4th International Alzheimer's Disease Conference

مؤتمر ألزهايمر الدولي الرابع ٢٠٢٠

Strategic Supporting Partner

مدينة الملك عبدالعزيز للعلوم والتقنية KACST

2-4 Jumada II 1441 / 27-29 January 2020
Conference Hall – KACST HQ
Riyadh, Saudi Arabia

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الجمعية السعودية الخيرية لمرض الزهايمر
SAUDI ALZHEIMER'S DISEASE ASSOCIATION

Advances in Alzheimer´s Disease and Aging Research

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Chief of Geriatrics, Landspitali University Hospital,
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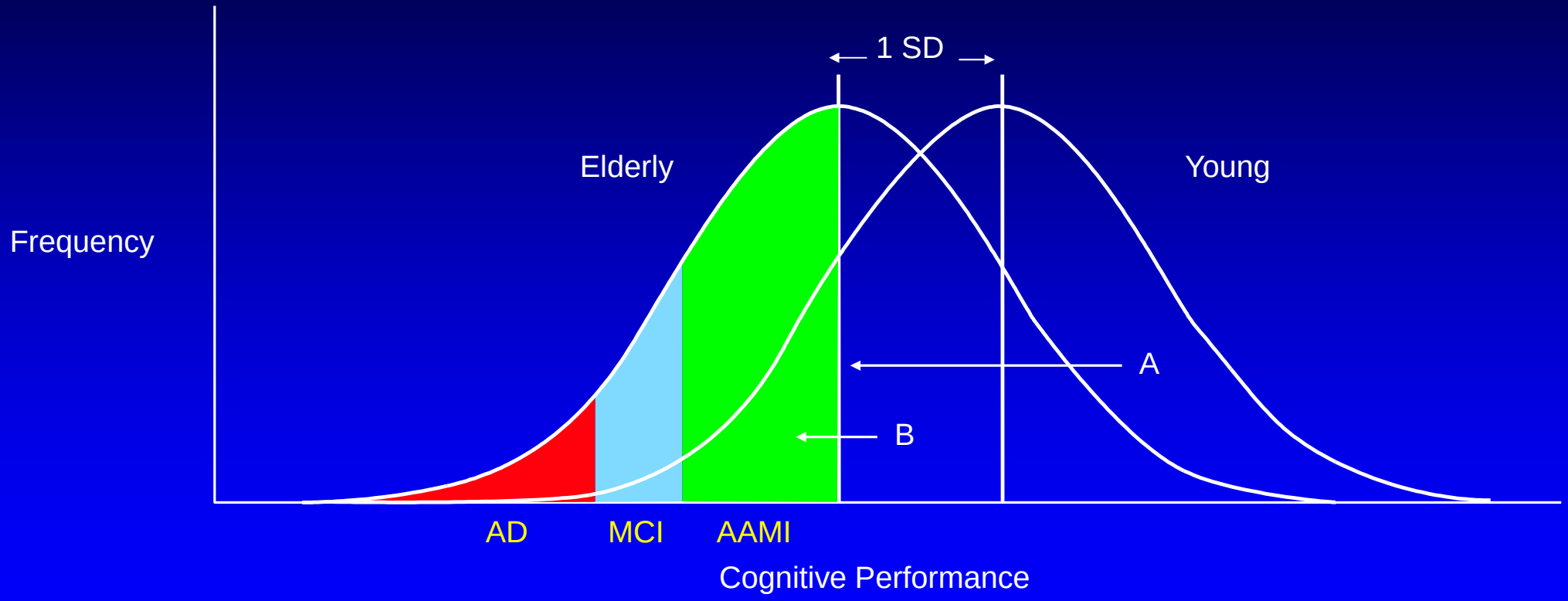
Aging, AAMI (ARCD), MCI, and AD



Adapted from Ferris and Kluger. *Aging, Neuropsychology and Cognition*, 1996.

Brain aging vs. Disease

- How should we understand the fact that three of the major symptoms of AD observed in vivo
  - disruption of episodic memory function,
  - brain atrophy,
  - and accumulation of amyloid protein

  are also found in many presumably healthy elderly?

- Given these commonalities, it can be argued that AD cannot be understood separately from its major risk factor – age.

What is normal aging?

Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus

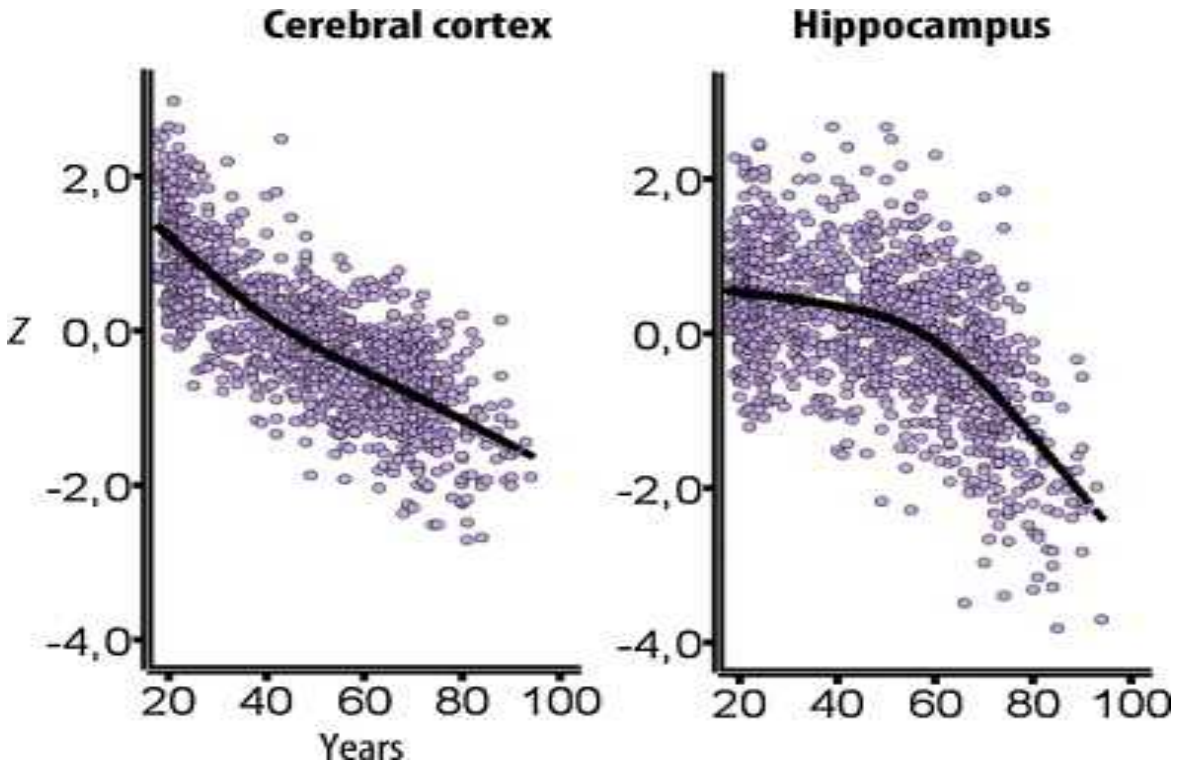


Fig. 5 Life-span trajectories of volumetric reductions. Cross-sectional estimates of adult life-span trajectories of total cerebral cortex volume and total hippocampal volume. ...

Anders M. Fjell , Linda McEvoy , Dominic Holland , Anders M. Dale , Kristine B. Walhovd

Progress in Neurobiology, 2014

What is normal aging?

