Aging Brain Research: Challenges and Opportunities

Centre for Networked Intelligence (CNI)
Indian Institute of Science
21 Jan 2026

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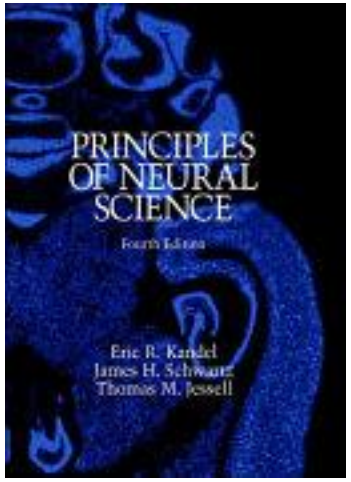
Sources:
Internet and



January 2026

Introduction – Healthy and Aging Cells

- Healthy cells have the ability to divide, produce energy, involve in waste removal, nutrition uptake etc.
- **Hayflick Limit:** It refers to the maximum number of times a normal human somatic (body) cell can divide before it permanently stops and enters a state called cellular **senescence**.
- Aged cells stop dividing but are metabolically active

Human	40-60 divisions	~80 years
(Galapagos Turtle	*~110 divisions.*	*~100+ years)*

Introduction - Aging

Cell senescence has been defined as an induced, irreversible state of cell cycle arrest.*

**He S, Sharpless NE. Senescence in health and disease. Cell. 2017;169:1000–1011*.

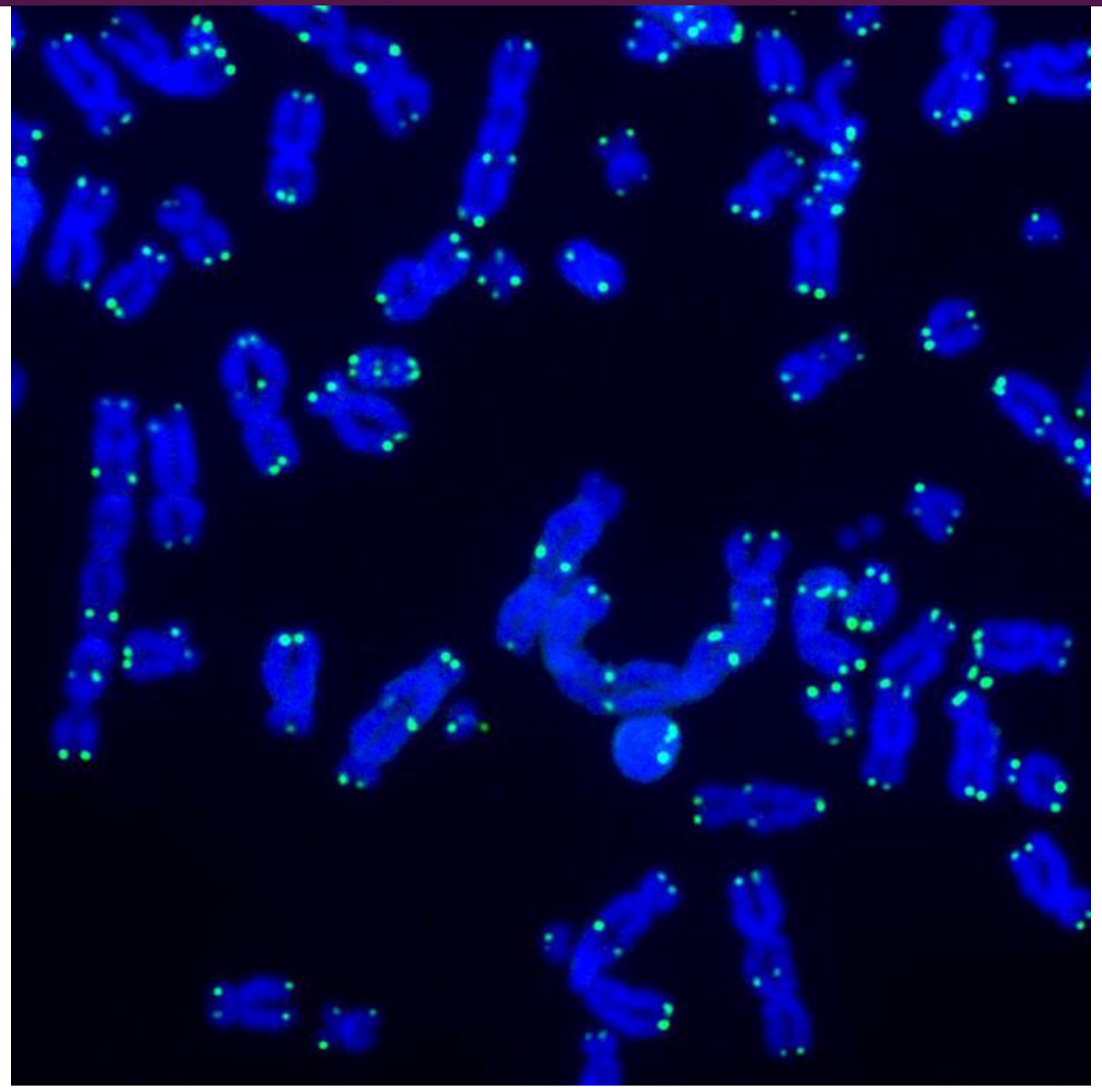
These cells do not die but secrete substances that harm healthy cells.

Stanford Medicine researchers found consistent nonlinear patterns in molecular markers of aging, with substantial dysregulation occurring at two major periods occurring at approximately **44 years and 60 years** of chronological age.**

***Xiaotao Shen, Chuchu Wang, Xin Zhou, Wenyu Zhou, Daniel Hornburg, Si Wu & Michael P. Snyder, Nature Aging volume 4, pages 1619–1634 (2024)*

Introduction - Aging

Within each of our cells, long strands of DNA are folded into chromosomes and capped with protective structures called telomeres, which play a crucial role in cellular aging.



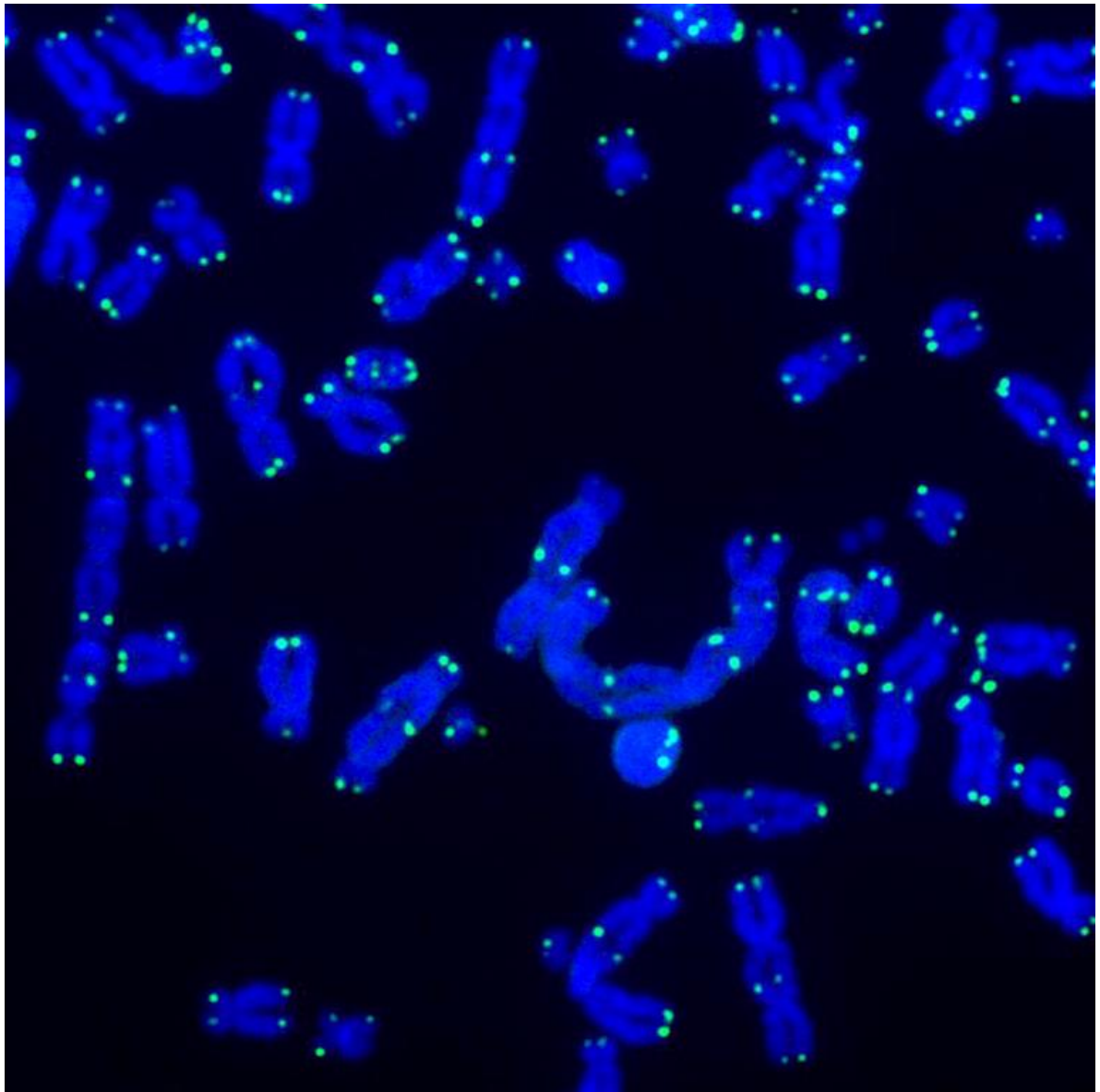
Microscopy image showing (green) telomeres, the protective caps at the ends of (blue) chromosomes.

Ref:Salk Institute

Introduction - Aging

But telomeres shorten as we age, eventually getting so whittled down that our chromosomes become exposed, and our cells die.

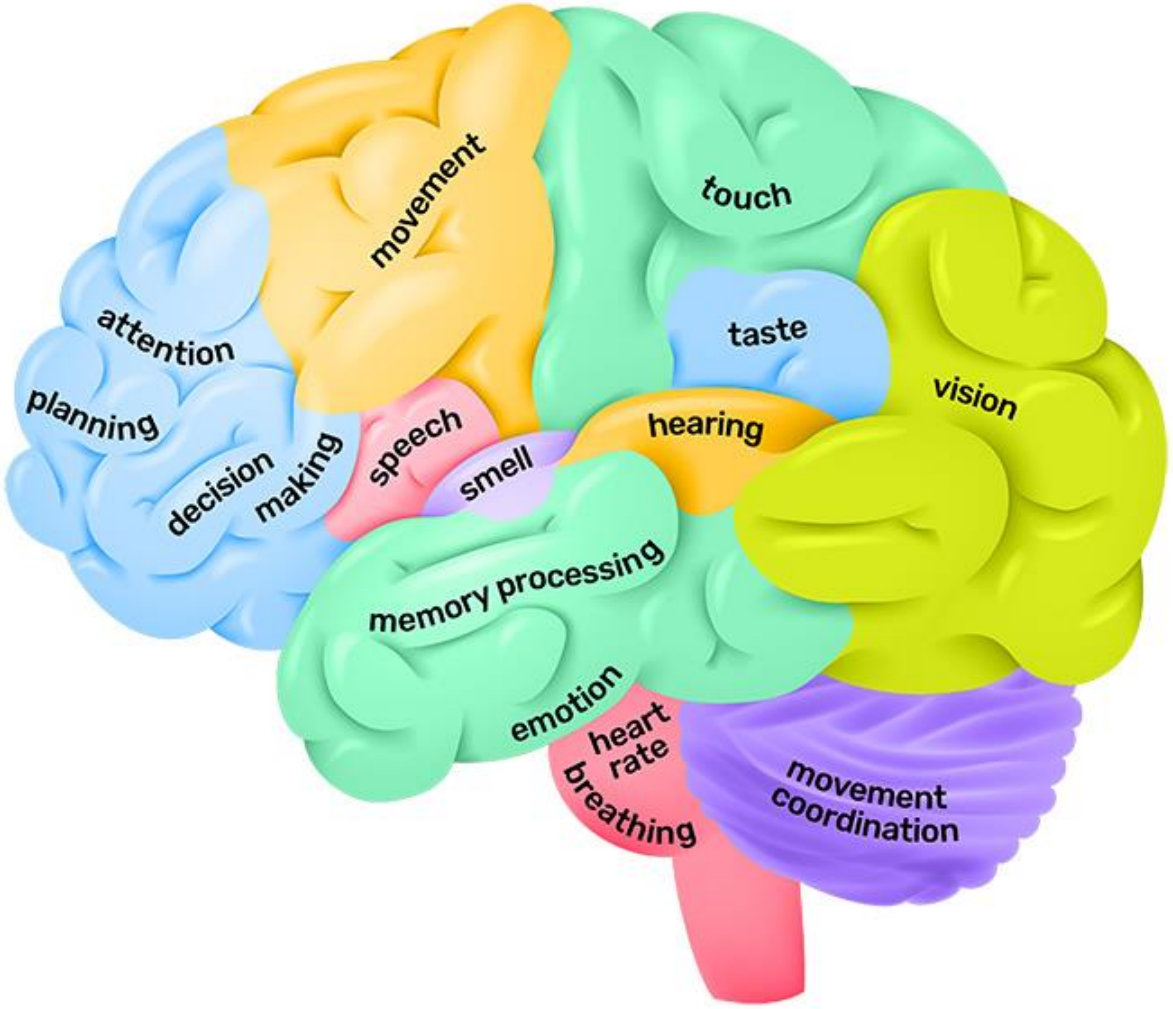
Permanent Cells that do not divide are Neurons, Cardiac myocytes, RBCs.



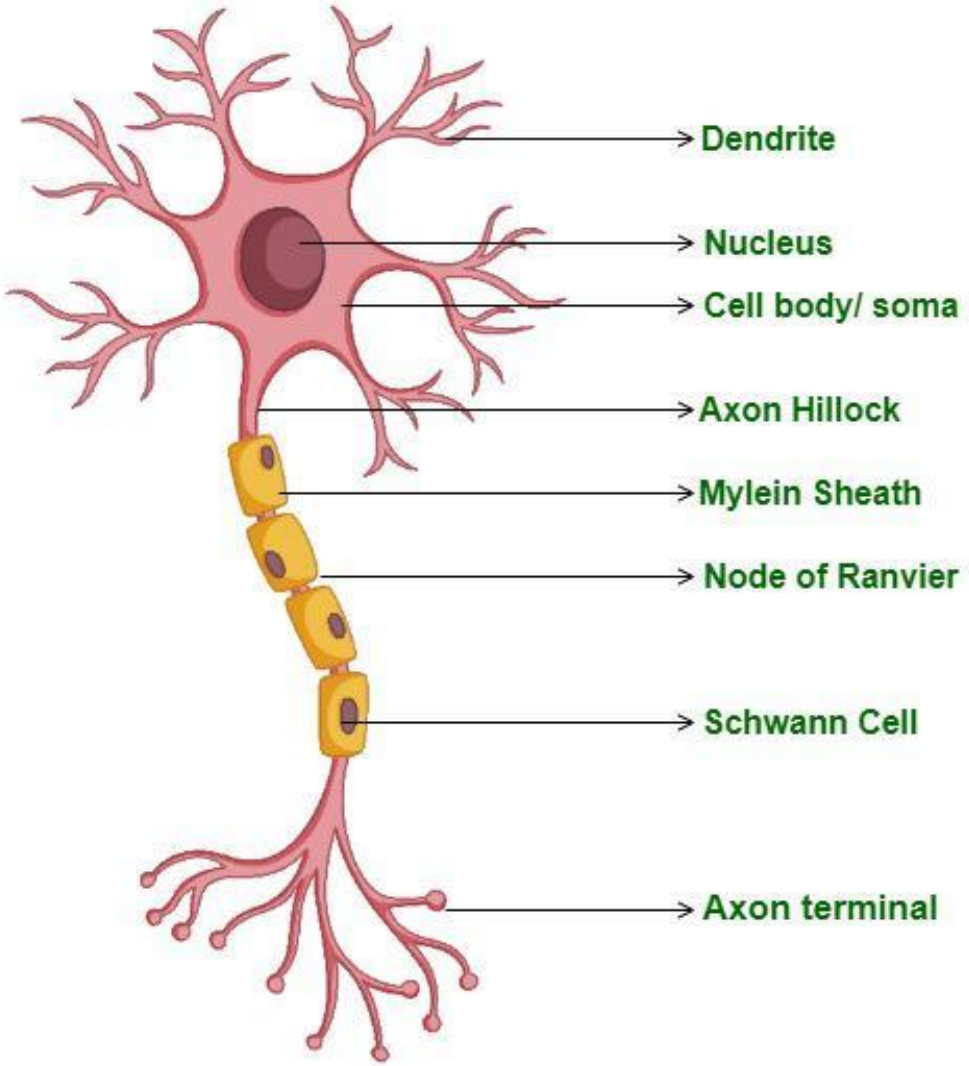
Microscopy image showing (green) telomeres, the protective caps at the ends of (blue) chromosomes, which play a crucial role in cellular aging.

