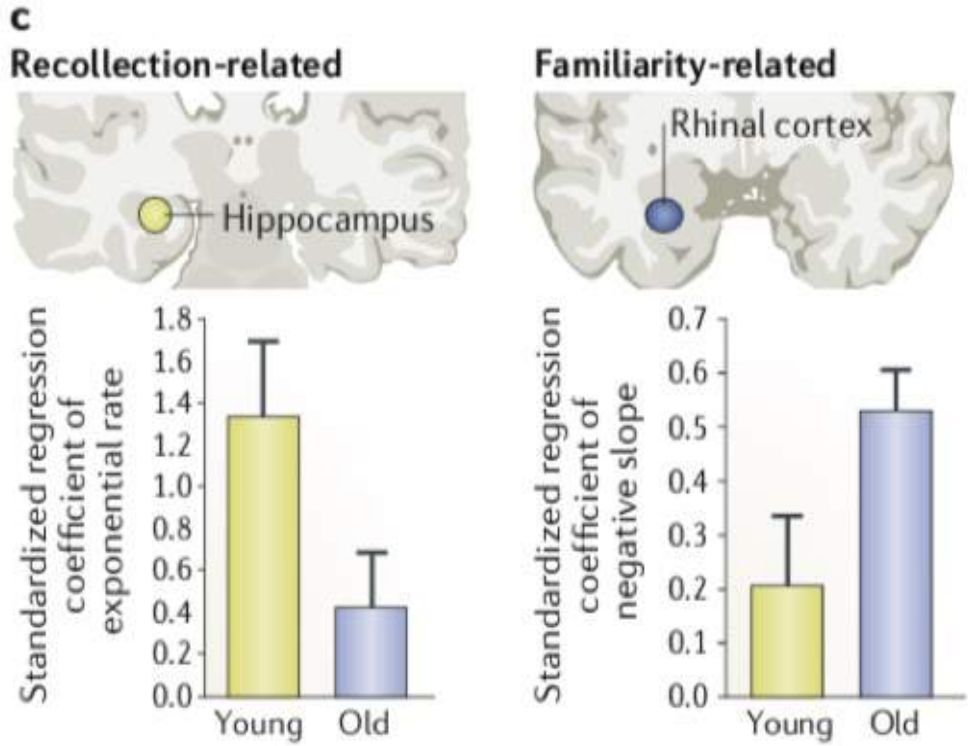
Compensation by Upregulation

- Older adults show a greater increase in activity, and an earlier decline than younger adults.
- Because of reduced neural resources, they would tend to show greater activity in the same regions as younger adults at lower levels of task difficulty but lower activity at higher levels of task difficulty.



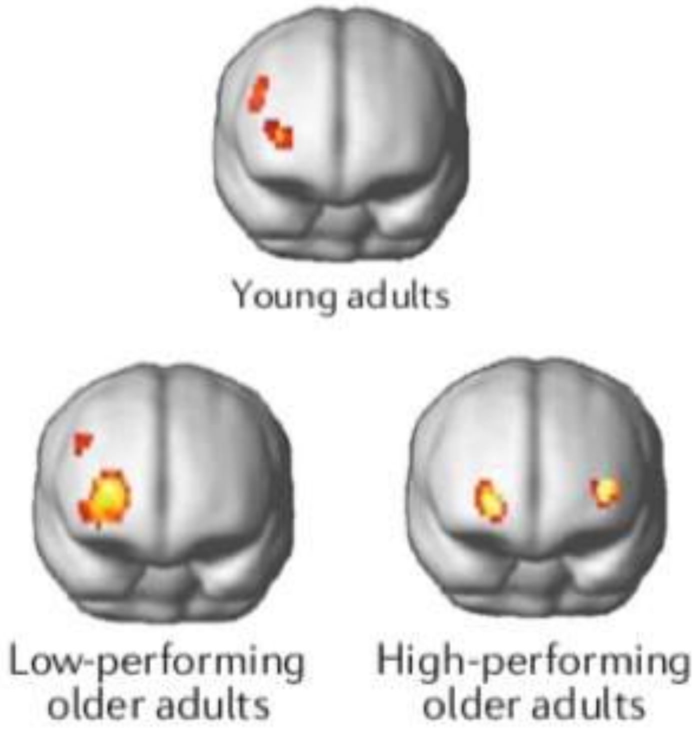
Compensation by Selection

- Another mechanism of compensation is the recruitment of neural circuitry associated with cognitive processes that are available to but not engaged by young adults.
- Older adults may engage a less effective but also less demanding process, whereas younger adults may prefer a more effective but more demanding one.