Effects of aging, amyloid and Alzheimer's disease on the cerebral cortex and the hippocampus

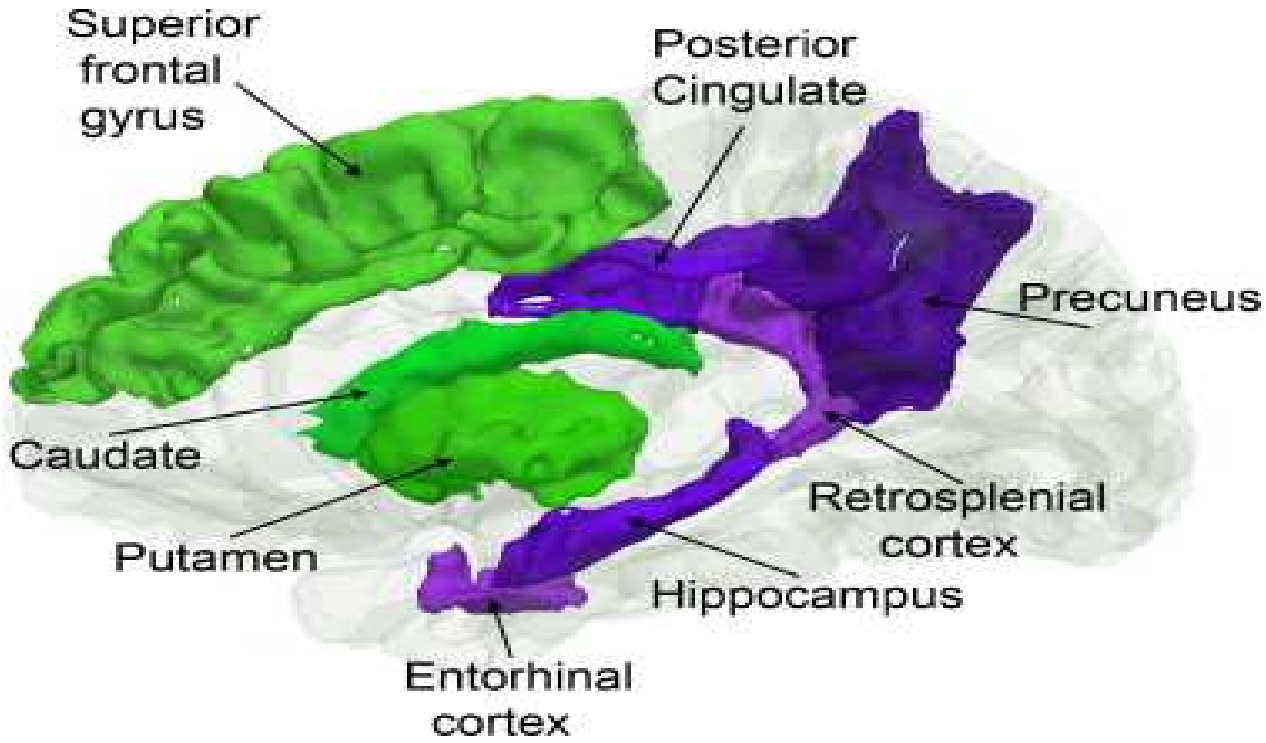


Fig. 8 Fronto-striatal vs. temporo-parietal networks. While normal aging affects a fronto-striatal network important for cognitive control and executive function (green structures), AD has additional effects on a temporo-parietal network important for episodic memory

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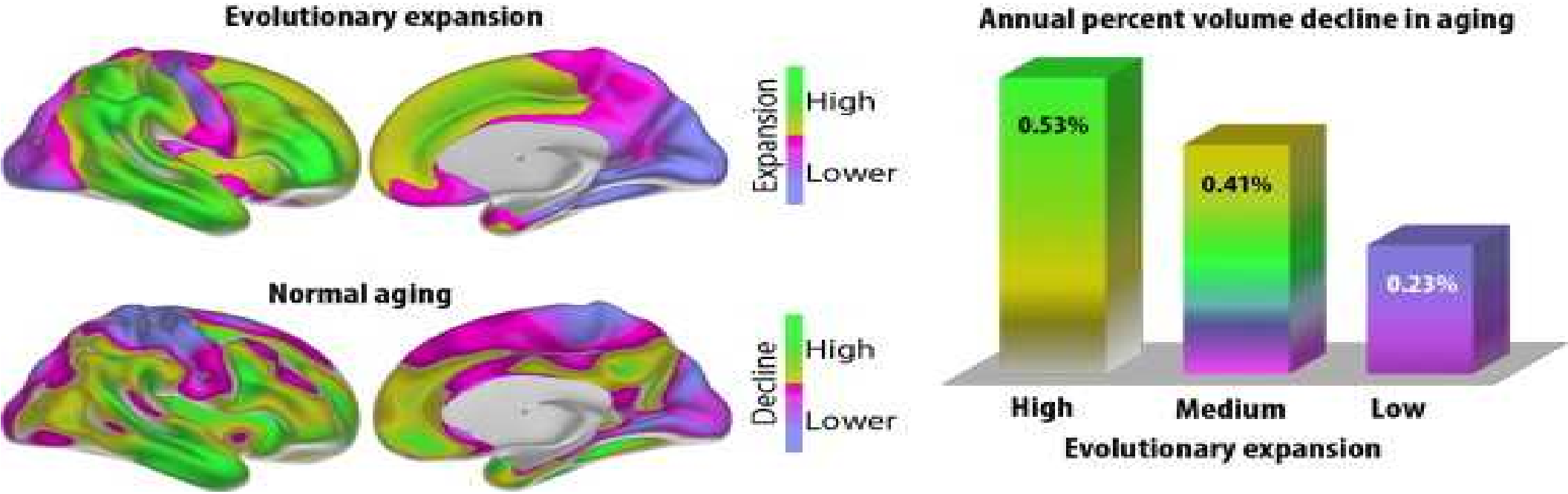


Fig. 9 Cortical expansion across primates and volume decline in aging. Upper panel shows regions of high vs. lower cortical expansion from macaque monkeys to humans

Anders M. Fjell , Linda McEvoy , Dominic Holland , Anders M. Dale , Kristine B. Walhovd

Progress in Neurobiology, 2014

DMN; Default Mode Network

•The Default Mode Network consists of a specific set of brain areas that decrease activity during performance of a wide range of tasks, and that are *typically also active during periods of rest or introspection.*

•The different DMN structures are densely interconnected to each other and limbic structures by polysynaptic connections, with few connections to sensory and motor areas.

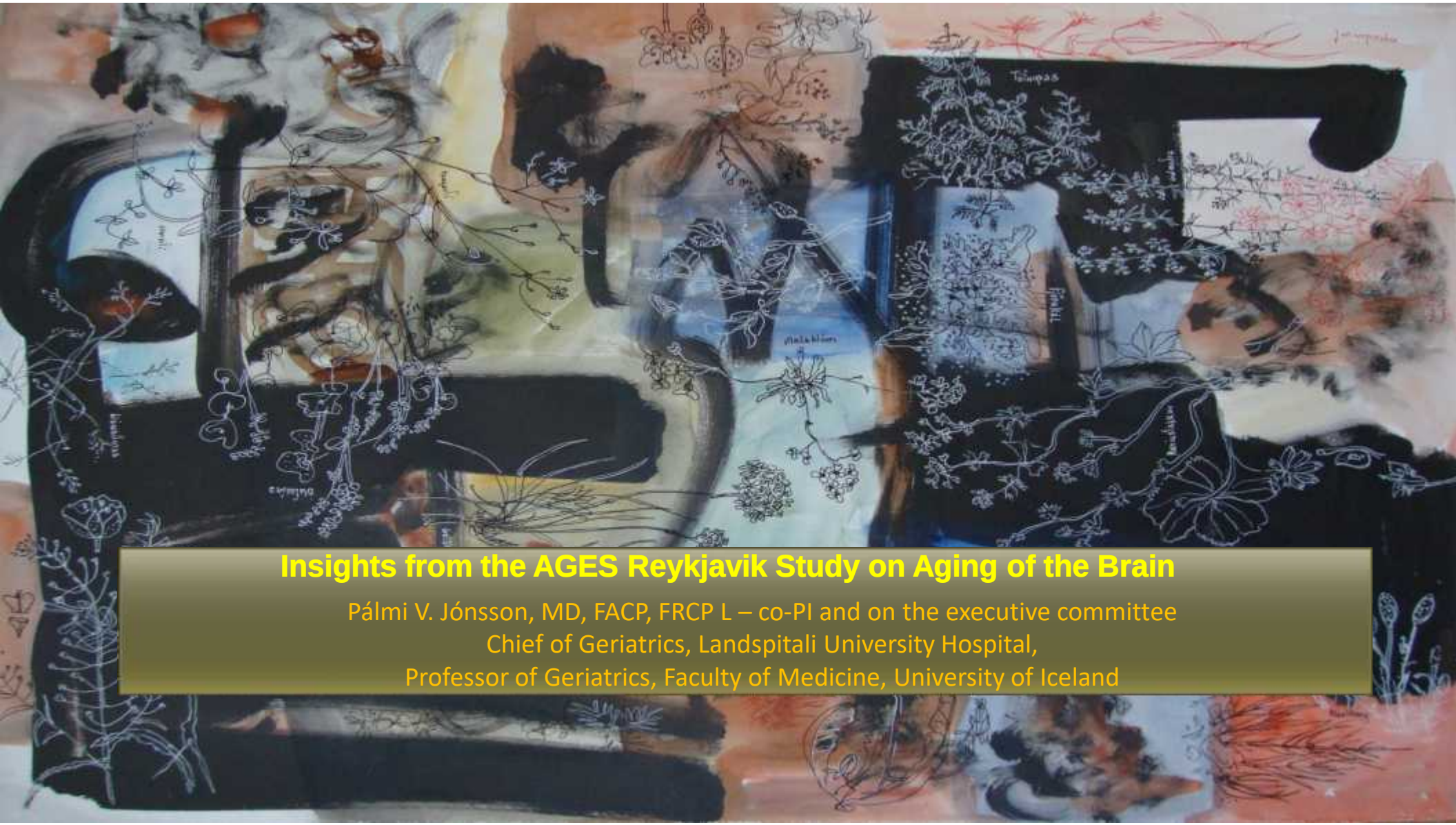
•DMN maps onto a network of core brain areas involved in episodic memory and imagination and is therefore highly relevant for the understanding of episodic memory problems in aging.