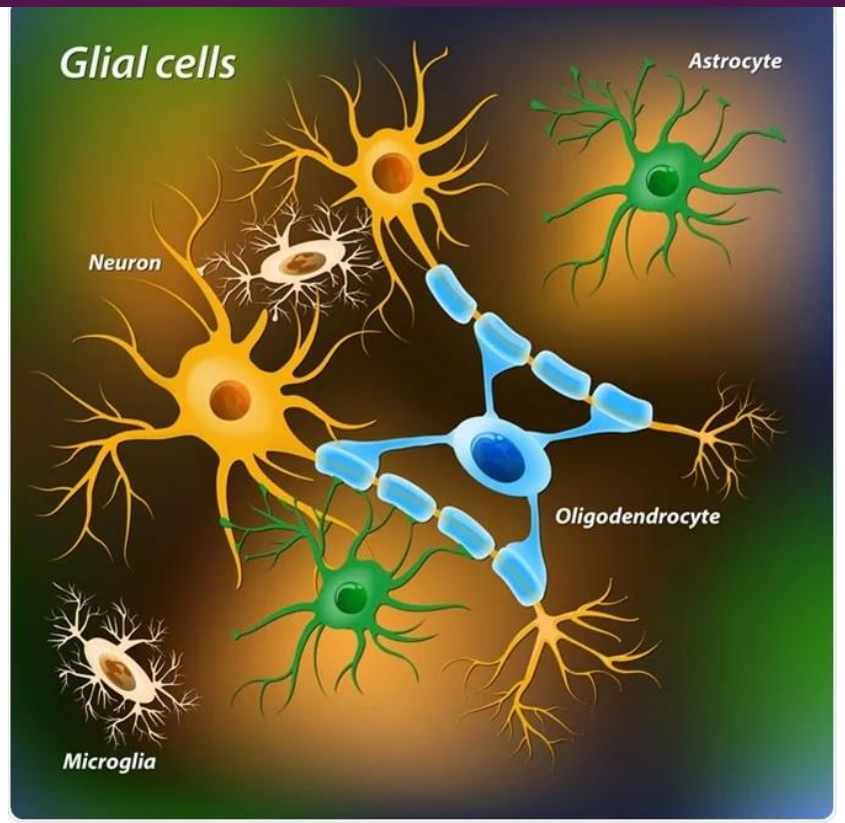
Source:Salk Institute

Introduction- Human Brain



Cells in the Brain



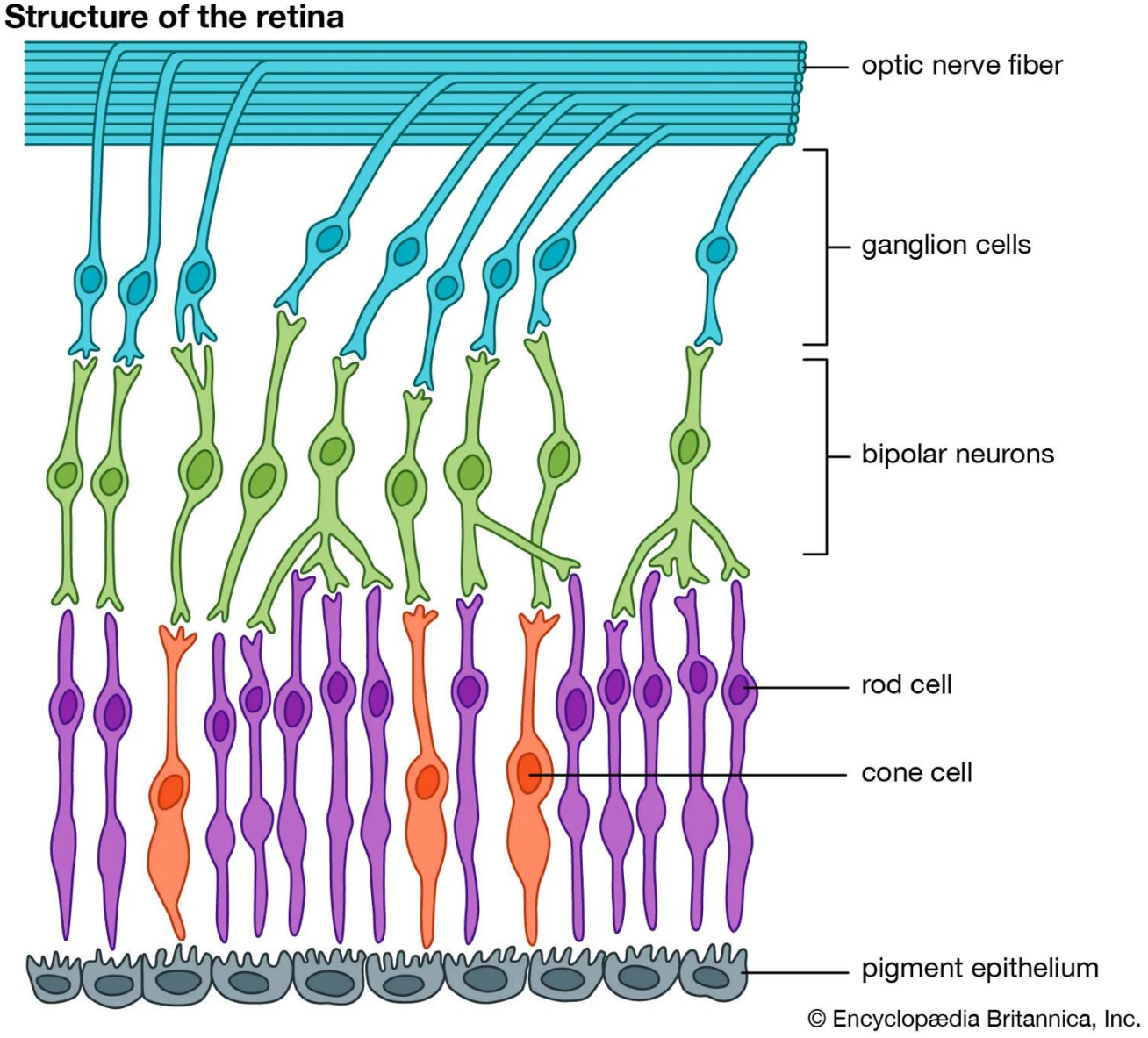


Astrocytes: Nutritional support, blood-brain barrier maintenance, ion balancing.
Oligodendrocytes: Axonal insulation (myelin) for faster signaling.
Microglia Immune surveillance, debris cleanup, and synaptic pruning.

~99% of neurons are formed before birth! Mature Neurons do not divide

Source: Internet

Retina is an extension of the Brain



Source: Internet

Touch and Hearing Pathways

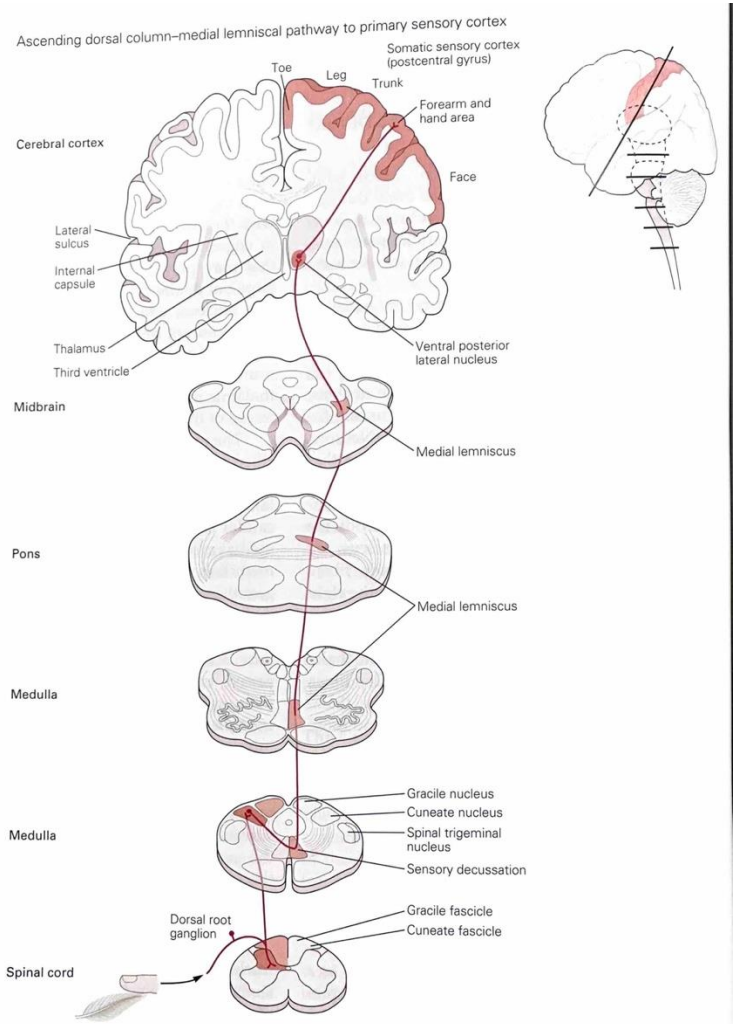


Figure 18-4 The medial lemniscus is a major afferent pathway for somatosensory information. Somatosensory information enters the nervous system through the dorsal root ganglion cells. The flow of information ultimately leads to excitation of the somatosensory cortex. Fibers representing different parts of the body maintain an orderly relationship to each other and form a neural map of the body surface that is maintained at each stage of information processing and ultimately in the neocortex.

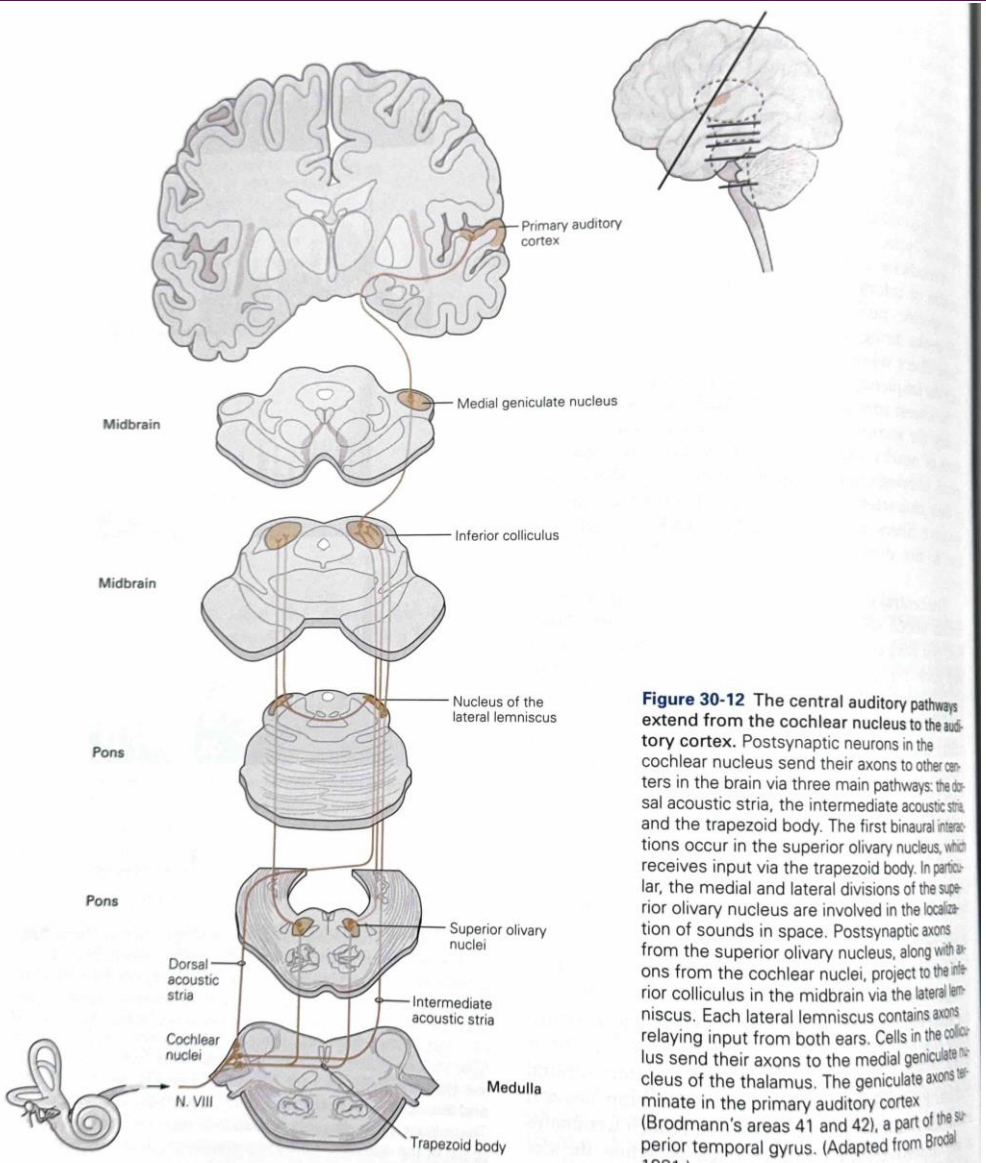
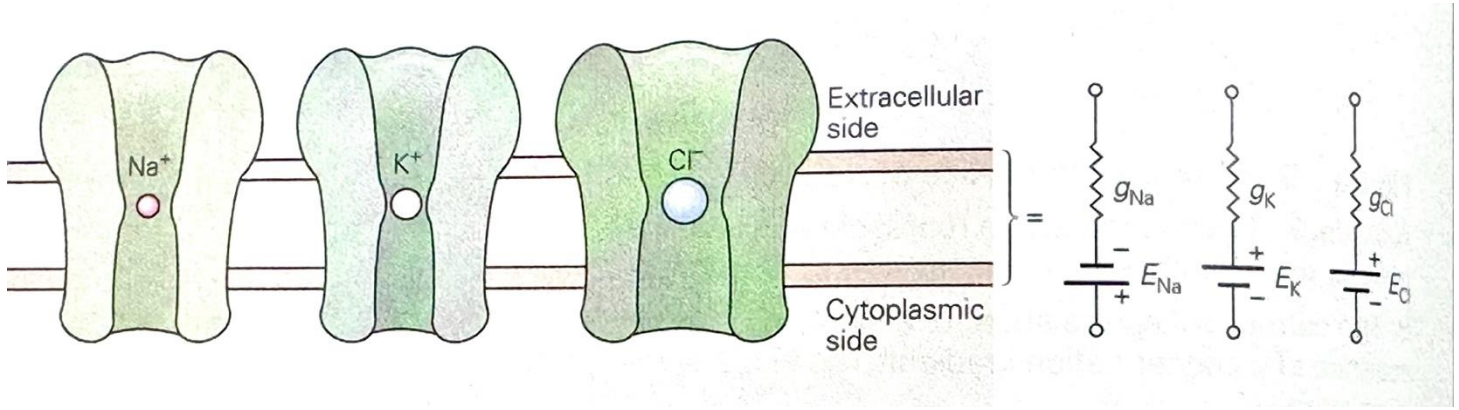


Figure 30-12 The central auditory pathways extend from the cochlear nucleus to the auditory cortex. Postsynaptic neurons in the cochlear nucleus send their axons to other centers in the brain via three main pathways: the dorsal acoustic stria, the intermediate acoustic stria, and the trapezoid body. The first binaural interactions occur in the superior olivary nucleus, which receives input via the trapezoid body. In particular, the medial and lateral divisions of the superior olivary nucleus are involved in the localization of sounds in space. Postsynaptic axons from the superior olivary nucleus, along with axons from the cochlear nuclei, project to the inferior colliculus in the midbrain via the lateral lemniscus. Each lateral lemniscus contains axons relaying input from both ears. Cells in the colliculus send their axons to the medial geniculate nucleus of the thalamus. The geniculate axons terminate in the primary auditory cortex (Brodmann's areas 41 and 42), a part of the superior temporal gyrus. (Adapted from Brodal 1981.)