Compensation by Reorganization

- The closest analogy: Development of **new neural mechanisms following brain damage** (e.g. recovery from aphasia following a left-hemisphere stroke)
- Older adults often show more bilateral patterns of brain activity than younger adults.
- Reorganization due to ageing and due to brain damage differs in several ways: the time course of ageing is slow, whereas the course of brain injury is fast.
- Which time course is better for reorganization?



Cognitive Training

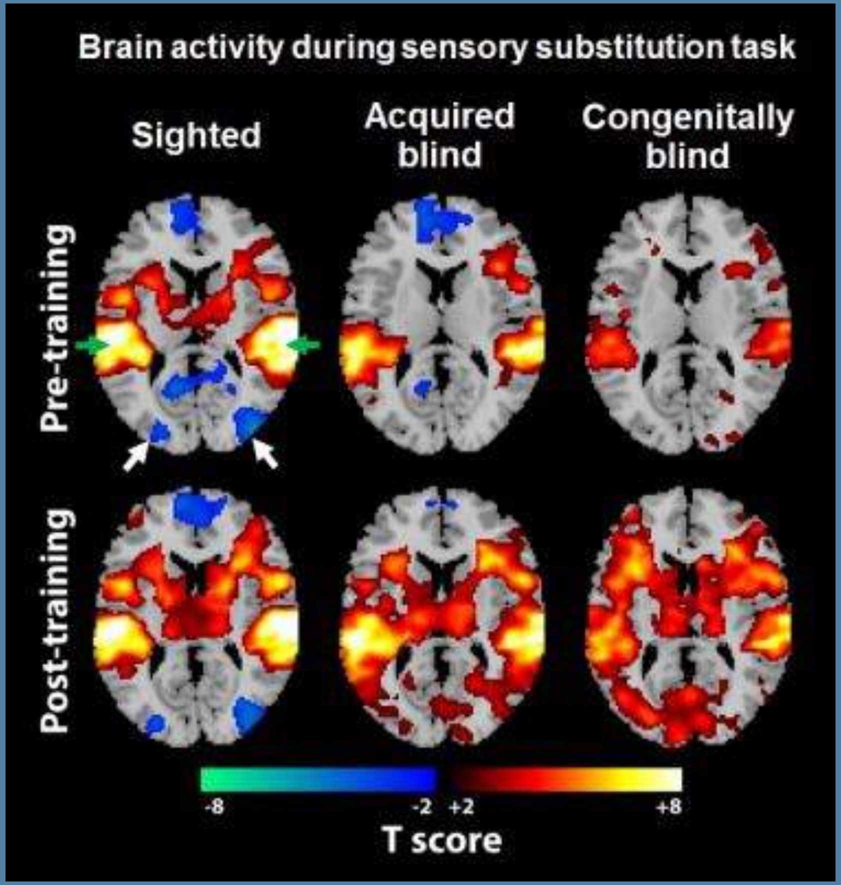
Cognitive Training in aged brain

- Past experiences, expertise, and cognitive status will all play important roles in understanding tasks and have the potential to effect change in neural structure or function.
- Perhaps the most unambiguous evidence is when training increases the thickness or volume of neural structures:
- When older adults were trained to juggle for 90 days, **mid temporal regions, hippocampus and nucleus accumbens,** which are related to **complex motor behaviors**, showed gains in neural volume relative to a control group.