•Structural and functional aspects of DMN are affected both in normal aging and AD.

•Interestingly, the default mode network (DMN) is almost completely encapsulated in the high declining regions.

The Aging – AD pathology homology is critical to understand

- Aging itself is the major risk factor for sporadic AD.
  - Rather than necessarily reflecting early signs of disease, these changes may be part of normal aging, and may inform on why the aging brain is so much more susceptible to AD than is the younger brain.
  - Regions characterized by a high degree of life-long plasticity are vulnerable to detrimental effects of normal aging, and that this age-vulnerability renders them more susceptible to additional, pathological AD-related changes.
- It will be difficult to understand AD without understanding why it preferably affects older brains.
  - A model that accounts for age-related changes in AD-vulnerable regions independently of AD-pathology is needed.



Insights from the AGES Reykjavik Study on Aging of the Brain

Pálmi V. Jónsson, MD, FACP, FRCP L – co-PI and on the executive committee
Chief of Geriatrics, Landspitali University Hospital,
Professor of Geriatrics, Faculty of Medicine, University of Iceland

Ann Intern Med 1998 Jun 1;128(11):941-5. **Letter from Reykjavik.** Jónsson PV[1].

A struggle for independence in Norway brought the first Vikings to Iceland in **the ninth century, some 800 farmers, each with 25 persons**. Nature's gifts supported a good life for the next 300 years, and **by the year 1200 the population** is estimated to have been **78 000**, close to the maximum that the farmland could sustain.

But life in Iceland **between 1300 and 1900 was extraordinarily hard with repeated deadly infectious epidemics and hunger due to volcanic eruptions and hard weather.** The **population hovered around 50 000 during these centuries but eventually crept back up, reaching 78 000 in 1901,** the same size it had been 700 years earlier.

The AGES study

A continuum of the Reykjavik Study, a heart study established in 1967.

- A collaborative project with National Institute on Aging
- Participants aged between 67 and 95 years
- Both sexes

- 5700 participants in AGES I, began in 2002
- 3200 participants in AGES II, began in 2007
- More than 1200 variables per person
- Making use of available data and obtaining extensive phenotypes for epidemiological and genetic studies of healthy aging
- Each study participant contributed 3 half days to the study

COG 1; 45 minutes

for all participants of AGES

- MMSE (Mini mental state examination)
- DSST (Digit symbol substitution test)
- Memory for a word list + source memory
- CANTAB (SWM: spatial working memory) computerized
- Figure comparison
- Stroop test for interference (colors, words)
- Digit span
- Delayed recall for the word list
- Assessment of time: how long have you been here
- Post-exam assessment

Cognitive function

Speed of processing composite includes:

Digit Symbol Substitution Test (DSST) (Wechsler 1955),
Figure Comparison (Salthouse et al. 1991),
Modified Stroop Test (Stroop 1935)
- parts I (Word Reading), and part II (Color Naming)

Memory composite includes:

a modified version of the California Verbal Learning Test,
Immediate and delayed recall. (Delis et al. 1987)

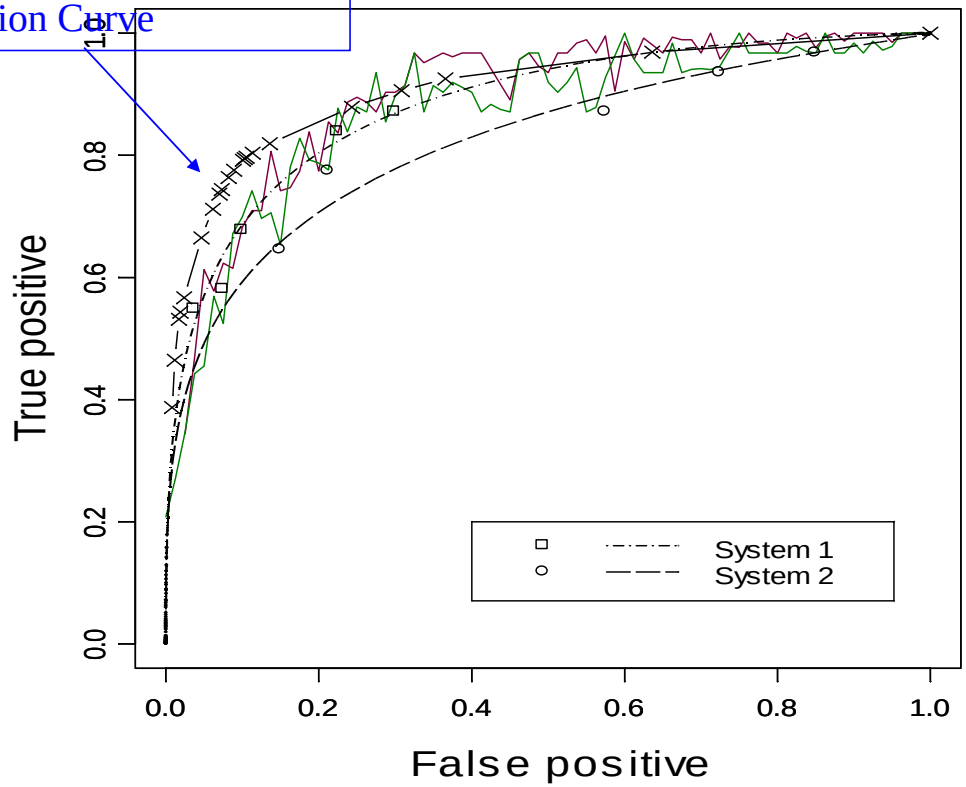
Executive function composite includes:

Digits Backward (Wechsler 1955),
Shortened version of the CANTAB Spatial Working Memory test (Robbins et al. 1994)
Stroop Test part III (Tabachnick et al. 2001) (Word-Color Interference)

Composite measures were computed by converting raw scores on each test to standardized z-scores and averaging the z-scores across the tests in each composite. Details have been described elsewhere (Saczynski et al. 2008)

Combined Curve for DSST and MMSE

Optimal Decision Curve



True pos
Over 90%
False pos
Under 40%

- The "best" rule:
  DSST ≤ 17 OR MMSE ≤ 23

  Sensitivity=0.92

  Specificity=0.70

COG 2; 45 minutes

diagnostic tests for those who fail COG 1

- Clock test
- Nonverbal memory: immediate recognition of faces shown on a computer
- Verbal memory: immediate memoyr for a word list
- Copying and immediate memory: Rey-Osterrieth, simplified
- Wordfluency: S-words and animals
- Token test: language comprehension
- Trails, 4 parts
- Naming of pictures (blcack and white drawings)
- Go/no-go test
- Delayed memory(faces, wordlist, picture)
- Post-exam assessment