Neural Communication – Ion Channels



g_ : Conductances

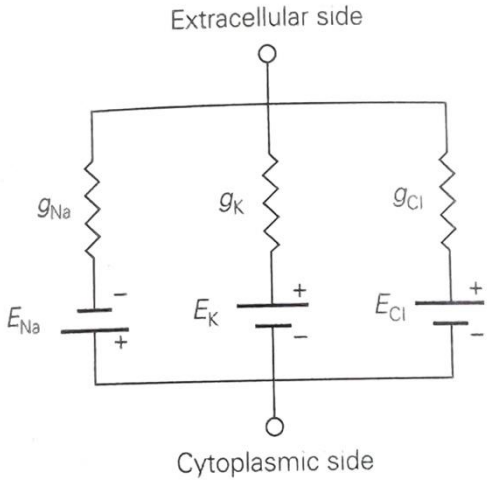
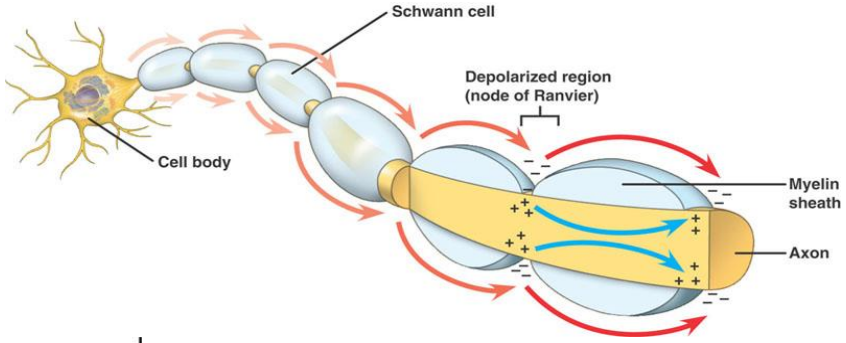
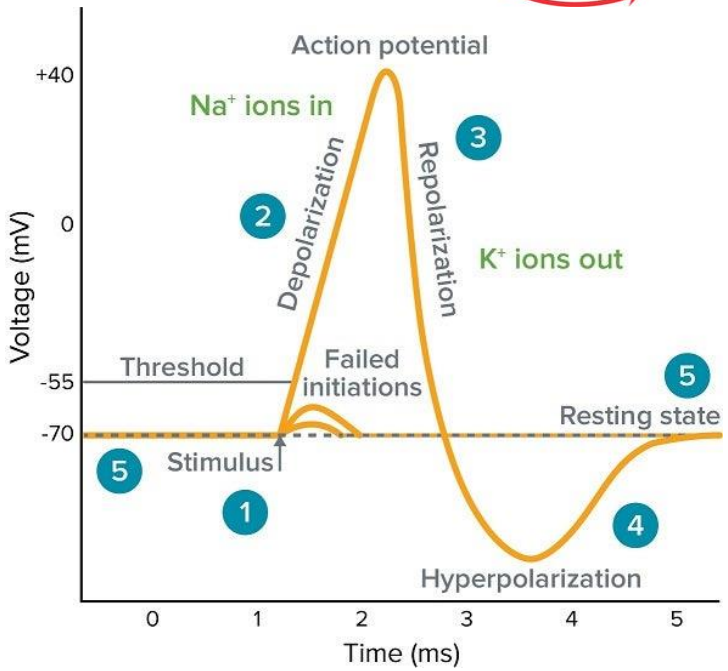


Figure 7-9 The passive current flow in a neuron can be modeled using an electrical equivalent circuit. The circuit includes elements representing the ion-selective membrane channels and the short-circuit pathways provided by the cytoplasm and extracellular fluid.

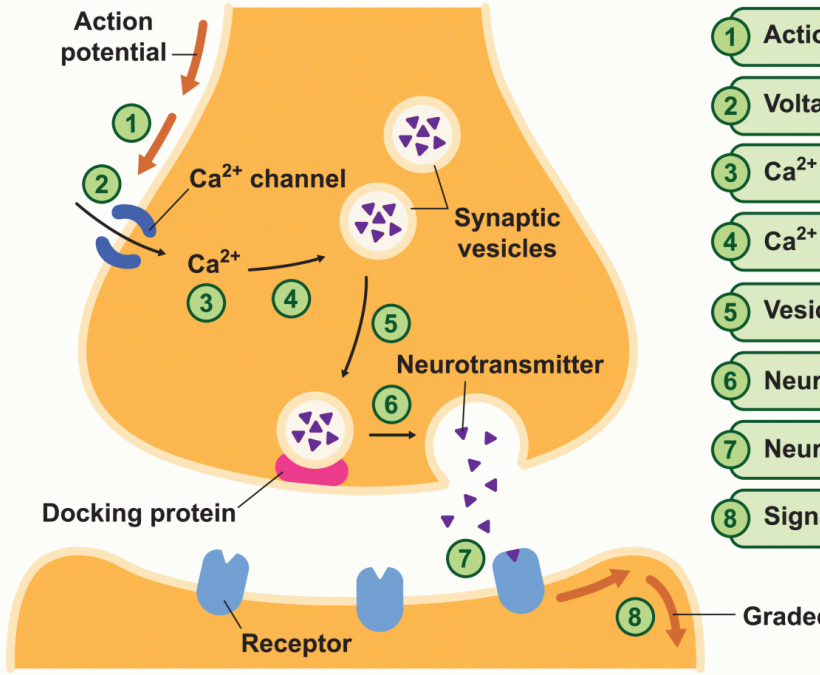
Neural Communication

Intracellular "WIRED" Communication





Intercellular "WIRELESS" Communication



1. Action potential arrives at axon terminal
2. Voltage-gated Ca2+ channels open
3. Ca^{2+} enters the presynaptic neuron
4. Ca^{2+} signals to neurotransmitter vesicles
5. Vesicles move to the membrane and dock
6. Neurotransmitters released via exocytosis
7. Neurotransmitters bind to receptors
8. Signal initiated in postsynaptic cell

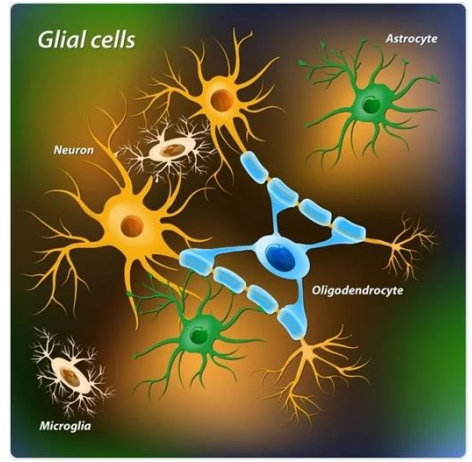
Sodium, Potassium, Calcium ion channels/pumps

Source: Internet

Cognition

All forms of knowing and awareness, such as perceiving, conceiving, remembering, reasoning, judging, imagining, and problem solving.

Adapted from the American Psychological Association's Dictionary of Psychology

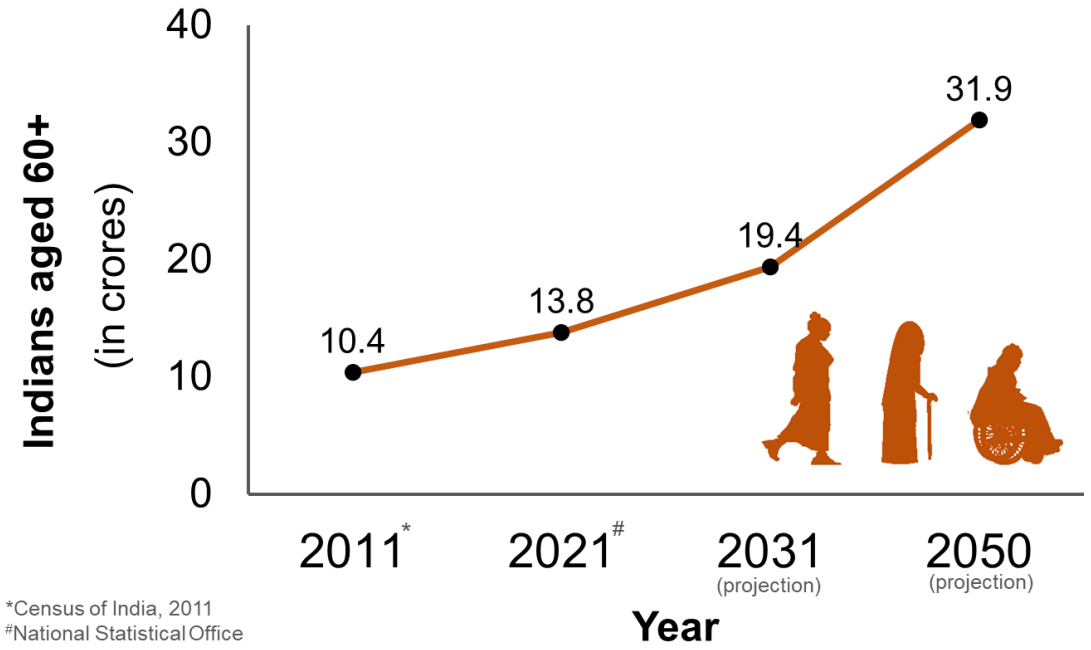


Cognitive decline due to Healthy Aging

Neurons do not divide!

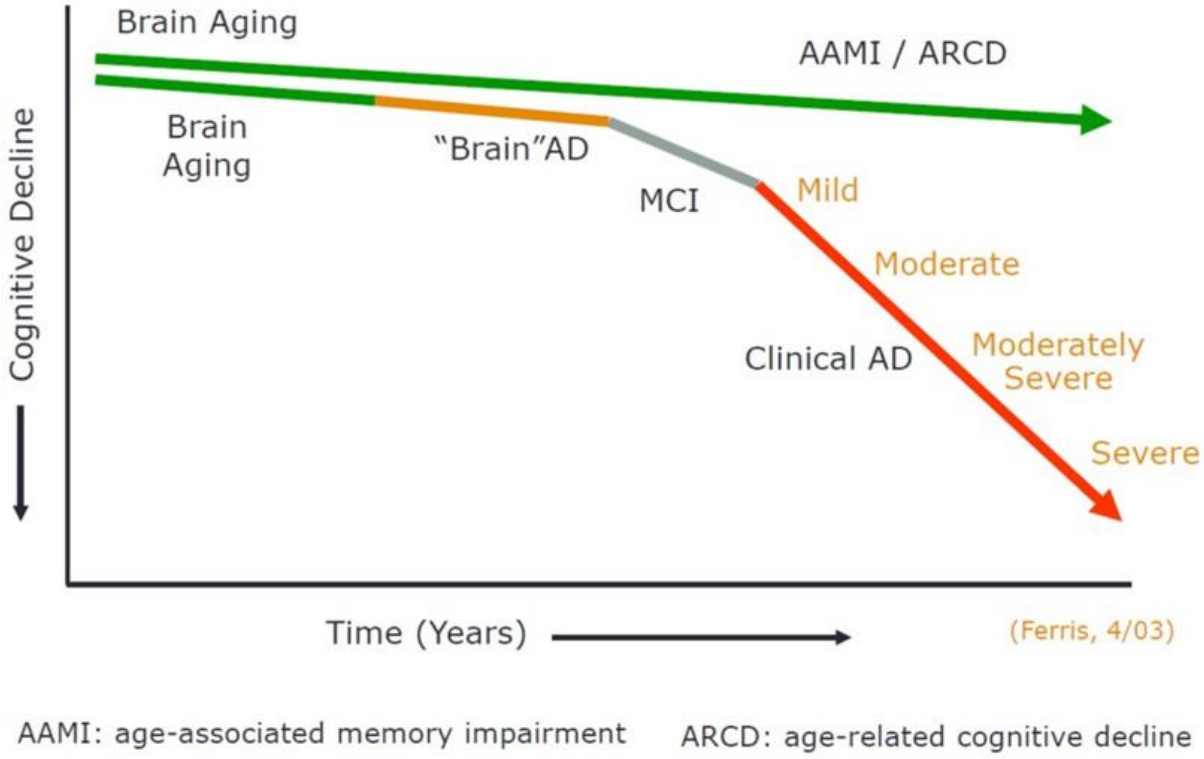
The cognitive decline seen in "healthy" aging is therefore not caused by neurons dying, but by the aged glial environment failing to provide the nutrients, insulation, and cleaning services those neurons require to function.

Towards Healthy Aging



*Census of India, 2011
#National Statistical Office

Steady rise in India's dementia burden



AAMI: age-associated memory impairment ARCD: age-related cognitive decline

Healthy Aging and Diseased Aging

Dementia

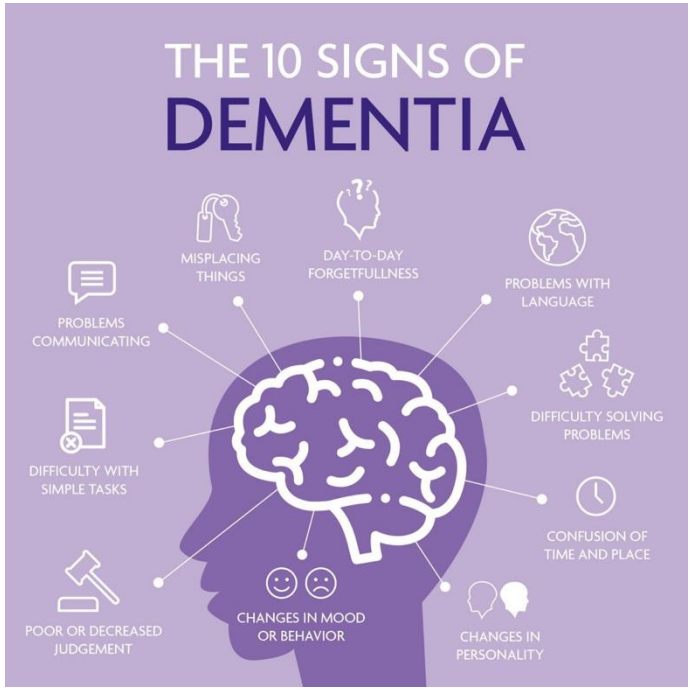


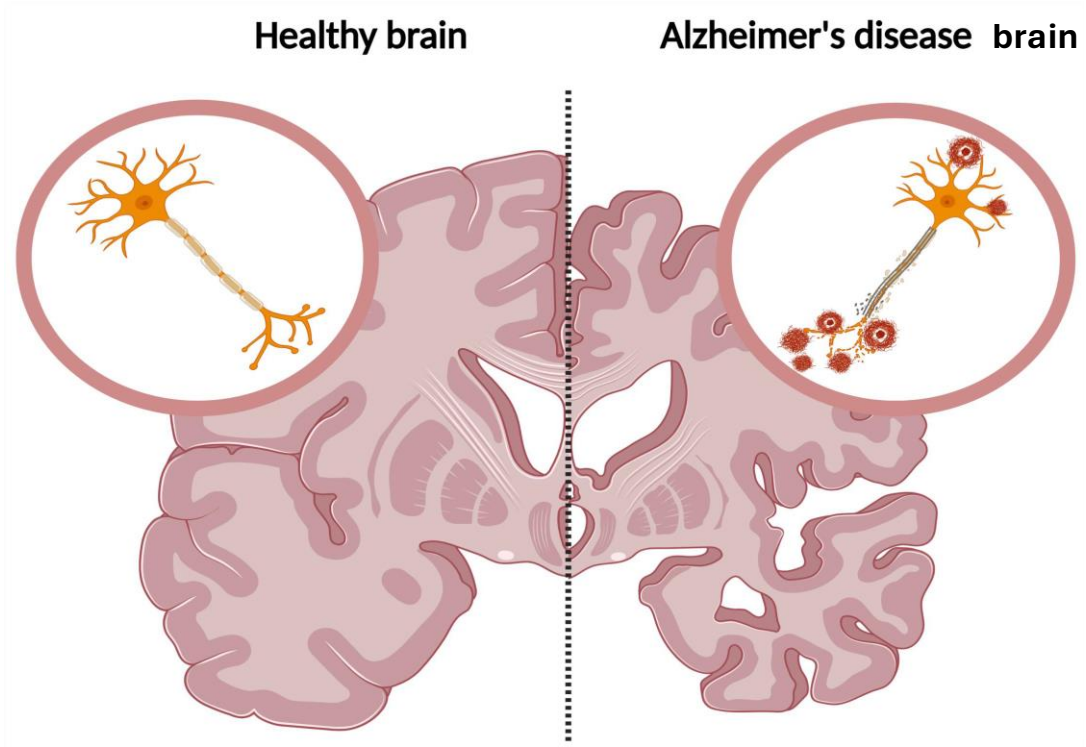
Table 1. The most common dementias and their distinguishing brain pathological features