Old vs. Young: Strategy or capacity

- The rich knowledge base that accrues as we age provides an excellent mechanism for utilizing wisdom and knowledge to facilitate performance, rather than a true change in the neurocognitive system.
- Many changes in activation as a result of training reflect flexibility in deployment of resources due to strategy change rather than a manifestation of plasticity resulting in an increase in intrinsic neural or cognitive capacity.
- Younger adults have more neural plasticity than old, and that the young are most likely to show an increase in intrinsic neural capacity with training, whereas the **old are more likely to recognize gains due to flexibility in strategy use.**

Blindness
Cross Modal Neuroplasticity



Cognitive training: Behavioral change

- Enhanced neural activity is facilitative for old adults, so training enhances neural activation and behavioral function in older adults.
- Nyberg et al reported that mnemonic training in older adults resulted in an increase in activations in occipito-parietal regions, but only for those who showed a training related behavioral improvement.
- Young adults: improvement in these regions and frontal regions.
- Six weeks of attentional training in older adults resulted in an increase in cerebral blood flow to the prefrontal cortex during rest, combined with a decrease in distractibility.

“Far transfer” phenomenon

- One important aspect of training studies is whether the training results in broad changes in processing abilities that transfer to other unrelated tasks (“far transfer”) or whether it is only the trained ability that improves.
- The training improvements in some older adults are manifested for prolonged periods of time, even years later.
- Working memory training, has shown evidence for far transfer from training on a working memory task to improvement in general intelligence.

Duration of cognitive training

- Cognitive training in older adults has resulted in gains over time for periods ranging from 3 months to 5 years.
- Extensive training (1 hour per day for 8 to 10 weeks) on a series of computerized tasks showed improvements in verbal memory despite no training specifically on memory, was maintained three months later in digit span forward scores.
- Older men who played a demanding spatial navigational game every other day for 4 months exhibited stability of hippocampal volume over a 4-month period, whereas control subjects declined.
- These trained subjects showed an increase in structural integrity of the hippocampus which was maintained when training ceased.

Social vs. computer setting

- Unlike cognitive training that relies on computer training and may deprive individuals of social engagement and pursuit of satisfying activities, immersion in a social learning environment has the potential to confer cognitive protection while meeting basic psychological needs for social interactions and purpose in life.
- The crucial role of **enjoyment**