ROC analysis
For AVLT and
Trails determines
Flow to MC

MRI of the brain

- **Semi-quantitative analysis**
- **Quantitative analysis**

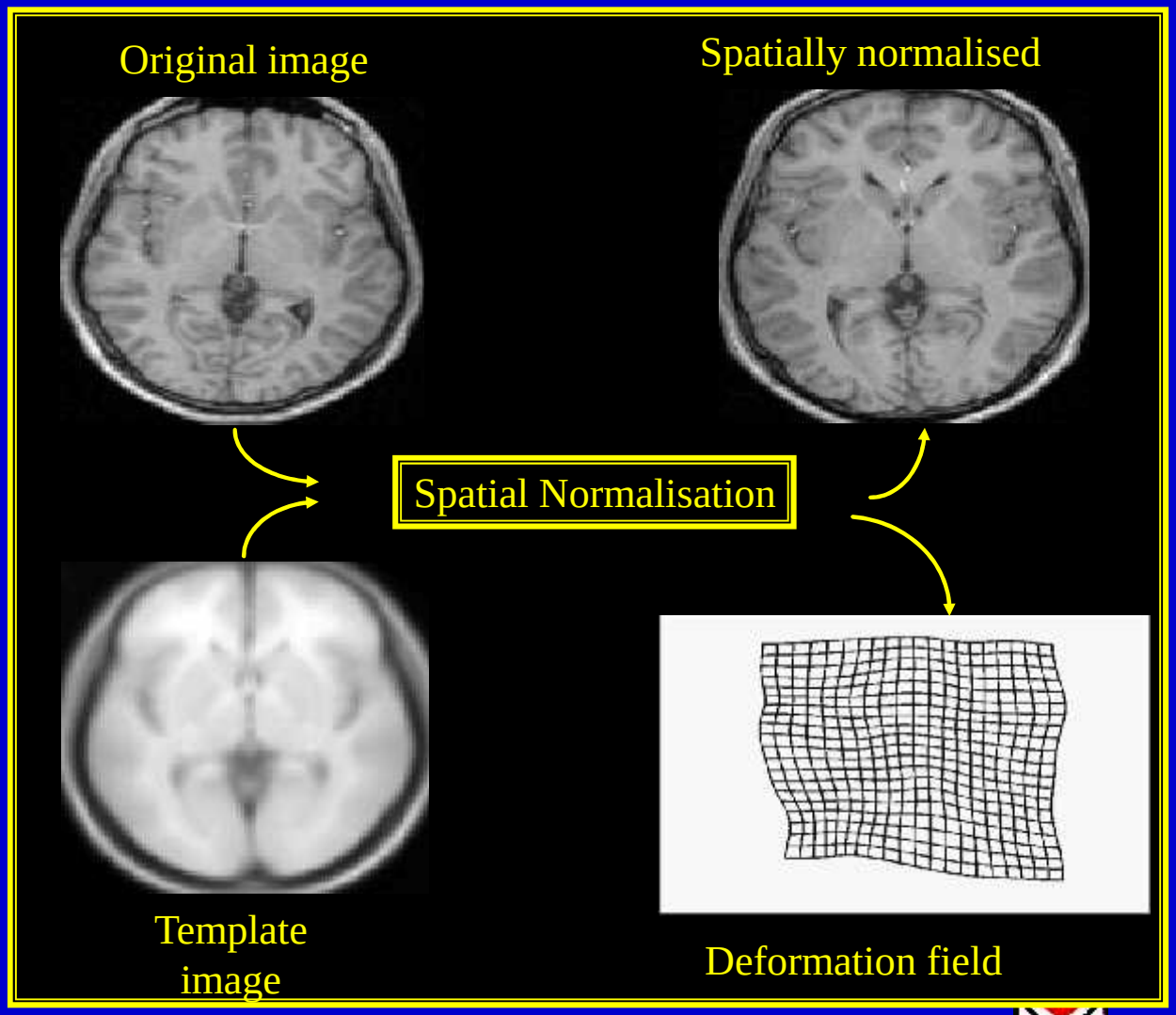
Spatial Normalisation

Determine the spatial transformation that minimises the sum of squared difference between an image and a linear combination of one or more templates.

Begins with an affine registration to match the size and position of the image.

Followed by a global non-linear warping to match the overall brain shape.

Uses a Bayesian framework to simultaneously maximise the smoothness of the warps.

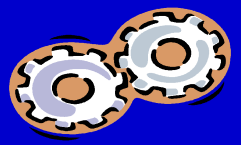


Automatic Segmentation of Four-Tissue Types

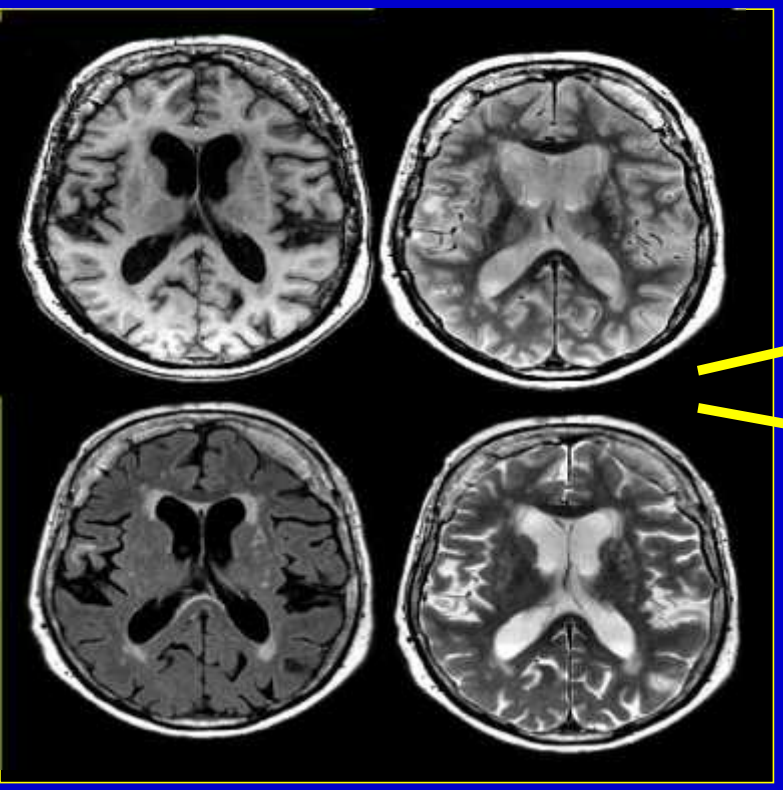
The goal of the image analysis pipeline is to generate automatic brain tissue segmentation of WM, WMH (WM Lesions), GM and CSF following the input of multi-spectral MR images (from left to right and top to bottom): T1-, PD,- FLAIR and T2-weighted images.