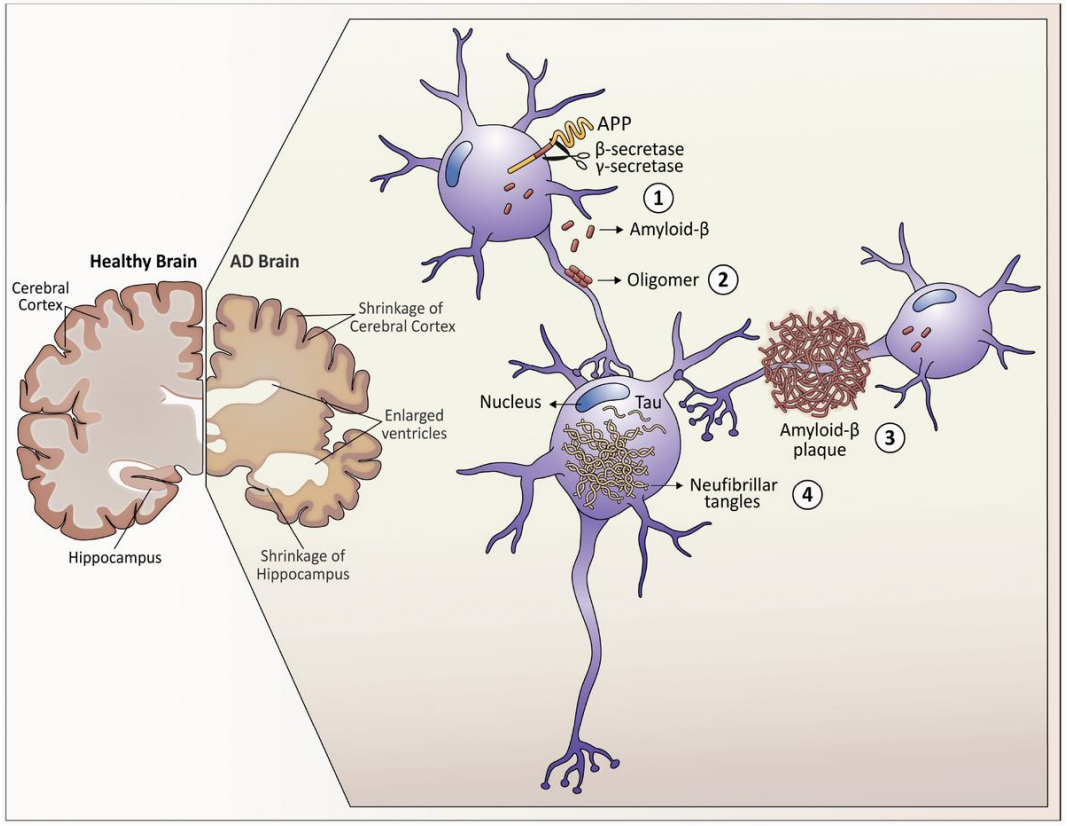
Dementia	Approximate proportion of all dementias (%)	Distinguishing brain pathological features*
Alzheimer disease	60–80	Amyloid-β plaques and tau neurofibrillary tangles
Vascular dementia	13	Cerebrovascular pathology
Dementia with Lewy bodies	3.1–7.1	α-Synuclein protein clusters
Frontotemporal dementia	3.0	Frontal and temporal lobe atrophy, abnormal tau, TDP-43, fused sarcoma protein
Dementia due to Parkinson disease	3.6	α-Synuclein deposits

*Note that several features may be present, and different sources cite different single and multiple features.

Ref: A blueprint for Dementia Research, World Health Organization, 2022

Pathology of Disease

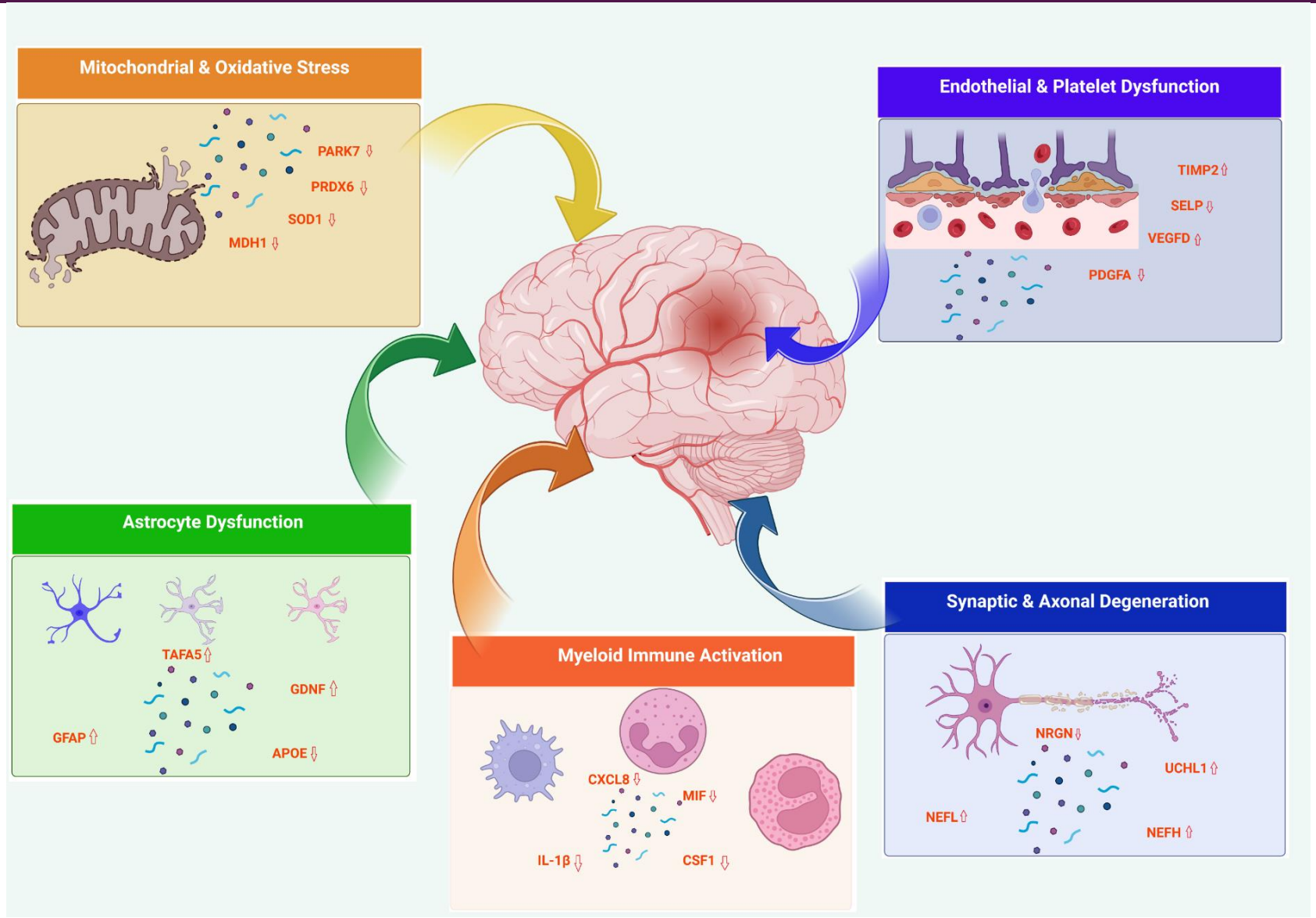




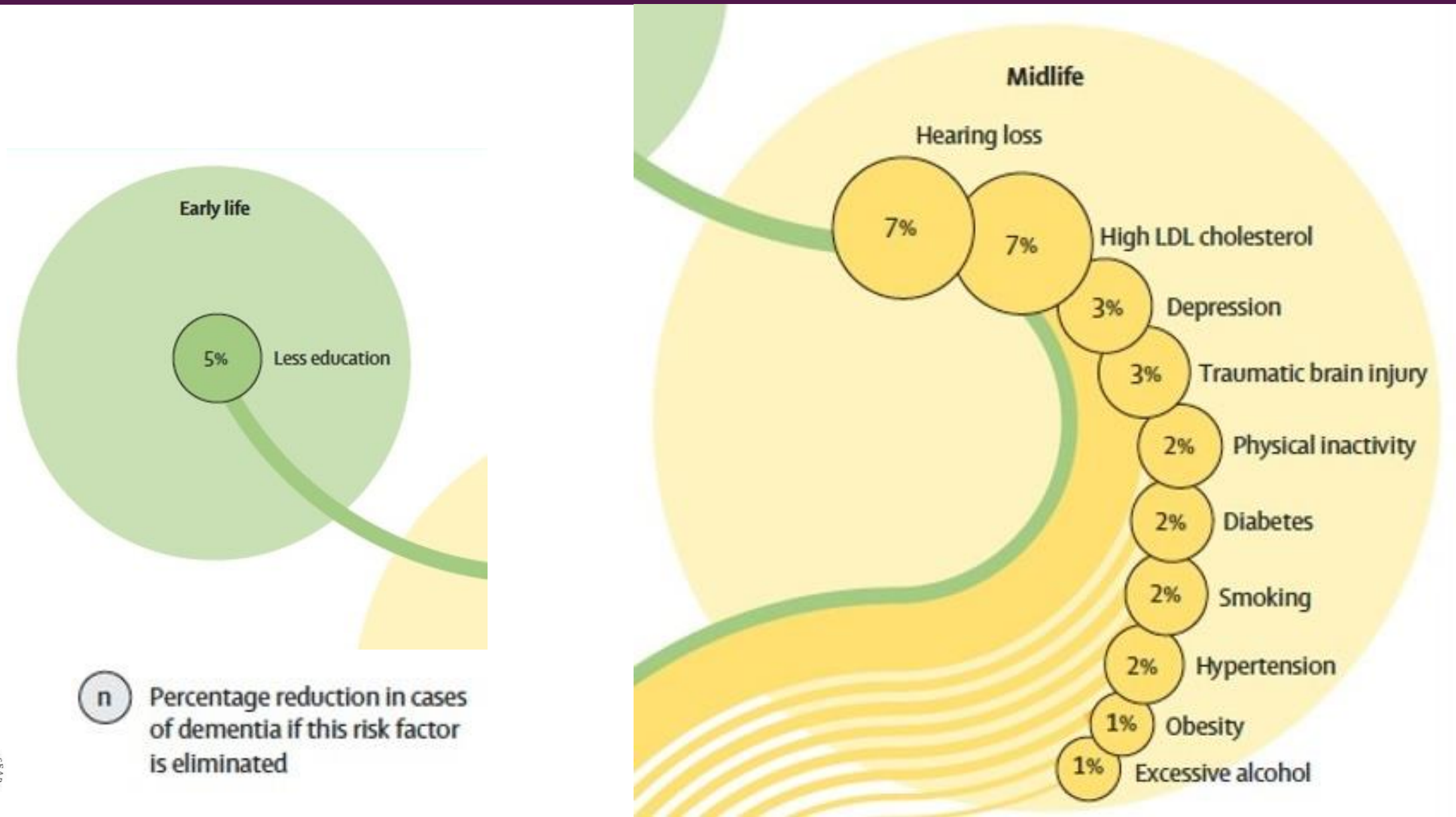
Gomez et al., Aging (2020)

Misfolded proteins lead to formation of Plaques and Tangles that inhibit neuronal functioning. Cerebrospinal fluid (CSF) and blood plasma can be used for estimating the concentration of the proteins