The Role of Neuroimaging

From experience to neuroimaging

Experience

↓

Neural Activity Patterns

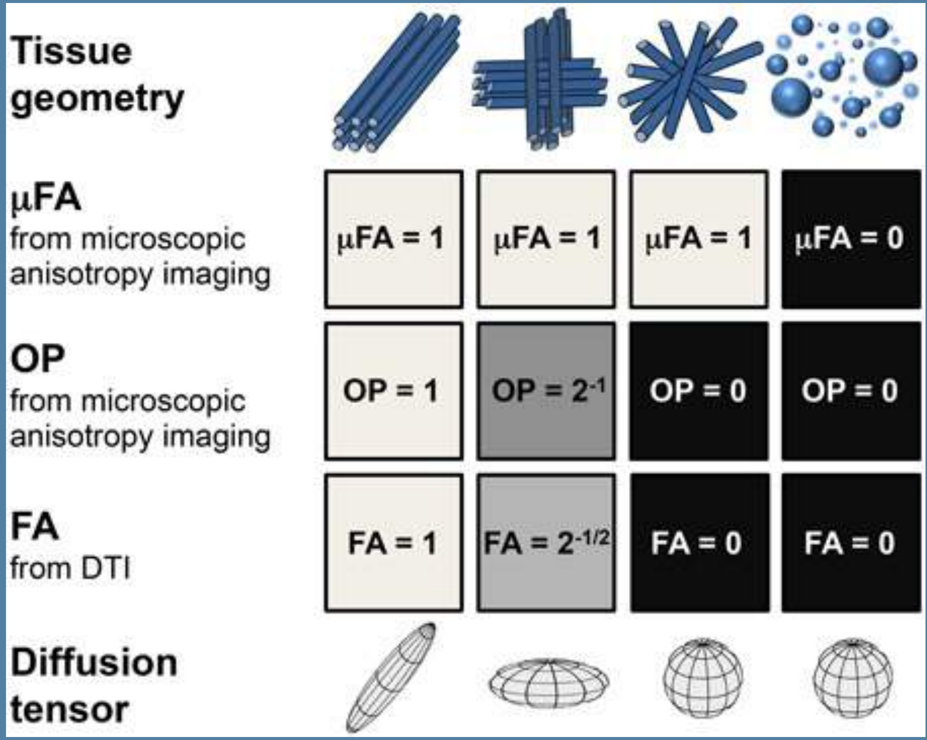
↓

Structural Features

The Importance of neuroimaging

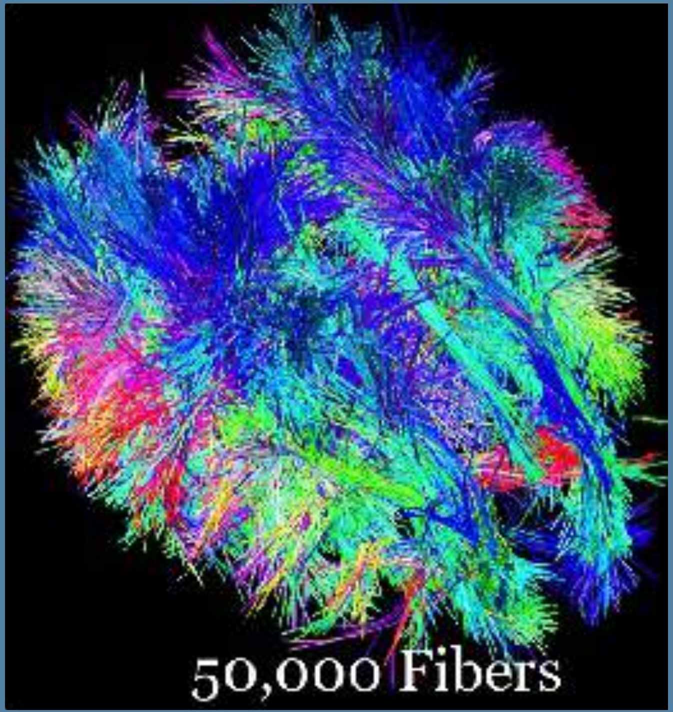
- Neuroimaging techniques offer certain advantages, as they can be repeatedly performed in the same individual and provide whole-brain measures of brain structure and function.
- Studies on inter-regional correlations of **cortical thickness** reveal that gray matter anatomical networks parallel functional organizational patterns, that they are modified during development and that they are sensitive to training.

MRI: Fractional Anisotropy (FA)