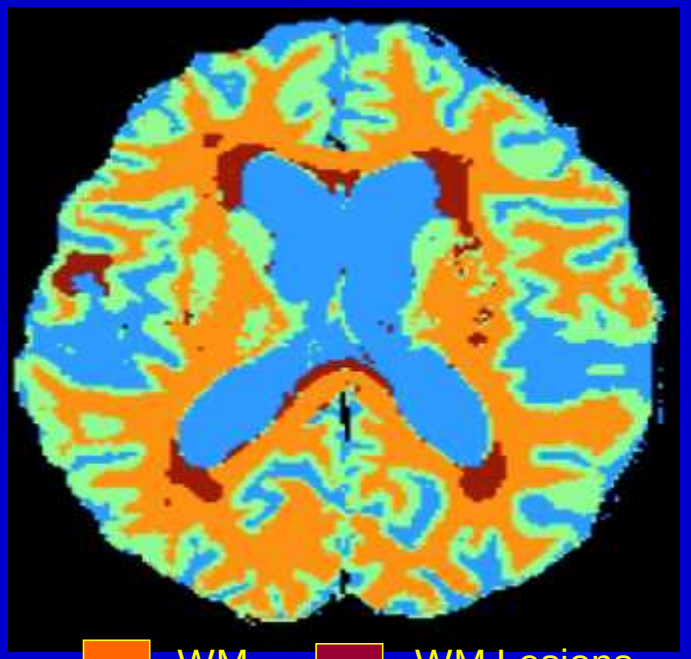
Raw (DICOM) Images

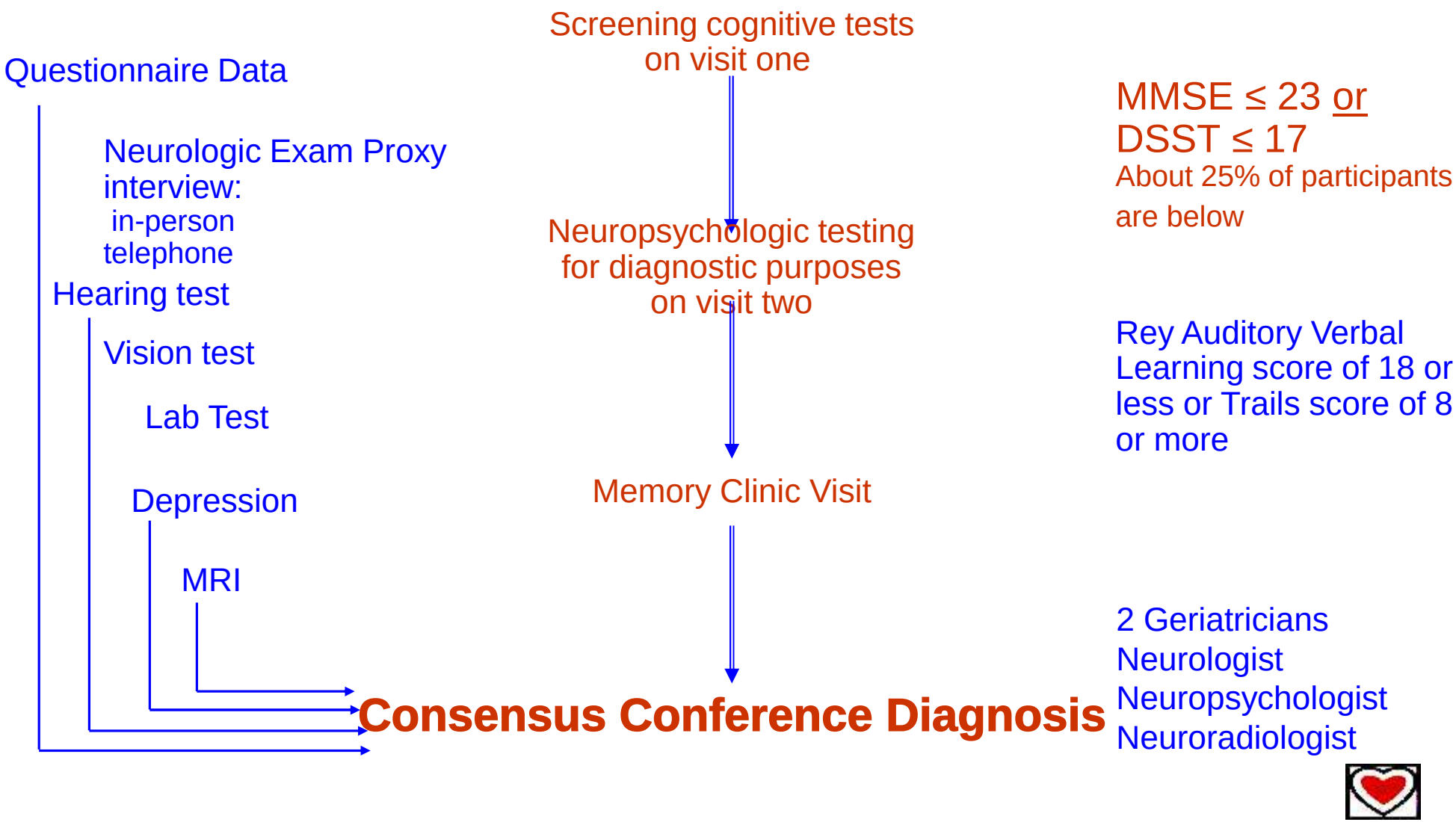
Image Processing



Resultant Segmentation






Questionnaire Data
Neurologic Exam Proxy
interview:
in-person
telephone
Hearing test
Vision test
Lab Test
Depression
MRI
Screening cognitive tests
on visit one
Neuropsychologic testing
for diagnostic purposes
on visit two
Memory Clinic Visit
Consensus Conference Diagnosis
MMSE ≤ 23 or
DSST ≤ 17
About 25% of participants
are below
Rey Auditory Verbal
Learning score of 18 or
less or Trails score of 8
or more
2 Geriatricians
Neurologist
Neuropsychologist
Neuroradiologist


Mid life to late life associations

American Journal of Epidemiology
Published by Oxford University Press on behalf of the Johns Hopkins Bloomberg School of Public Health 2015. This work is written by (a) US Government employee(s) and is in the public domain in the US.

Vol. 181, No. 9
DOI: 10.1093/aje/kwu331
Advance Access publication:
March 24, 2015

Original Contribution

Overweight and Obesity in Midlife and Brain Structure and Dementia 26 Years Later

The AGES-Reykjavik Study **et. al.**

High adiposity in midlife might increase risk for late-life brain pathology, including dementia.

In midlife, the prevalence of overweight was 39% and that of obesity was 8%.

After a mean follow-up of 26.2 (standard deviation, 4.9) years, midlife overweight and obesity were not associated with infarct-like brain lesions (relative risk (RR) = 0.82, 95% confidence interval (CI): 0.61, 1.10), cerebral microbleeds (RR = 0.69, 95% CI: 0.37, 1.32), total brain volume ($\beta = 0.05$, 95% CI: −0.34, 0.45), white matter lesions volume ($\beta = -0.10$, 95% CI: −0.20, 0.01), or dementia (RR = 0.91, 95% CI: 0.49, 1.72) compared with normal weight.

These findings do not support the hypothesis that high body mass index in midlife modulates the risk for dementia.

J Gerontol A Biol Sci Med Sci, 2010 Dec;65(12):1369-74. Chang M et. al.

The effect of midlife physical activity on cognitive function among older adults: AGES--Reykjavik Study.

RESULTS:

Among the participants, no midlife PA was reported by 68.8%, ≤ 5 hours PA by 26.5%, and >5 hours PA by 4.5%.