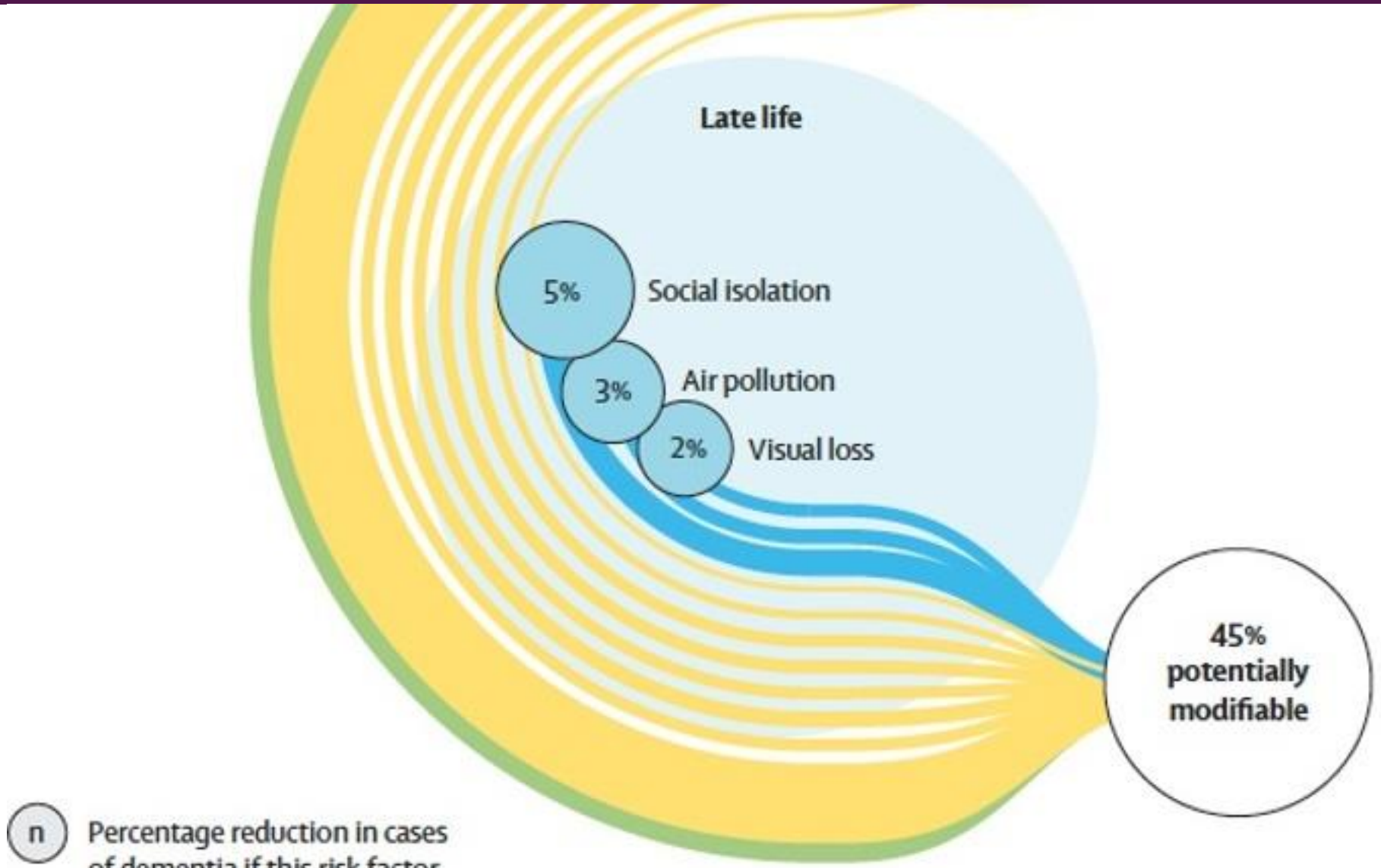
Multi-System Proteomic Drivers



Risk Factors – Lancet Study 2024



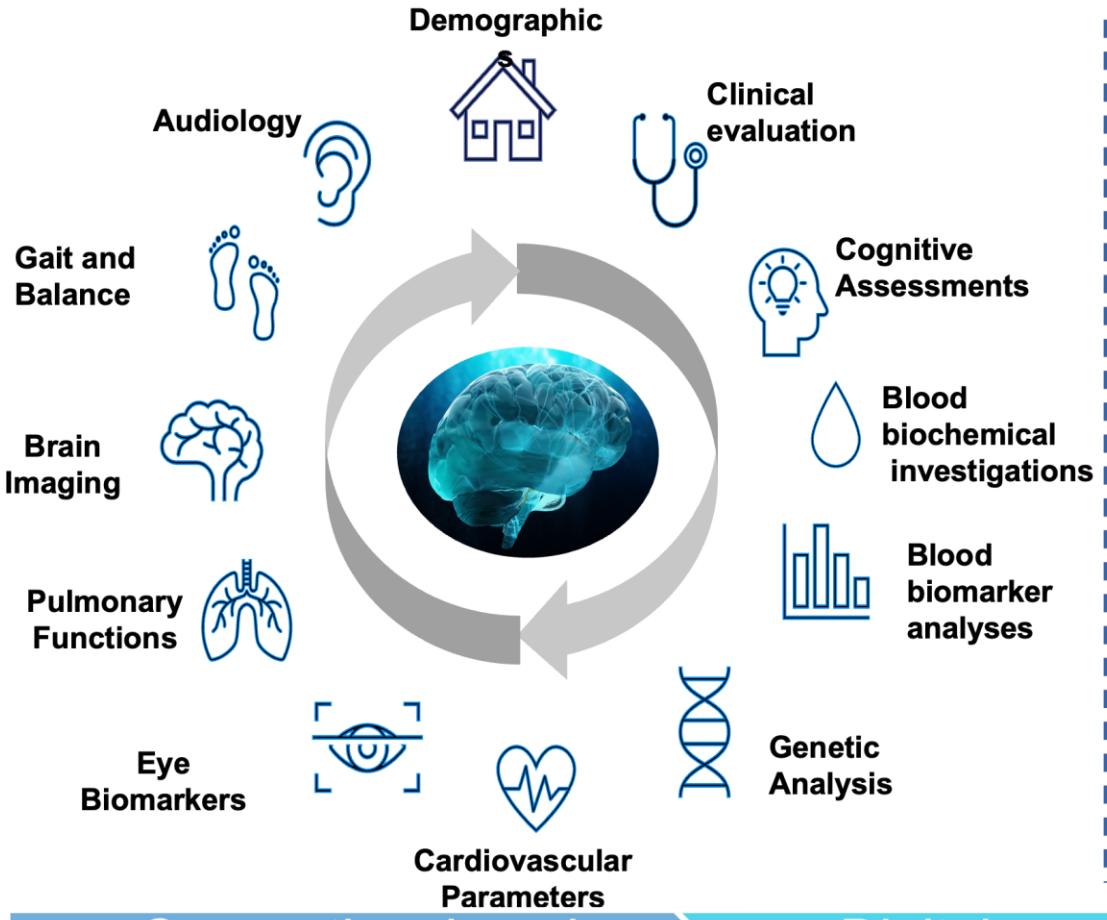
Risk Factors – Lancet Study 2024



Need Cohort Studies

Ref: A blueprint for Dementia Research, World Health Organization, 2022

Assessments leading to Biomarkers



- Battery of Digital assessments
- Wearable devices
- High end proteomics platforms
- Global and national insights

Conventional markers measured in CBR → Digital assessment battery and Proteomics → Composite multimodal biomarker

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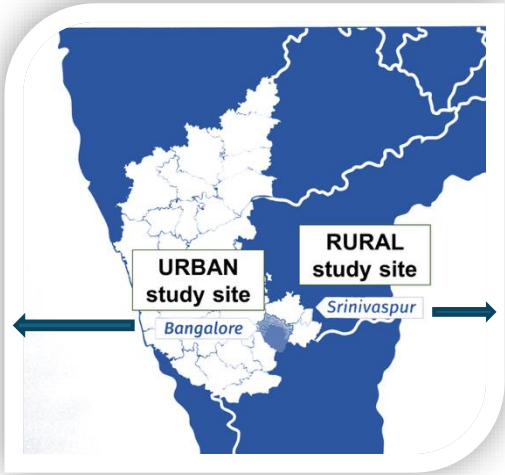
Community-Based Cohorts at CBR

- ✓ Tertiary Occupation
- ✓ High literacy
- ✓ More migration
- ✓ More multilinguals
- ✓ More genetic heterogeneity
- ✓ Follow-up every year

2015
1,000 subjects

TATA TRUSTS

Tata Longitudinal Study on Aging (TLSA)



2018
10,000 subjects

SANSCOG

Srinivaspura Aging, NeuroSenescence and COGnition study

- ✓ Agricultural community
- ✓ Low literacy
- ✓ Lesser migration
- ✓ More mono and bilinguals
- ✓ Less genetic heterogeneity
- ✓ Follow-up every 2 years

First-of-its-kind, large-scale, longitudinal cohort studies on aging to identify risk factors and protective factors of dementia.

Subjects above the age of 45 years

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Infrastructure

OCT

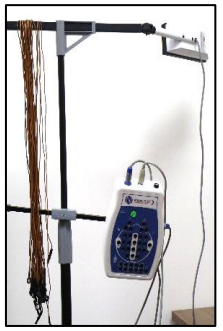
Audiometry

Gait Assessment

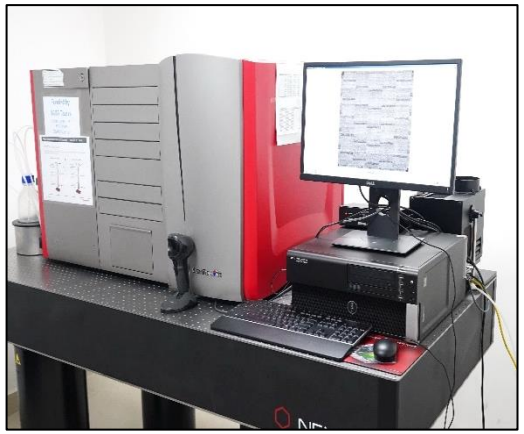
Cardiac Autonomic Function Testing

Spirometry

ECHO
Carotid Doppler



EEG

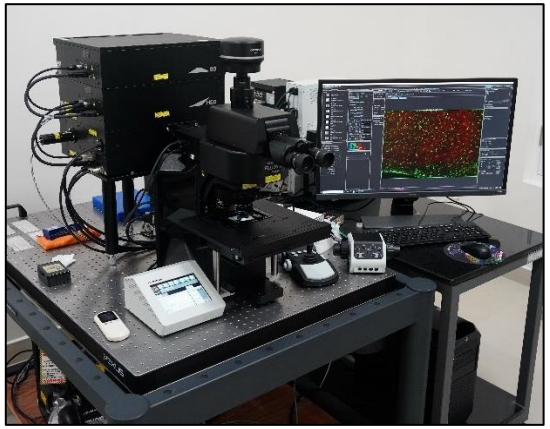


Genome Sequencing and GWAS
Novaseq 6000

Biobank
ISO 20387:2018

3T MRI
PRISMA

Storage and
HPC Cluster



Confocal Microscope

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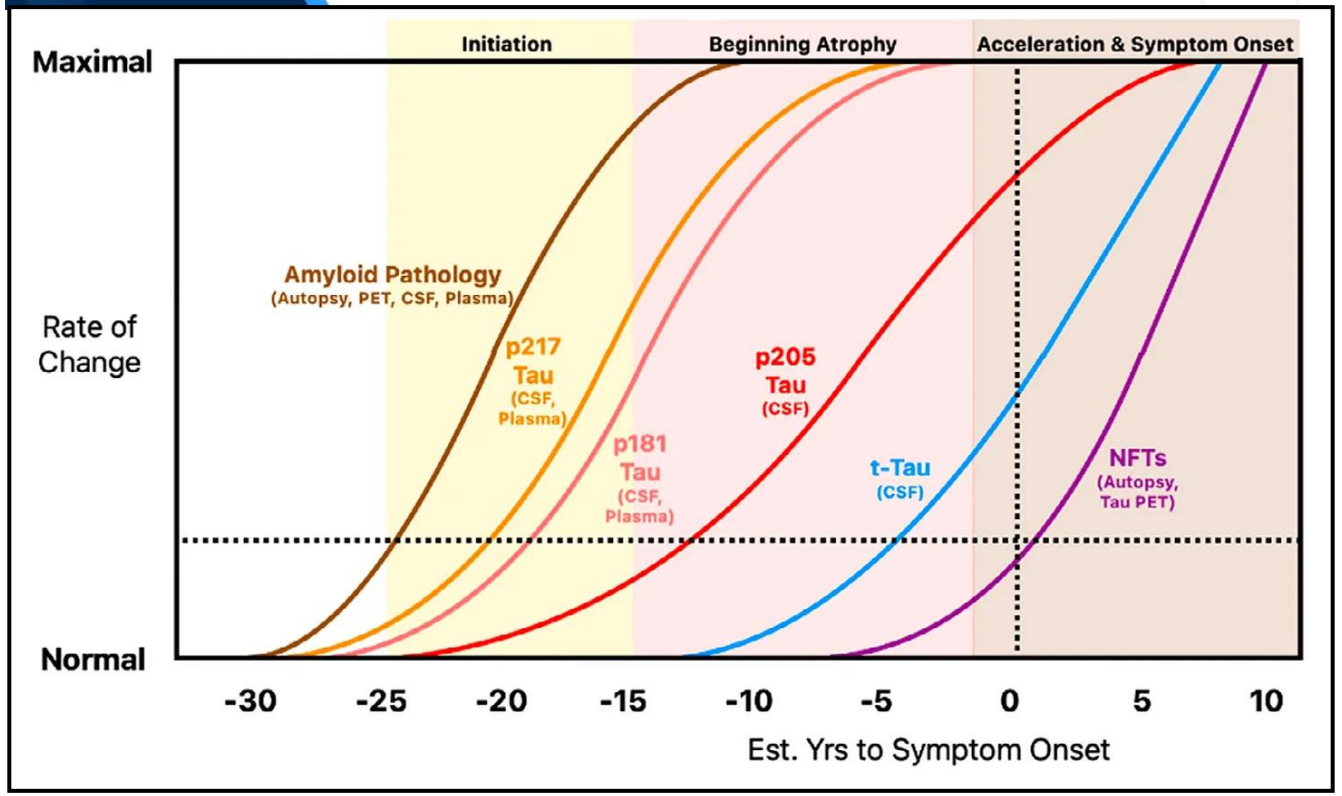
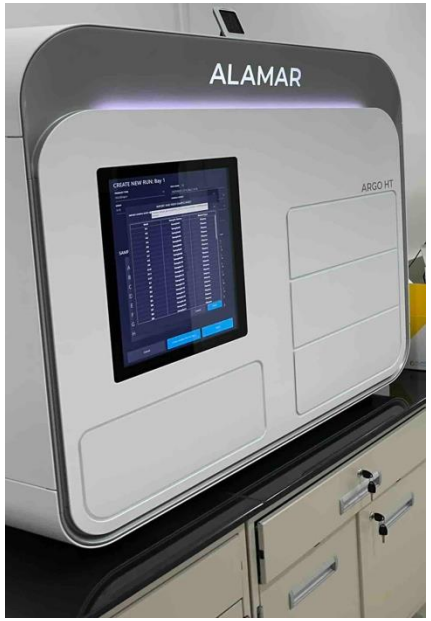
Proteomics