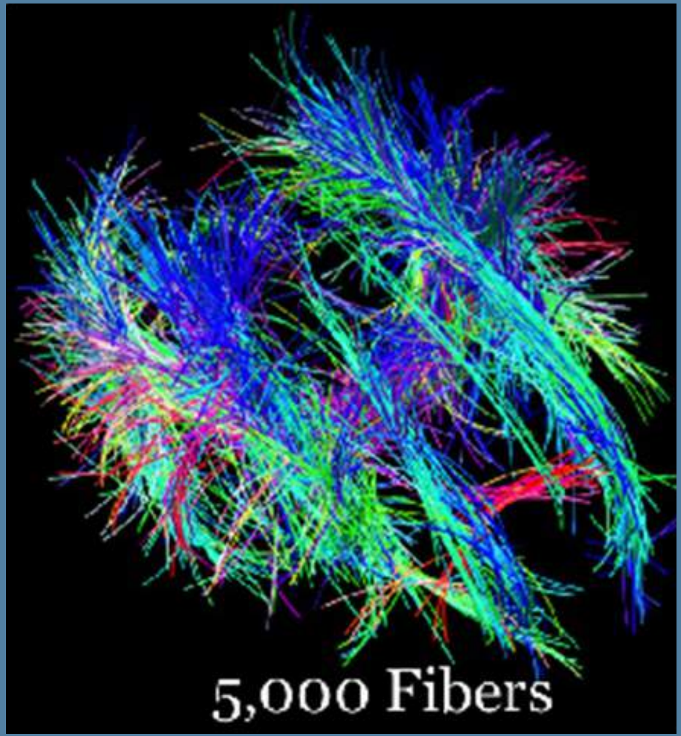


Whole brain tractography in patient with Alzheimer's disease

Healthy Control



Alzheimer's disease



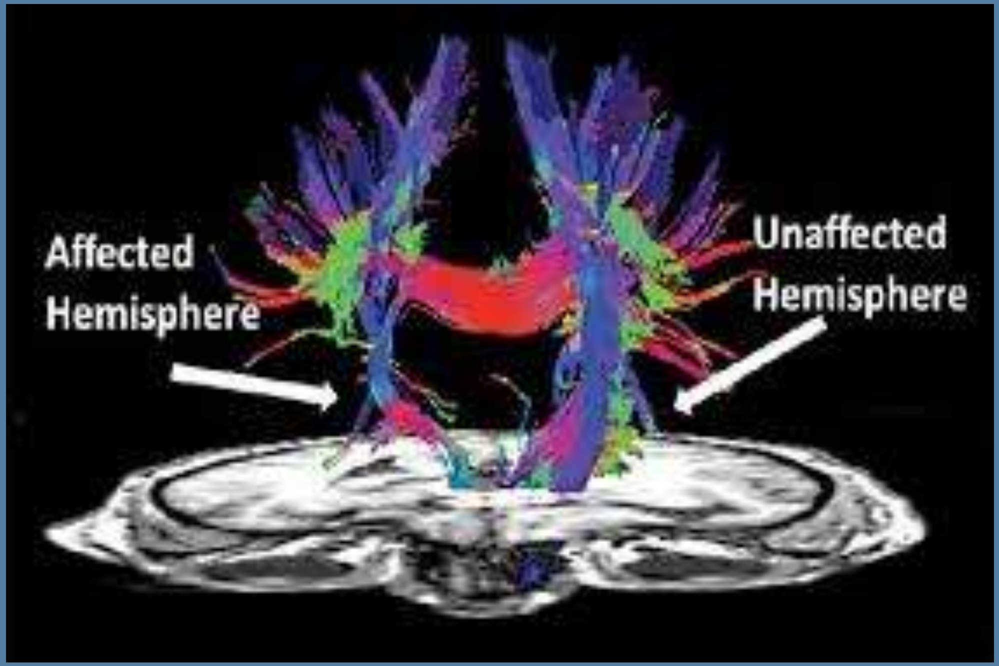
Experience-dependent vs. pre-existing factors

- Heritability studies in twin populations can quantify the degree to which environmental or genetic factors explain variation in gray or white matter measures.
- **Gray Matter:** Genetic influences are most notable in the frontal and temporal lobes, including areas related to language.
- **White Matter:** Genetic factors explain about 75–90% of the variation in fractional anisotropy in large regions, particularly in parietal and frontal lobes.
- Other white matter regions, such as the **corpus callosum**, show much stronger evidence for environmental influence.