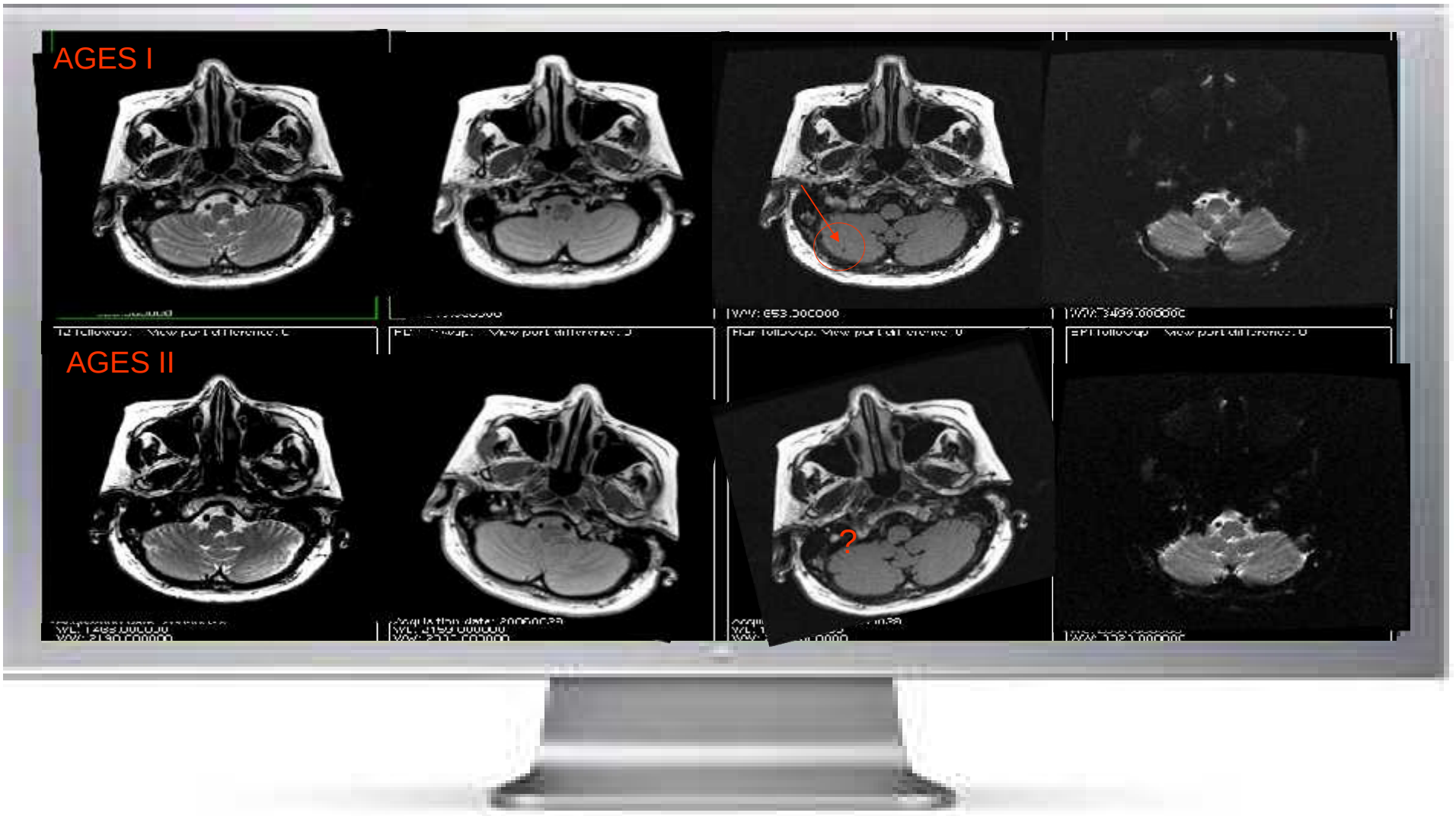
Excluding participants with dementia compared with the no PA group, PA groups had significantly faster speed of processing , better memory and executive function after controlling for demographic and cardiovascular factors.

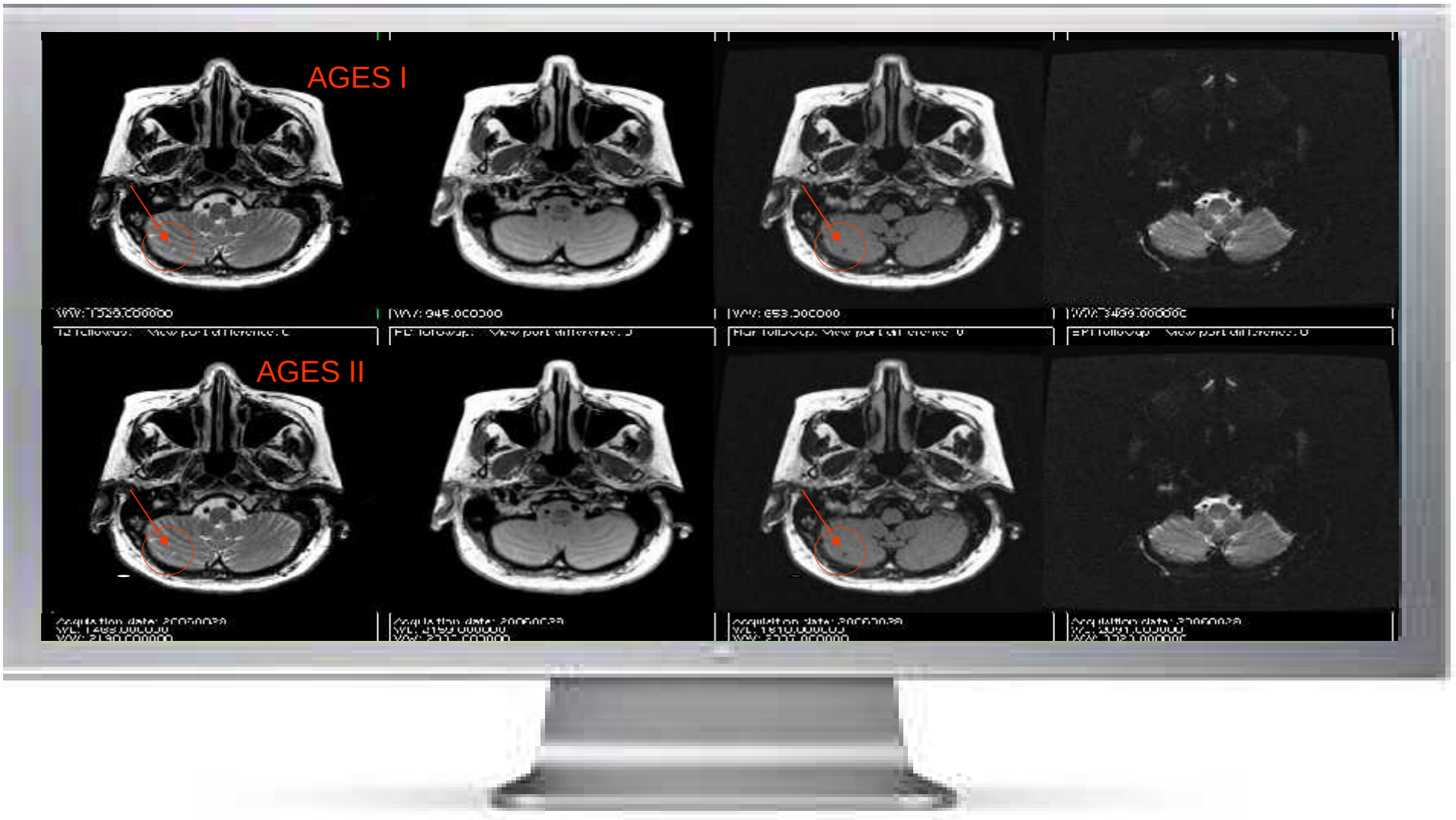
The ≤ 5 hours PA group was significantly less likely to have dementia in late life (odds ratio: 0.6, 95% confidence interval: 0.40-0.88) after adjusting for confounders.

CONCLUSION:

Midlife PA may contribute to maintenance of cognitive function and may reduce or delay the risk of late-life dementia.


Imaging Results


AGES I
AGES II
?


AGES I
AGES II

Neuroimage 2012 Feb 15;59(4):3862-70. Sigurdsson S et. Al.

Brain tissue volumes in the general population of the elderly: the AGES-Reykjavik study.

A reduction in both normal white matter (NWM)- and gray matter (GM) volume contributed to the brain shrinkage.

After adjusting for intra-cranial volume, **women had larger brain volumes compared to men** (3.32%, $p < 0.001$)

The longitudinal analysis showed **a greater rate of annual change in total brain volume for men** (-0.70%, 95%CI: -0.78% to -0.63%) **than women** (-0.55%, 95%CI: -0.61% to -0.49%).

Birth Size and Brain Function 75 Years Later

AUTHORS: Majon Muller, MD,[a,b] Sigurdur Sigurdsson, MSc,[c] Olafur Kjartansson, MD,[c,d] Palmi V. Jonsson, MD,[c,e] Melissa Garcia, MPH,[a] Mikaela B. von Bonsdorff, PhD,[a,f] Ingibjorg Gunnarsdottir, PhD,[g] Inga Thorsdottir, PhD,[g] Tamara B. Harris, MD,[a] Mark van Buchem, MD, PhD,[h] Vilmundur Gudnason, MD, PhD,[c] and Lenore J. Launer, PhD[a]

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WHAT'S KNOWN ON THIS SUBJECT: The fetal origins of adult disease hypothesis proposes that suboptimal fetal development may condition the later risk of disease, particularly cardiovascular disease. However, this hypothesis has never been tested for diseases of the aging brain.

WHAT THIS STUDY ADDS: This first study of its kind provides clinical measures suggesting that small birth size, as an indicator of an adverse intrauterine environment, has lifelong consequences for brain tissue volume and cognitive function. In addition, it shows that the effects of a suboptimal intrauterine environment on late-life cognitive function were particularly present in those with lower educational levels.

Neurobiol Aging 2016 May;41:86-92. Muller M et. al.