131 proteins related to neurodegeneration

250 proteins related to inflammation

SIMOA





First installation in India

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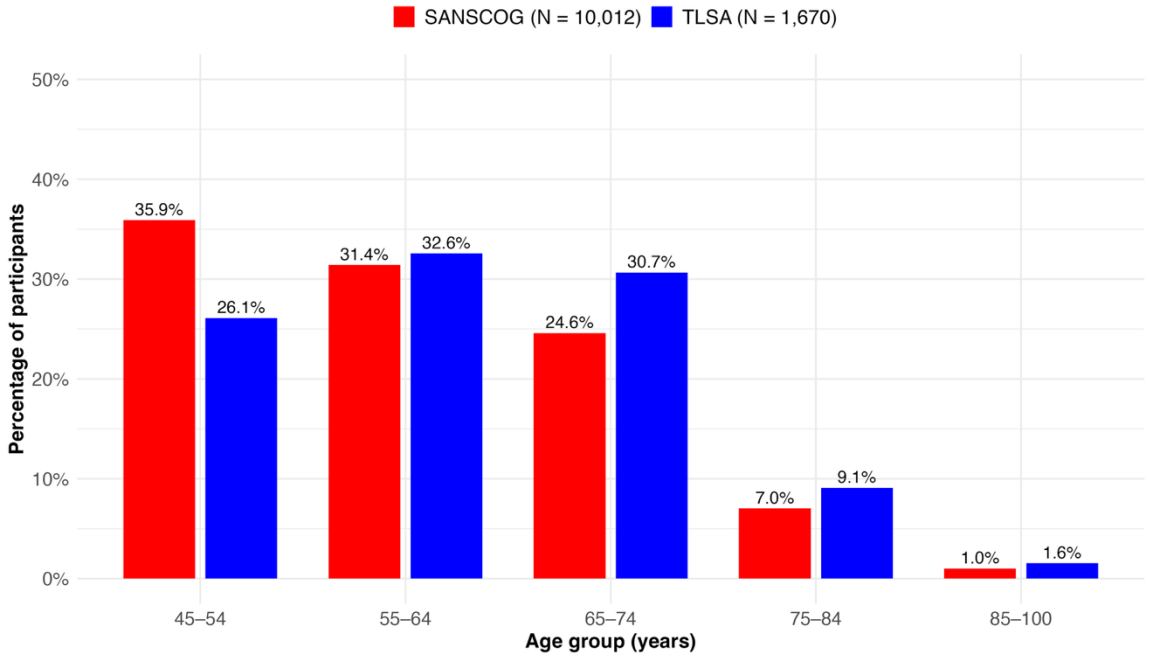
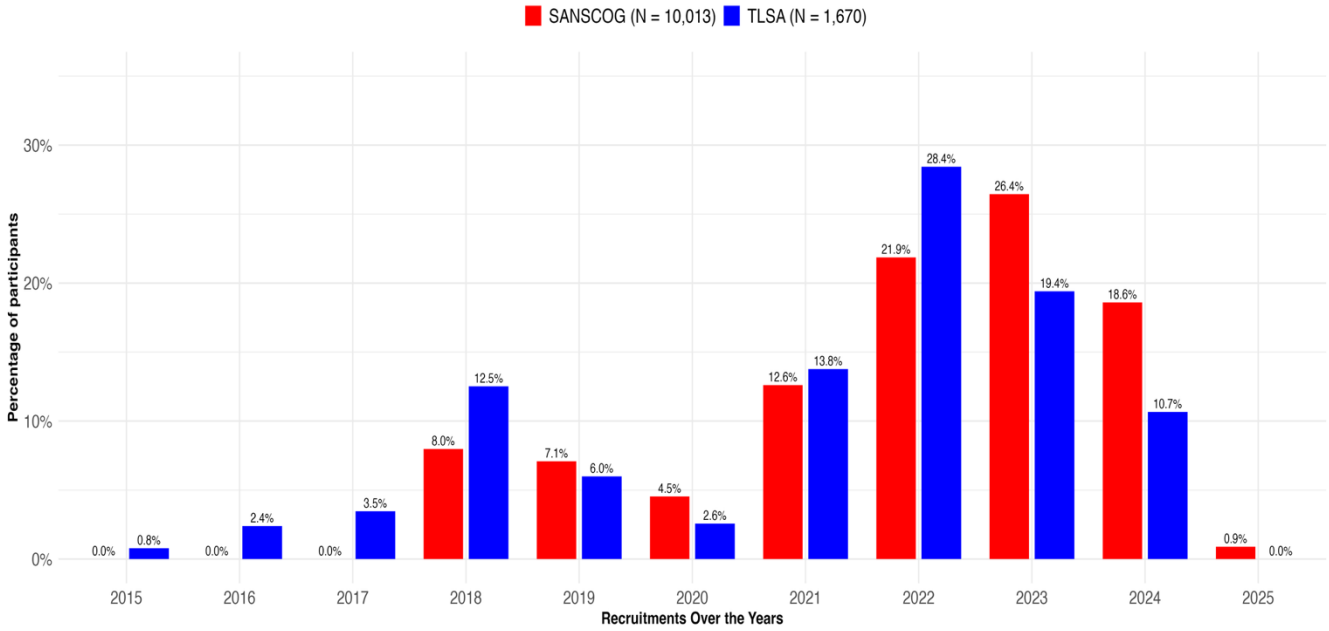
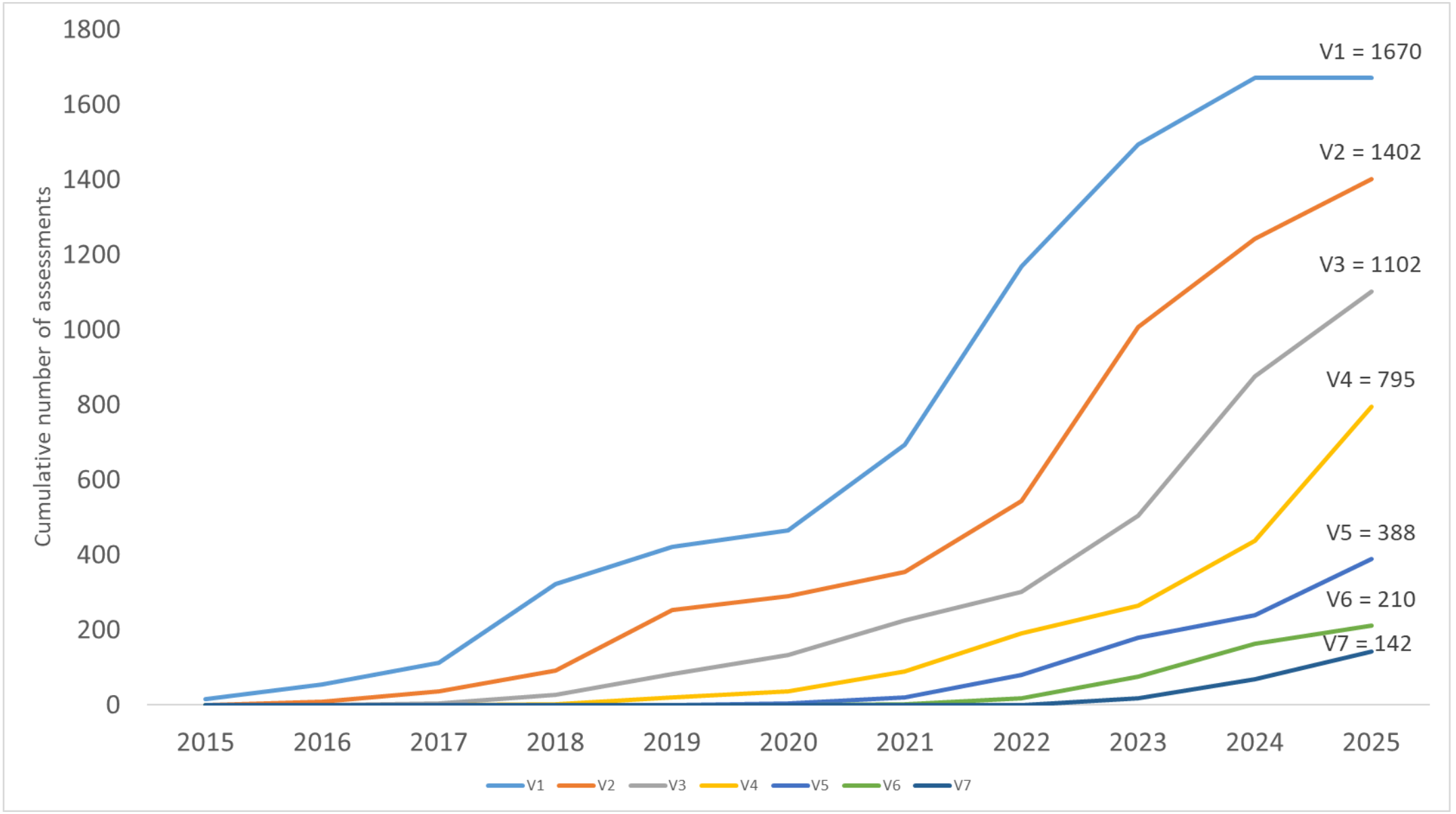
Fact Sheets


SANSCOG (N = 10,012)
TLSA (N = 1,670)
Percentage of participants
50%
40%
30%
20%
10%
0%
35.9%
26.1%
31.4%
32.6%
24.6%
30.7%
7.0%
9.1%
1.0%
1.6%
45–54
55–64
65–74
75–84
85–100
Age group (years)


SANSCOG (N = 10,013)
TLSA (N = 1,670)
Percentage of participants
30%
20%
10%
0%
0.0%
0.8%
0.0%
2.4%
0.0%
3.5%
8.0%
12.5%
7.1%
6.0%
4.5%
2.6%
12.6%
13.8%
21.9%
28.4%
26.4%
19.4%
18.6%
10.7%
0.9%
0.0%
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
Recruitments Over the Years

TLSA Facts (Follow-up every year)



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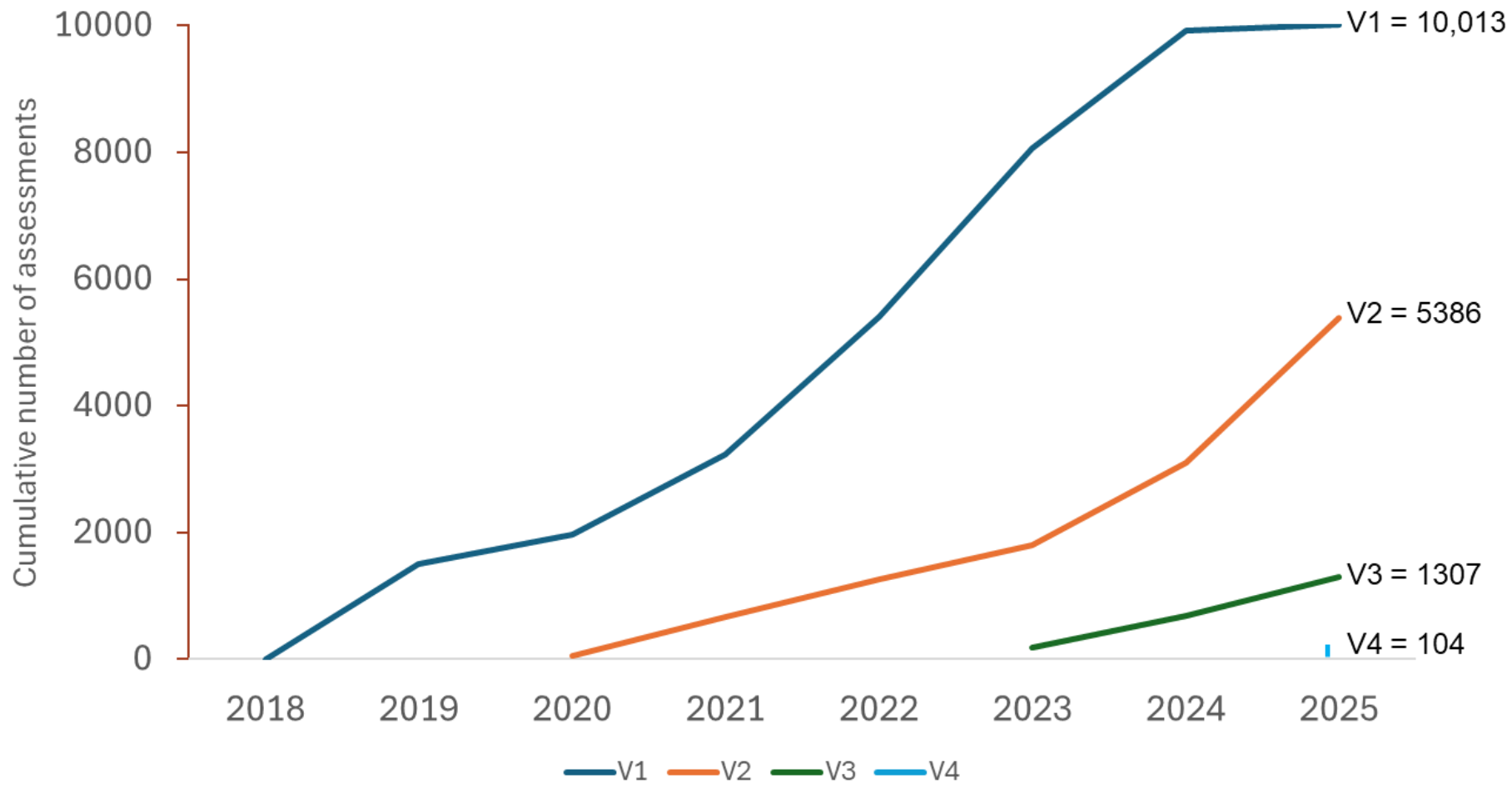
SANSCOG Facts (Follow-up every 2 years)



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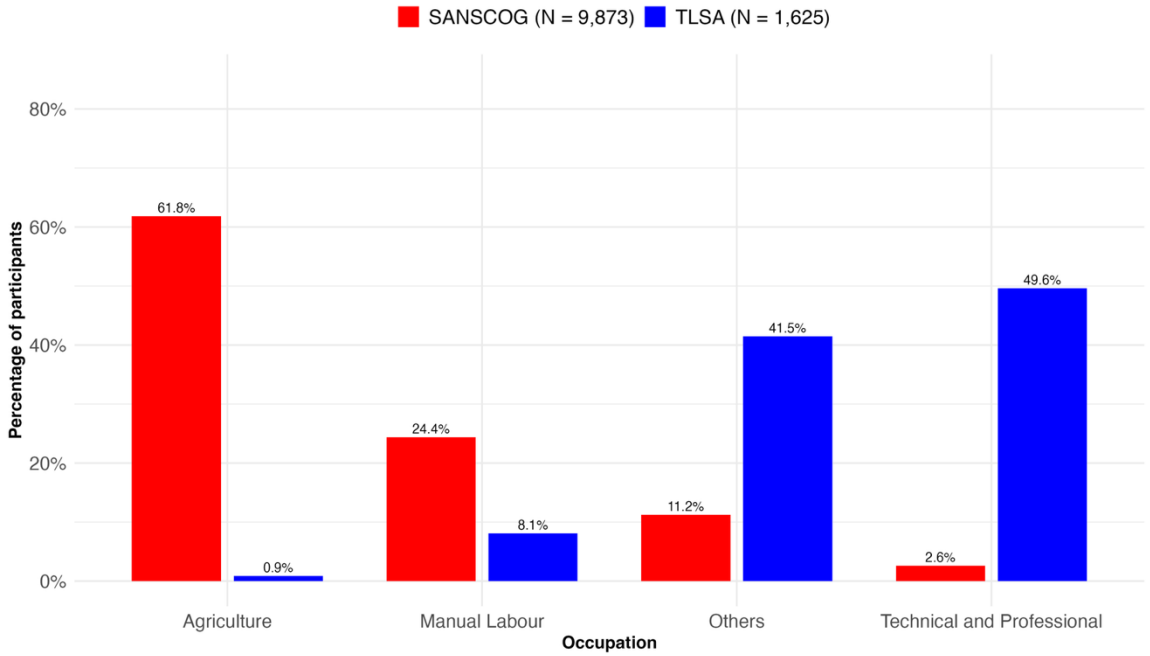