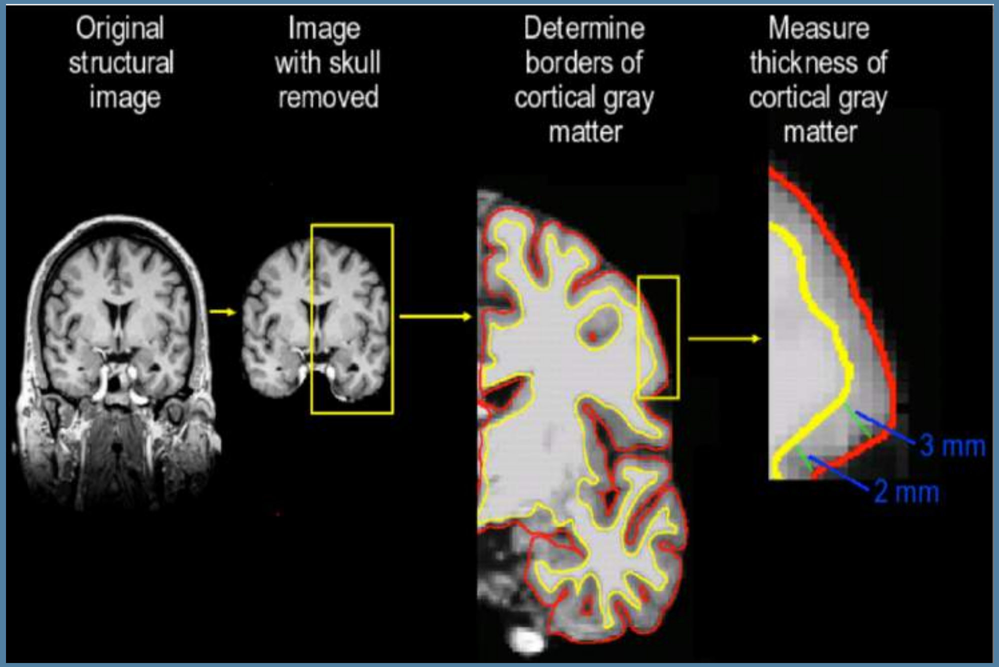
Diffusion Tensor Imaging (DTI)

- **Diffusion Tensor Imaging (DTI) is an MRI-based neuroimaging** technique which makes it possible to estimate the location, orientation, and anisotropy of the brain's **white matter tracts**.
- Diffusion imaging measures are sensitive to many tissue properties, including
- Variation in myelin, axon diameter and packing density, axon permeability
- The number of myelinated axons in a tract, the thickness of myelin, to determine the speed of impulse propagation and thus could contribute to increased functional performance with learning.