Late-life brain volume: a life-course approach.
The AGES-Reykjavik study

We investigated the combined effect of small birth size and mid-life cardiovascular risk on late-life brain volumes.

Compared with the reference group (high Ponderal Index/absence of mid-life CVRF), participants with lower Ponderal index/presence of mid-life CVRF (body mass index >25 kg/m^2, hypertension, diabetes, "ever smokers") had smaller total brain volume later in life;

The results suggest that exposure to an unfavorable intrauterine environment contributes to smaller brain volume in old age, but added to that is atrophy which is associated with mid-life cardiovascular risk.

Diabetic Care: 2009 Sep;32(9):1608-13. Sacynzi JS et. al.

Glycemic status and brain injury in older individuals:

the age gene/environment susceptibility-Reykjavik study.

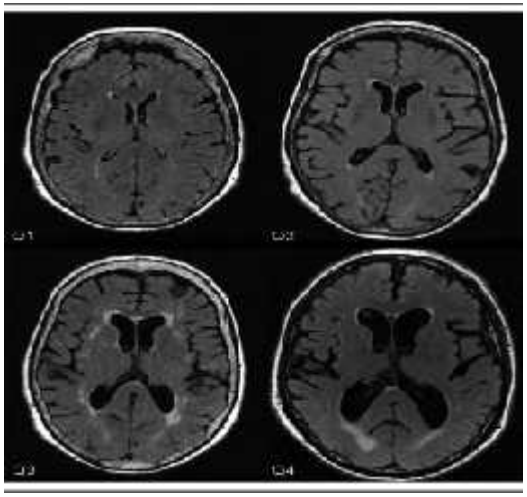
CONCLUSIONS:

- Type 2 diabetic participants have **more pronounced brain atrophy** and are more likely to have **cerebral infarcts**.

- Duration of type 2 diabetes is associated with brain changes, suggesting that type 2 diabetes has **a cumulative effect** on the brain.

Ann Neurol. 2009 Oct;66(4):485-93. Palm WM et. al.

Ventricular dilation: association with gait and cognition.



RESULTS:
Disproportion between ventricular and sulcal CSF volume, defined as the highest quartile of the VV/SV z score, was associated **with gait impairment (odds ratio [OR], 1.9;** 95% confidence interval [CI], 1.1-3.3) and **cognitive impairment (OR, 1.8;** 95% CI, 1.1-3.0). We did not find an association between the VV/SV z score and bladder dysfunction.

INTERPRETATION:

The prevalence and severity of gait impairment and cognitive impairment increases with ventricular dilation

in persons without stroke from the general population,
independent of White Matter Lesion volume.

Stroke. 2009 Mar;40(3):677-82. Saczynski JS et. al.

Cerebral infarcts and cognitive performance: importance of location and number of infarcts.

CONCLUSIONS:

Having infarcts in >1 location is associated with

poor performance in memory, processing speed, and executive function,
independent of cardiovascular comorbidities,
white matter lesions, and brain atrophy,

suggesting that both the number and the distribution of infarcts jointly contribute to cognitive impairment.

Incidence of Brain Infarcts, Cognitive Change, and Risk of Dementia in the General Population

The AGES-Reykjavik Study (Age Gene/Environment Susceptibility-Reykjavik Study)

Background and Purpose—The differentiation of brain infarcts by region is important because their cause and clinical implications may differ. Information on the incidence of these lesions and association with cognition and dementia from longitudinal population studies is scarce.

Conclusions:

- Men are at greater risk of developing incident brain infarcts than women.

- Persons with incident brain infarcts decline faster in cognition and have an increased risk of dementia compared with those free of infarcts.

- Incident subcortical infarcts contribute more than cortical and cerebellar infarcts to incident dementia which may indicate that infarcts of small vessel disease origin contribute more to the development of dementia than infarcts of embolic origin in larger vessels.

Sigurdur Sigurdsson, MSc; et.al. Stroke. 2017;48:2353-2360

JAMA Neurology | Original Investigation

Large Perivascular Spaces Visible on Magnetic Resonance Imaging, Cerebral Small Vessel Disease Progression, and Risk of Dementia

The Age, Gene/Environment Susceptibility-Reykjavik Study

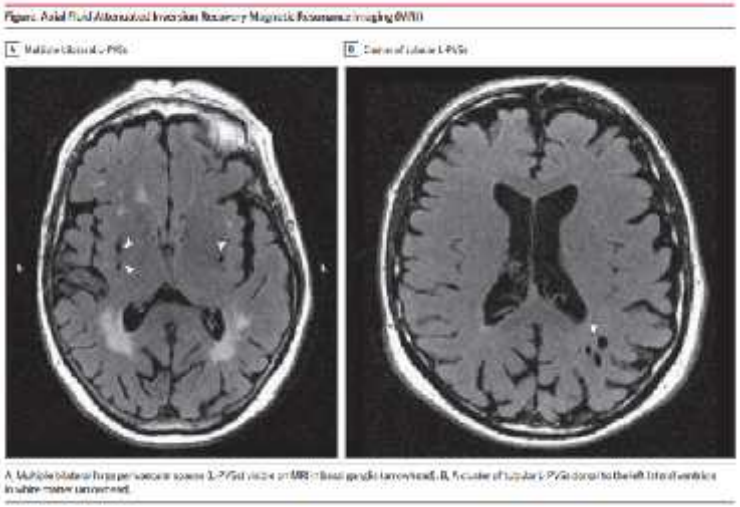
[author block]

Key Points

Question What is the effect of large perivascular spaces (diameters >3 mm) visible on magnetic resonance imaging on progression of magnetic resonance imaging hallmarks of cerebral small vessel disease, cognitive decline, and dementia in a general population?

Findings In this prospective, population-based cohort study of 2612 older adults, the prevalence of large perivascular spaces was 16.2%. Large perivascular spaces were associated with progression of subcortical infarcts, microbleeds, and white matter hyperintensities and decline in information processing speed and more than quadrupled the risk of vascular dementia during a 5-year follow-up.

Meaning Large perivascular spaces are prevalent in the older population, as markers of small vessel disease, they should be included in assessments of vascular cognitive decline.



IMPORTANCE With advancing age, an increased visibility of perivascular spaces (PVSs) on magnetic resonance imaging (MRI) is hypothesized to represent impaired drainage of interstitial fluid from the brain and may reflect underlying cerebral small vessel disease (SVD). However, whether large perivascular spaces (L-PVSs) (>3 mm in diameter) visible on MRI are associated with SVD and cognitive deterioration in older individuals is unknown.

CONCLUSIONS: Large PVSs are an MRI marker of SVD and associated with the pathogenesis of vascular-related cognitive impairment in older individuals.

Large PVSs should be included in assessments of vascular cognitive impairment in the older population and as potential targets for intervention

JAMA Neurol. 2017;74(9):1105-1112


Microvasclar disease and aging

J Neurolo Neurosurg Psychiatry. 2008 Sep;79(9):1002-6. Sveinbjörnsdóttir et. al.

Cerebral microbleeds in the population based AGES-Reykjavik study: prevalence and location.

RESULTS:

Evidence of CMBs was found in 218 participants (11.1% (95% CI 9.8% to 12.6%));

Men had significantly more CMBs than women (14.4% vs 8.8%; p = 0.0002, age adjusted). The prevalence of CMBs increased with age (p = 0.0001) in both men (p = 0.006) and women (p = 0.007).