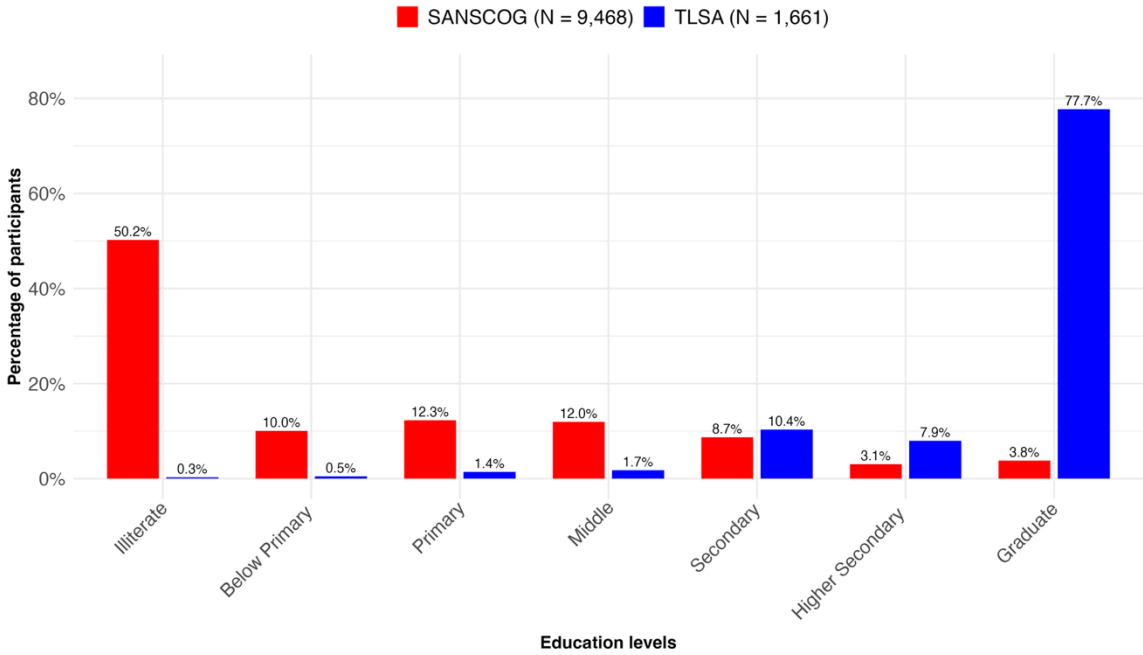

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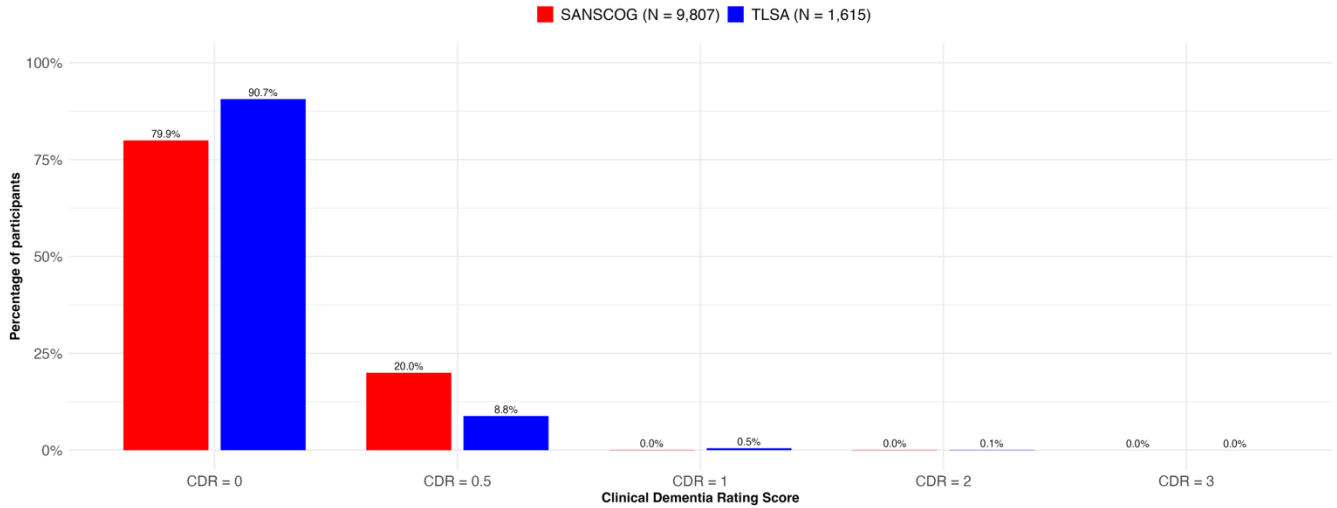
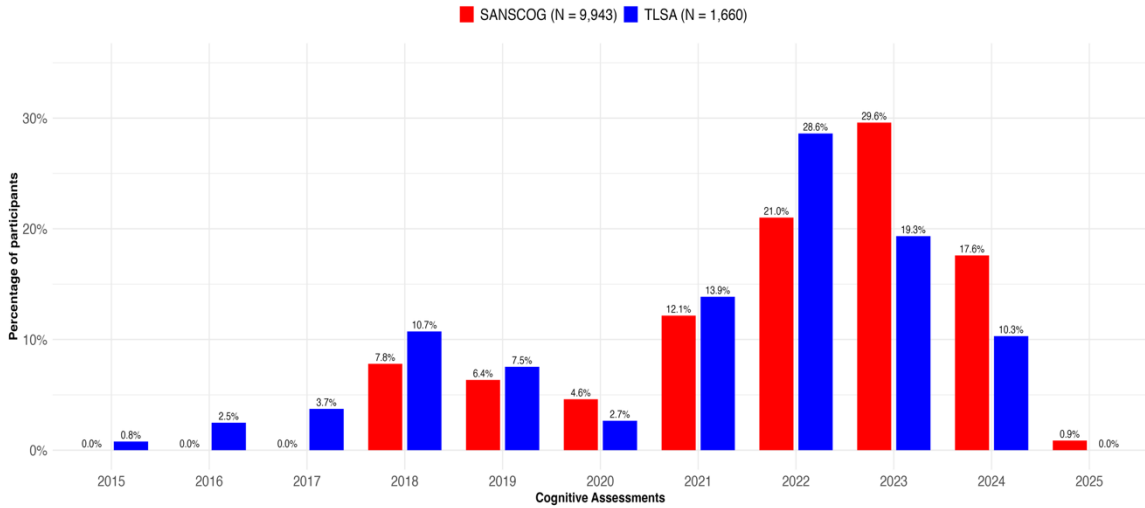

SANSCOG (N = 9,807)
TLSA (N = 1,615)
100%
75%
50%
25%
0%
Percentage of participants
79.9%
90.7%
20.0%
8.8%
0.0%
0.5%
0.0%
0.1%
0.0%
0.0%
CDR = 0
CDR = 0.5
CDR = 1
CDR = 2
CDR = 3
Clinical Dementia Rating Score


SANSCOG (N = 9,943)
TLSA (N = 1,660)
30%
20%
10%
0%
Percentage of participants
0.0%
0.8%
0.0%
2.5%
0.0%
3.7%
7.8%
10.7%
6.4%
7.5%
4.6%
2.7%
12.1%
13.9%
21.0%
28.6%
29.6%
19.3%
17.6%
10.3%
0.9%
0.0%
2015
2016
2017
2018
2019
2020
2021
2022
2023
2024
2025
Cognitive Assessments

Data

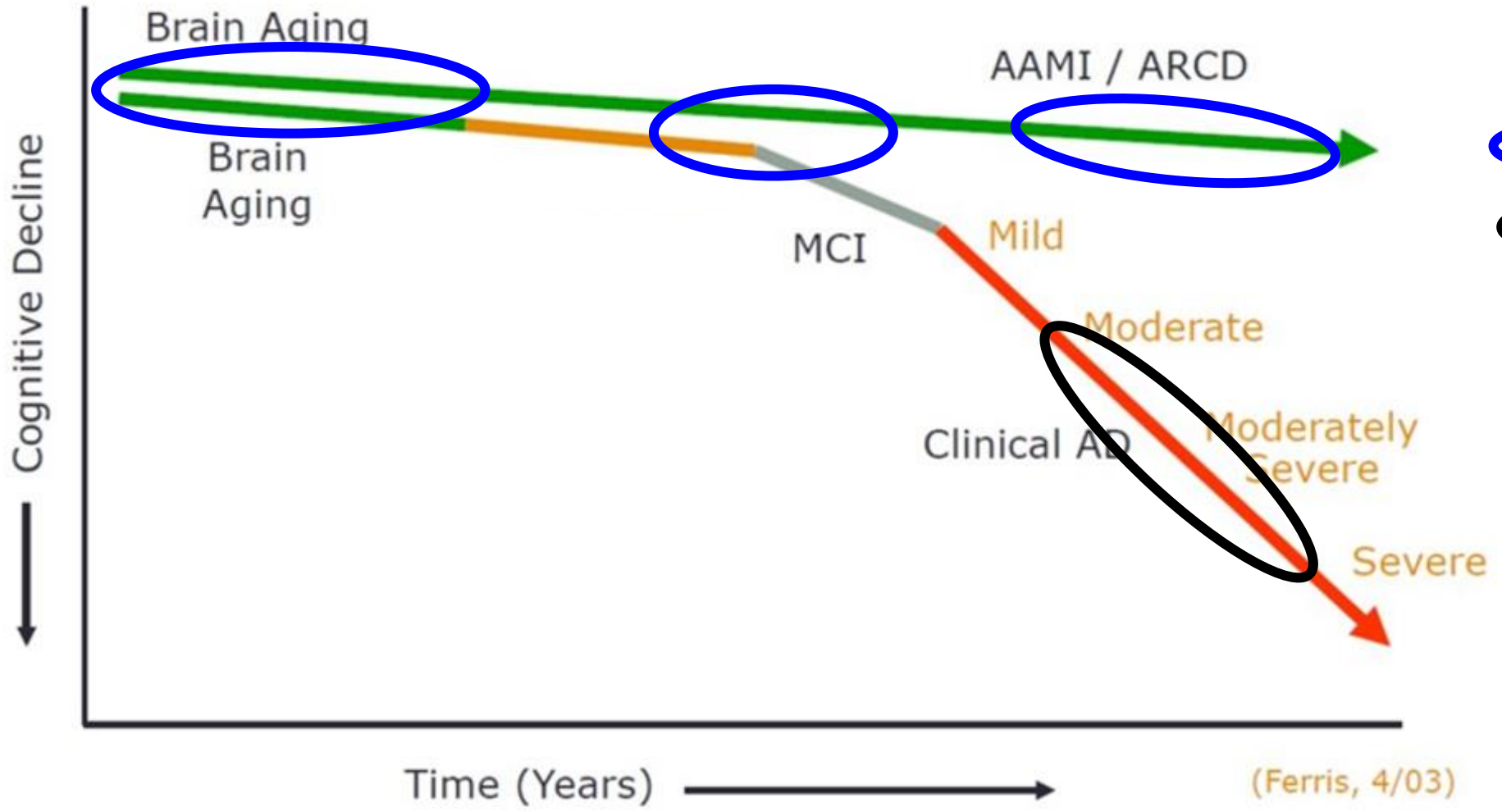
Each visit of the subject generates about 5 GB of data

One-time whole genomic sequencing data size is ~70 GB

We have ~ 2 PB of cohort data

Way Forward

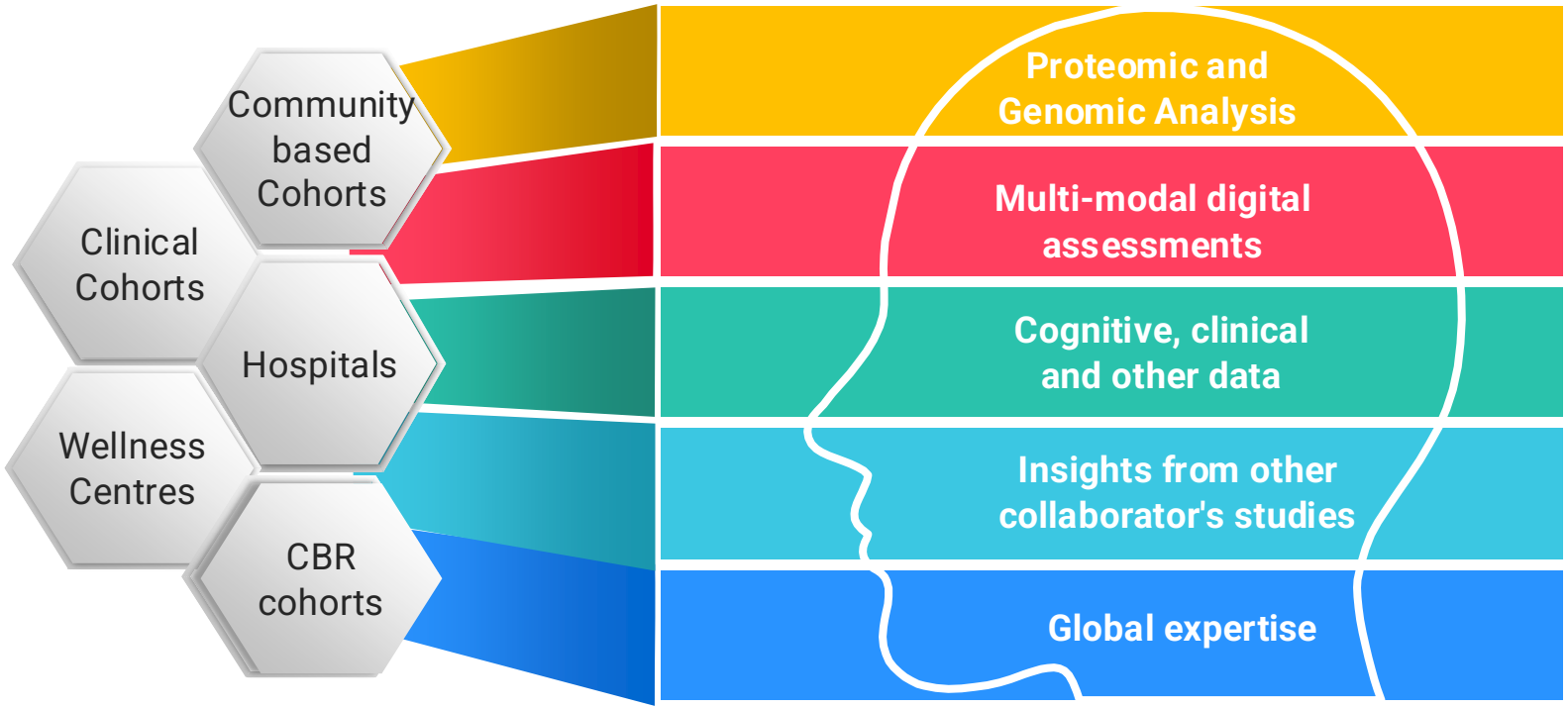
Cohorts

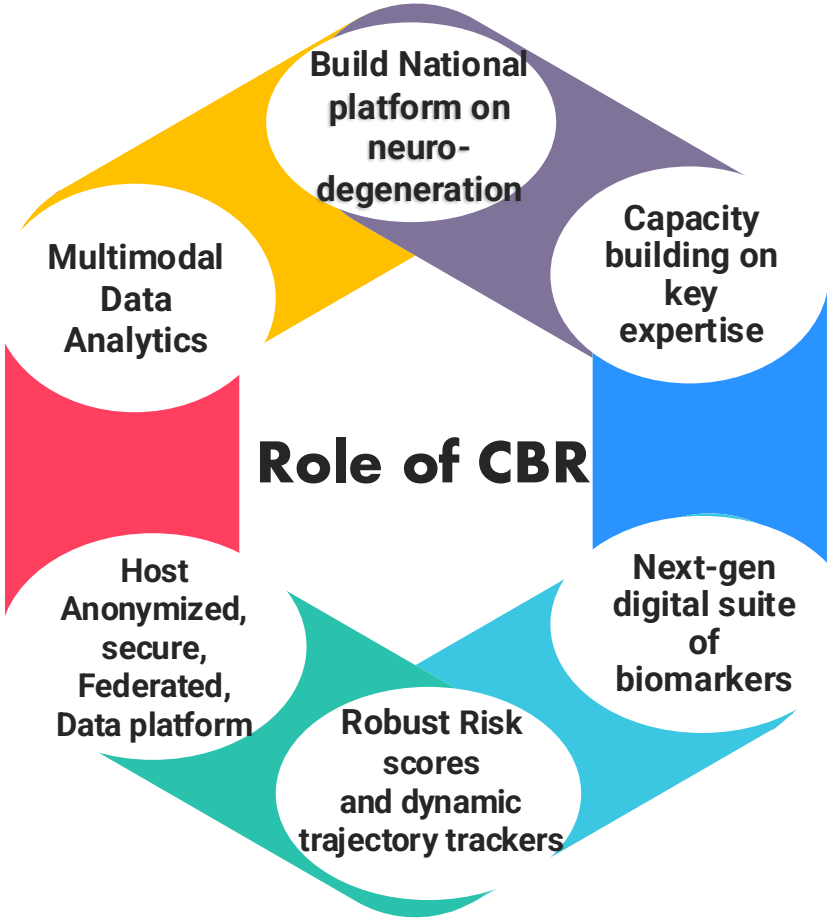


AAMI: age-associated memory impairment

ARCD: age-related cognitive decline

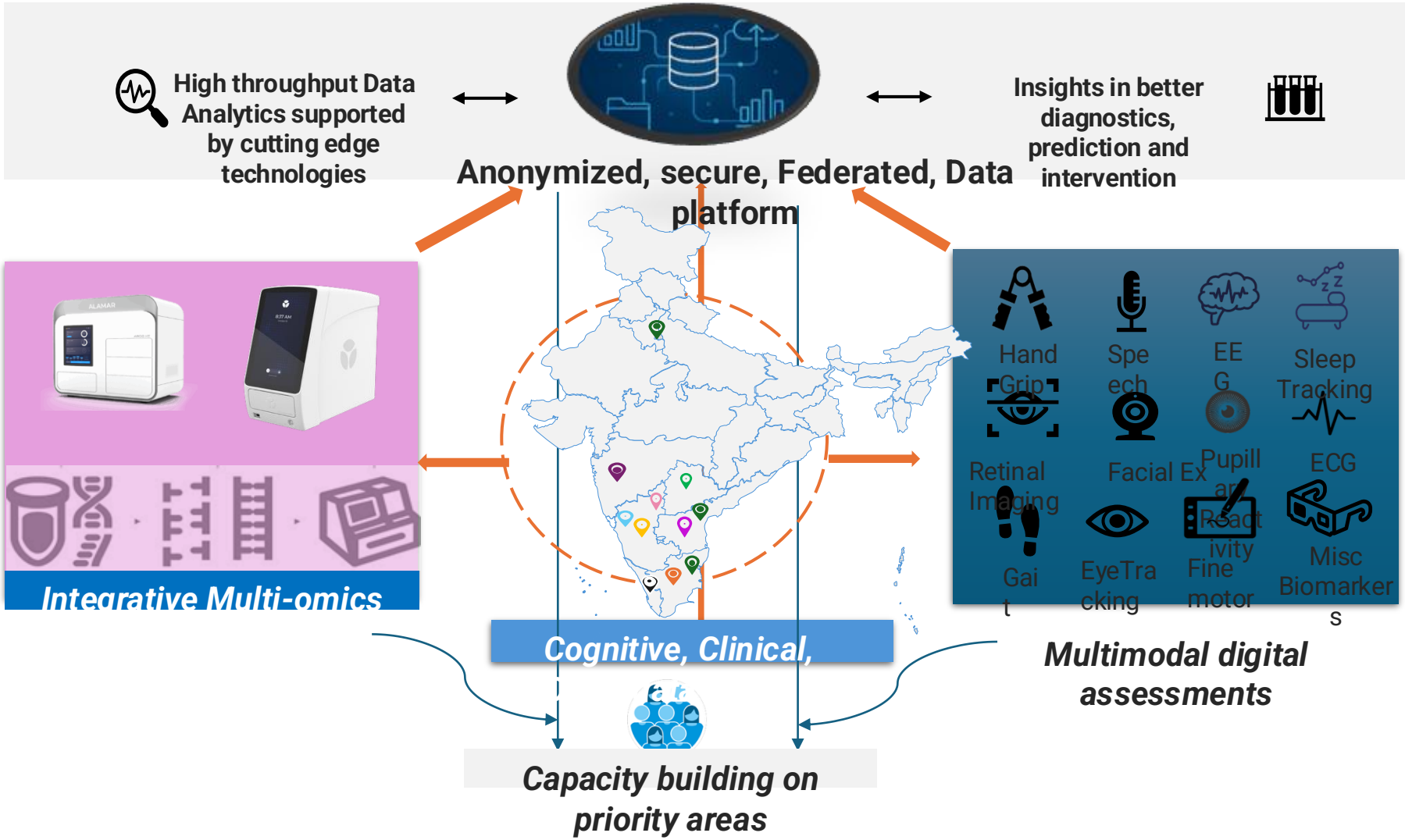
Building a National network for Healthy Brain Aging