Neuroimaging Technics

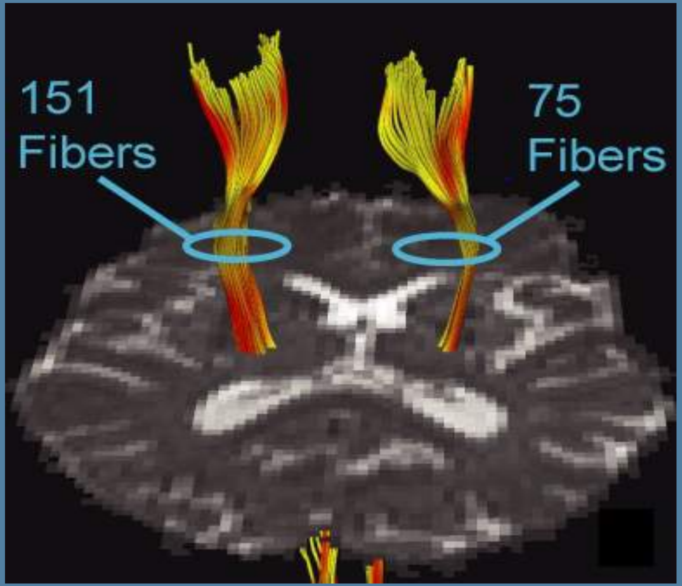


DTI: Stroke

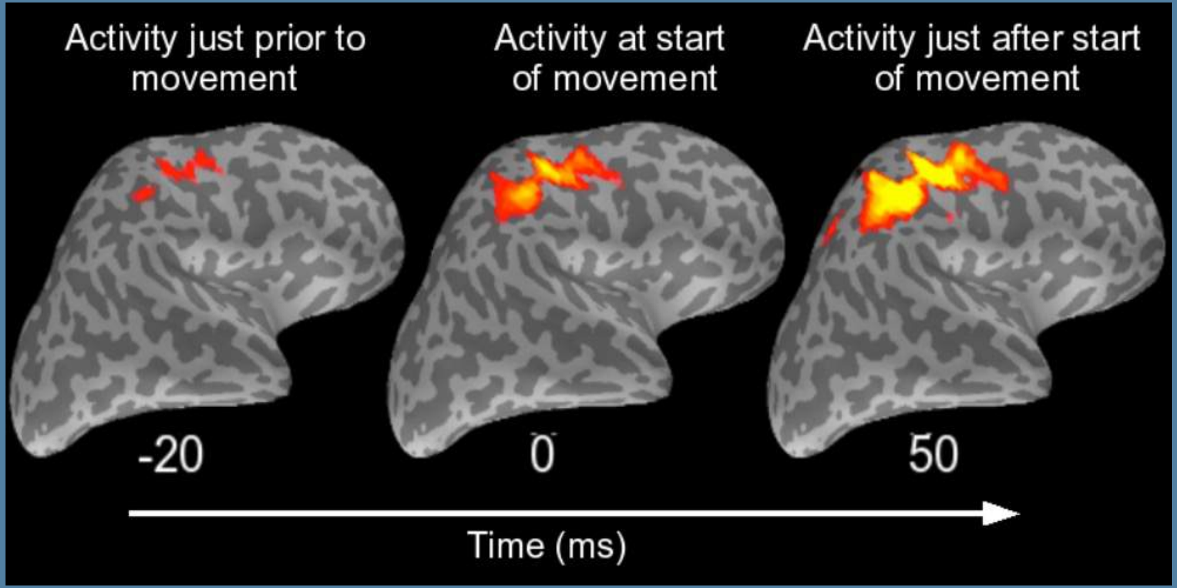


Cortical Thickness

Neuroimaging technics



DTI



Magnetoencephalography

Neuroimaging future

- Pushing the boundaries of image acquisition with sophisticated hardware can provide a new window on tissue microstructure at a level not previously achievable in human studies.
- In gray matter, imaging at ultra-high resolution, and with multiple signal modalities, allows measures to be taken in specific cortical layers or hippocampal subfields.
- In white matter, diffusion imaging can be adapted to generate axon diameter distributions or estimates of myelin microstructure.
- New developments in modeling of complex tissue architecture can provide greater sensitivity to specific cellular features.

Therapeutic Issues

Physical activity

- Regular physical activity improves prefrontal and parietal cortex blood flow and enhances executive function.
- Sedentary older adults who engage in aerobic exercise can delay shrinkage in prefrontal cortex, an area maximally sensitive to age-related volumetric shrinkage.
- Regular physical activity increases hippocampal volume in previously sedentary elderly adults,
- Fit individuals have larger hippocampal volumes than sedentary adults of the same age range.

Practice and age

- Practice of a **complex whole-body balancing task** results in **increased gray matter in frontal and parietal cortex** after just 2 days of training, and altered fractional anisotropy in corresponding white matter regions over 6 weeks of training.
- Practice leads to improvement in performance on motor - or any other - tasks and this process is associated with altered brain activity, occurring in a similar manner in young and older adults.
- Old people should be encouraged to abandon their pre-existing habits and replace these by new ones, continuously challenging the adaptability and flexibility of their brains.
- Personalized training to the capacity of each person allow abilities to improve over time following repeated cycles of reward to the subject.

Neuroplasticity: challenging practice

- A critical requirement for neuroplasticity to emerge is to make the practice context sufficiently difficult for the learner.
- One way to challenge the environmental context is to confront learners with practicing more than one task within each practice session.
- More specifically, rather than performing subtasks in a sequential, one after the other (less challenging), one can also apply a more demanding random practice regime such that learners have to switch tasks from trial to trial during practice (more challenging).

Aging and brain plasticity

- Older adults can equally cope with this increased contextual complexity as young adults do and that it benefits longer-term skill retention.
- New motor and other skills can be acquired at any age even though the progress may be somewhat attenuated in older.
- The importance of these results should not be underestimated in this highly dynamic world in which dramatic technical developments are implemented at a rapid pace.

Cognitive Behavioral Therapy and mindfulness

- Cognitive Behavioral Therapy (CBT), can produce volumetric changes in both prefrontal cortex in the case of chronic fatigue, and in amygdala in the case of chronic anxiety, and in brainstem area associated with well- being.
- Mindfulness-based stress-reduction has been shown to increase regional brain grey matter density in hippocampus, cerebellum, and prefrontal cortex, which are brain regions involved in learning and memory processes, emotion regulation, self-referential processing, and perspective taking.

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