CBR will be the coordinator for the network anchoring activities like high-through put proteomic analysis; secure, privacy protected, federated data management system, AI driven data analytics, capacity building and others

Towards Healthy Brain Aging



Summary: Towards Healthy Brain Aging

Enhancing Translation

Prediction

- Robust Risk scores
- Diagnostics
- Dynamic Trajectory trackers

Interventions

- Pharmacological
- Lifestyle based
- Apps and Devices

Enabling Discovery

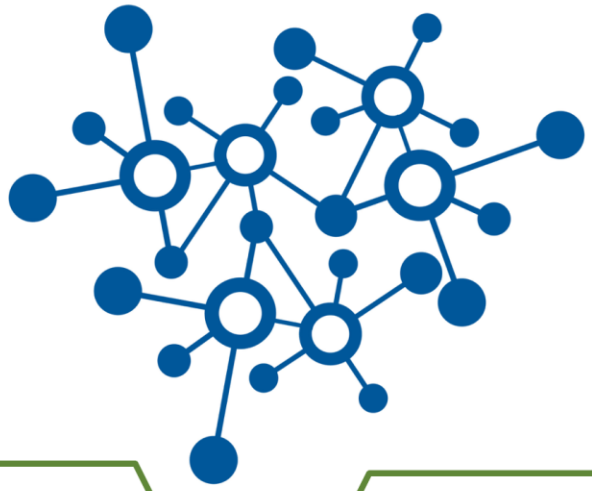
Federated, private, secure **Data Sharing Platform**

AI- Driven Multimodal **Data Analytics**

Integrative **Multi-omics Approaches**

Exploring synergy

- CBR Cohorts
- Other Cohorts



- Hospitals
- Public health Institutes
- International Consortiums

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Preliminary findings

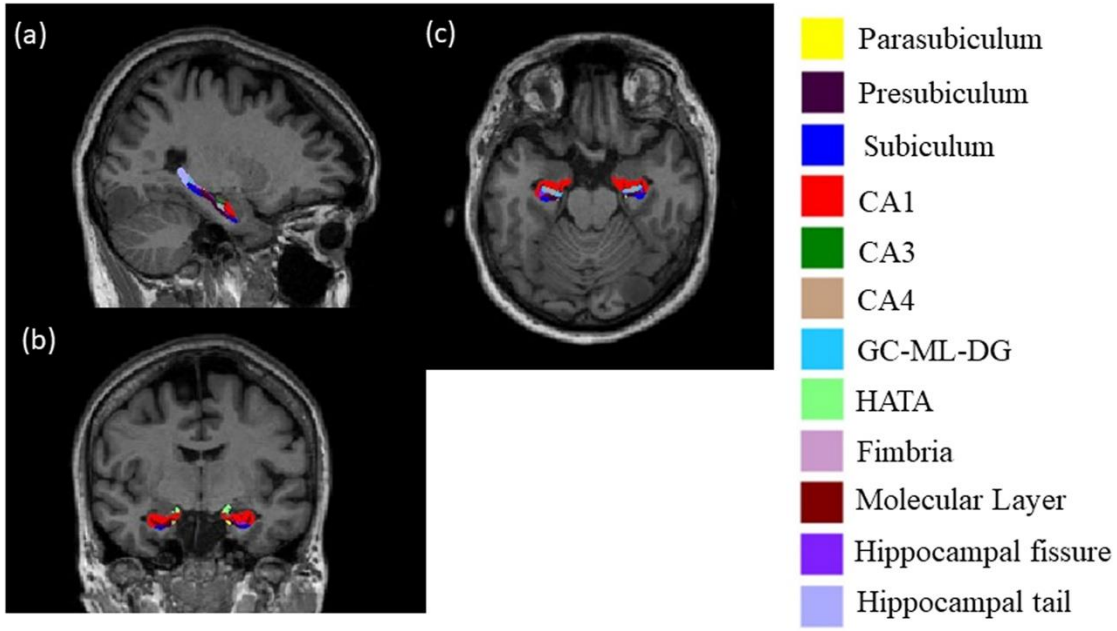
Early identification

Neuroimaging Biomarkers

Poor cognitive performance in individuals with MCI was predicted by—

- Lesser volume of **CA3 region** of Hippocampus
- Lesser **Amygdala subfield** volume (right central nucleus, right medial nucleus, right cortical nucleus and right whole amygdala)

(Singh et al., 2024a; Singh et al., 2024b).



Representative segmented T1 image of hippocampal subfields from a participant in (a) sagittal, (b) coronal, and (c) axial planes.

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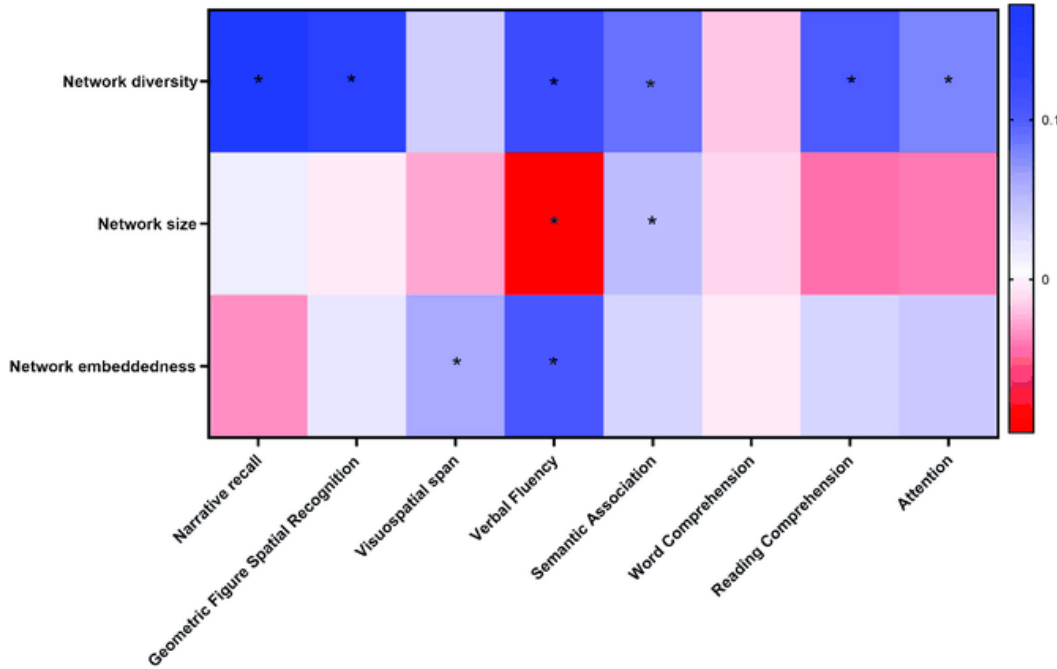
Risk factor control

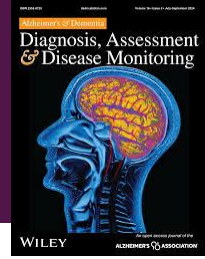
Social Isolation

Social connectedness, measured using Social Networking Index (SNI) was found to be associated with **better cognitive function** in both urban and rural cohorts *(Mensegere et al., 2024; Rai et al., 2024)*.

Parameter	β	95% CI		p-value	Adjusted R Square
		Lower	Upper		
ACE Total	0.07	0.054	0.798	0.025*	0.18
ACE Attention	0.02	-0.063	0.104	0.628	0.08
ACE Memory	0.09	0.070	0.371	0.004*	0.12
ACE Fluency	0.01	-0.084	0.134	0.656	0.12
ACE Language	0.04	-0.029	0.161	0.174	0.06
ACE Visuospatial	0.04	-0.024	0.167	0.142	0.12
Total GM Volume	0.08	1644.250	5202.873	<0.001**	0.76
Total WM Volume	0.04	-418.711	3901.680	0.114	0.69
Left Hippocampus	0.08	6.569	54.178	0.012	0.38
Right Hippocampus	0.09	10.739	60.547	0.005	0.39
WMH	-0.15	-0.539	-0.167	<0.001**	0.14

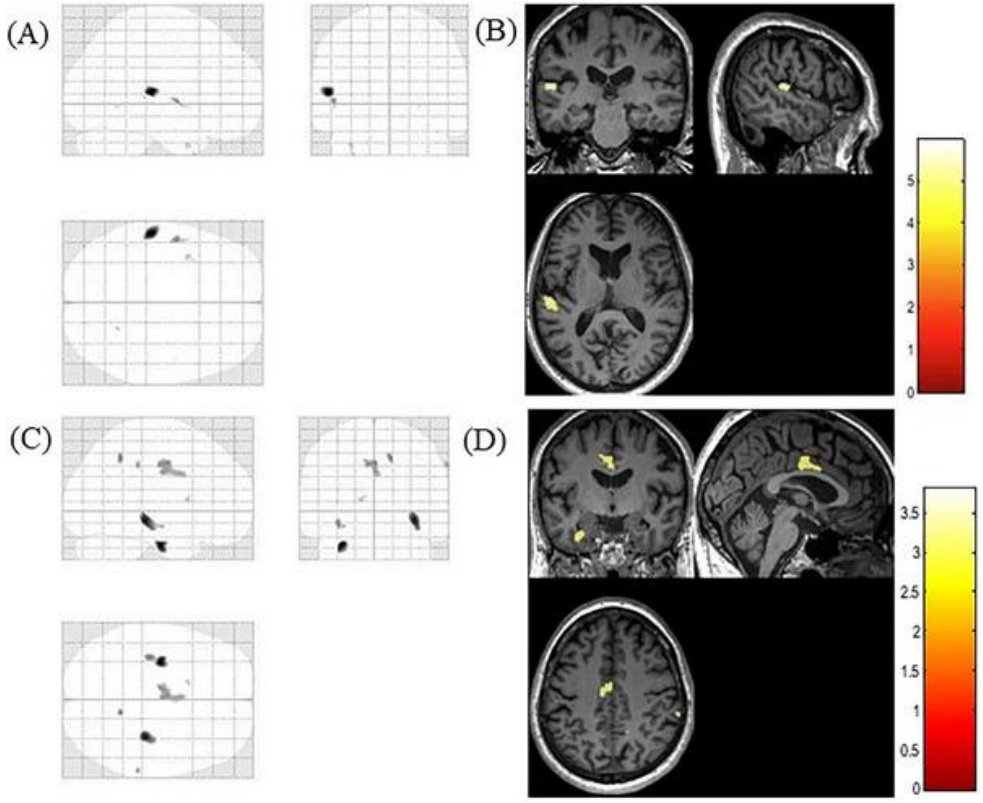


Undervalued risk factors



Hearing loss

- Participants with hearing loss are **1.69 times more likely to experience cognitive impairment** compared to those without HL *(Agrawal et al., 2025)*.
- **Significantly less gray matter in various temporal and hippocampal regions** in individuals with hearing loss and cognitive impairment as compared with normal hearing and normal cognition.



(A) Glass-brain view provided in SPM12. (B) overlay of the peak cluster on the background image of brain regions of lesser gray matter volume in normal hearing-cognitively impaired (NH-CI) participants compared to normal hearing-normal cognition (NH-NC) control participants. (C) Glass-brain view provided in SPM12. (D) overlay of the peak cluster on the background image of brain regions of reduced gray matter volume in hearing loss-cognitively impaired (HL-CI) participants compared to hearing loss-normal cognition (HL-NC) participants. All images are in neurological convention.

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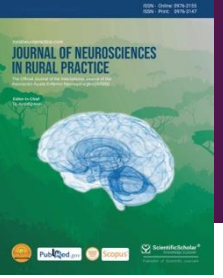
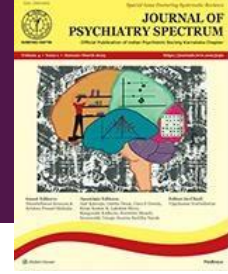


Protective factors



Monolinguals had higher odds of mild cognitive impairment when compared to **multilinguals** in the rural cohort *(Menon et al., 2024)*.

Participants in the urban cohort, trained in **Carnatic music** for at least 5 years were found to have better visuospatial abilities and executive functioning.

The **musicians** also had higher volumes of cortical grey matter in various brain regions and showed meta plasticity in cerebellum *(Ghosh et al., 2024a&b).*

Regular **physical activity** is also a factor that protects from cognitive decline *(Ghosh et al., 2023, HS et al., 2024).*

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About CBR

12 August 2014
CBR Registered as a Not-for-Profit Society
Generously funded by Pratiksha Trust

Feb 2015
Prime Minister
Laying the Foundation Stone
for the CBR Building

June 2022
Prime Minister
Inaugurating the CBR Building

Feb 2023
Signing of MoU with
Pratiksha Trust

Governing Board, chaired by Prof G Rangarajan, Director, Indian Institute of Science
International Advisory Board, chaired by Prof Steve Hyman, Broad Institute, MIT-Harvard
Scientific Advisory Committee, chaired by Prof Srinath Reddy, Public Health Foundation of India

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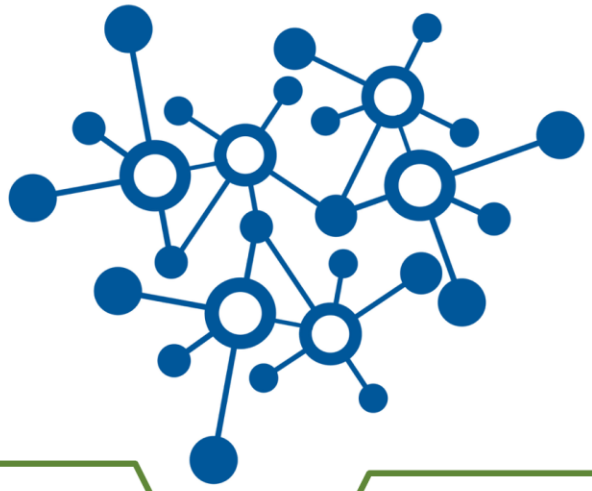

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