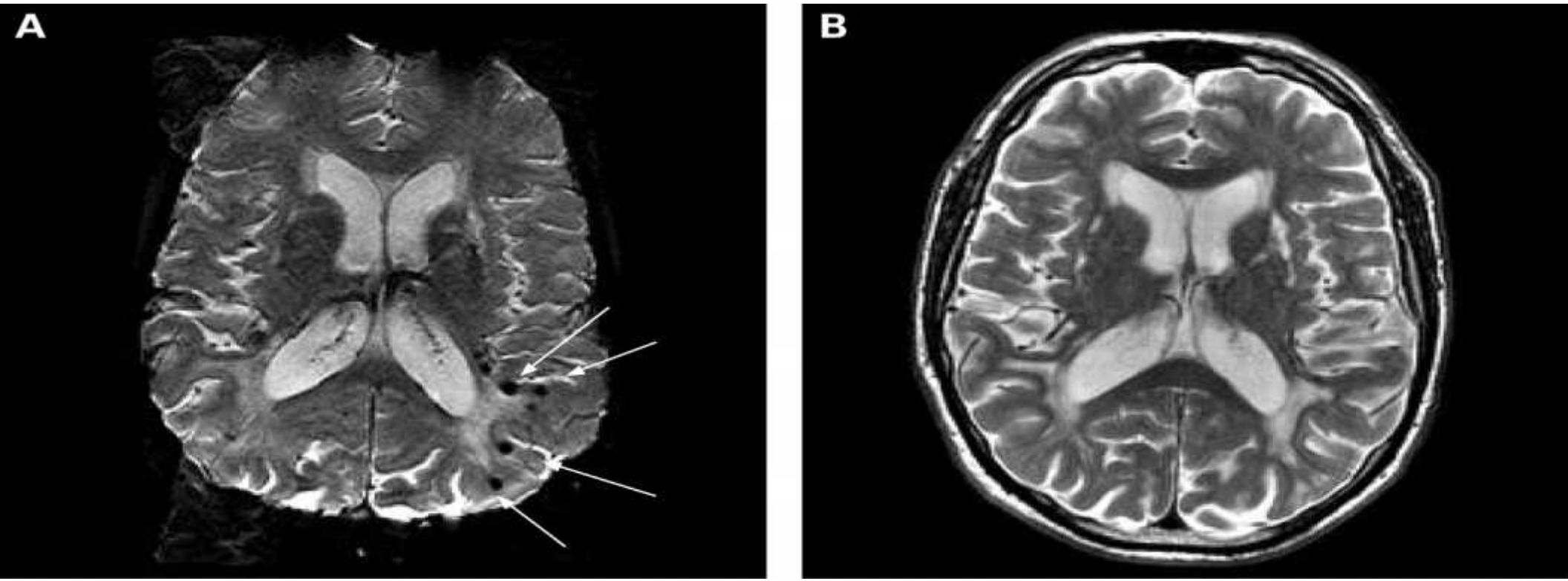
Having a CMB was significantly associated with a homozygote Apo E epsilon4epsilon4 genotype (p = 0.01).

CONCLUSION:

- Cerebral microbleeds are common in older persons.

- The association with homozygote ApoE4 genotype and finding a relative predominance in the parietal lobes might indicate an association with amyloid angiopathy.

Cerebral microbleeds (CMBs), as seen on T2* weighted gradient echo type echo planar (GRE-EPI) MRI.



Sveinbjornsdottir S et al. J Neurol Neurosurg Psychiatry 2008;79:1002-1006

JAMA Neurol 2015 Jun;72(6):682-8. Ding J et. al.

Risk Factors Associated With Incident Cerebral Microbleeds According to Location in Older People: The Age, Gene/Environment Susceptibility (AGES)-Reykjavik Study.

The spatial distribution of cerebral microbleeds (CMBs), which are asymptomatic precursors of intracerebral hemorrhage, reflects specific underlying microvascular abnormalities of cerebral amyloid angiopathy (lobar structures) and hypertensive vasculopathy (deep brain structures).

CONCLUSIONS:

Lifestyle and lipid risk profiles for CMBs were similar to those for symptomatic intracerebral hemorrhage.

Modification of these risk factors could have the potential to prevent new-onset CMBs.

Arterioscler Thromb Vasc Bopœ 2015 Aug;35(8):1889-95. Ding J et. al.

Carotid arterial stiffness and risk of incident cerebral microbleeds in older people: the Age, Gene/Environment Susceptibility (AGES)-Reykjavik study.

Age and high blood pressure are major risk factors for cerebral microbleeds (CMBs). However, the underlying mechanisms remain unclear and arterial stiffness may be important. We investigated whether carotid arterial stiffness is associated with incidence and location of CMBs.

CONCLUSIONS:

Our findings support the hypothesis that localized increases in carotid arterial stiffness may contribute to the development of CMBs, especially in a deep location attributable to hypertension.

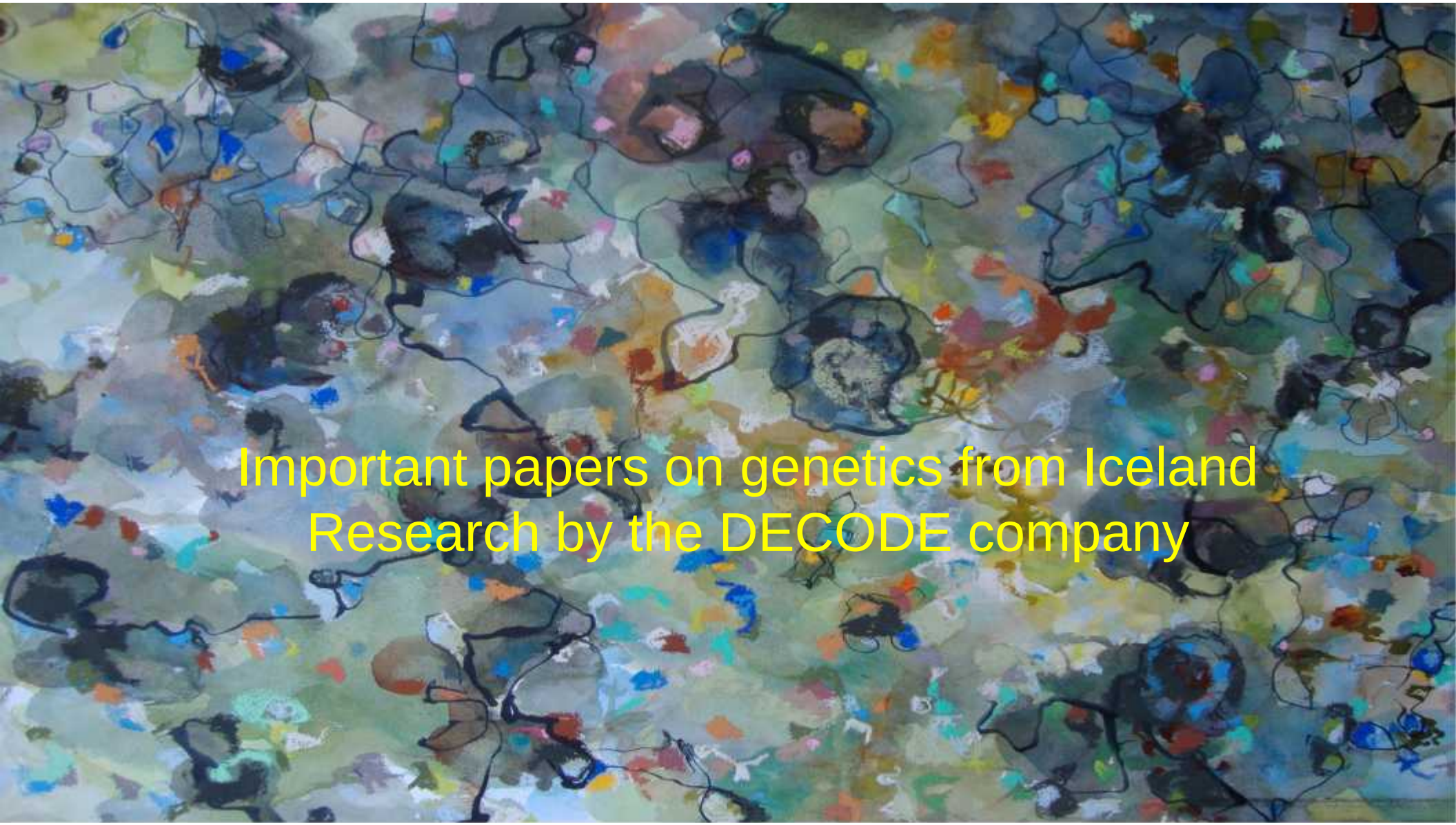
Hypertension 2016 Jan;67(1):176-82. Cooper LL et. al.

Cerebrovascular Damage Mediates Relations Between Aortic Stiffness and Memory.

Aortic stiffness is associated with cognitive decline.

Here, we examined the association between carotid-femoral pulse wave velocity and cognitive function and investigated whether cerebrovascular remodeling and parenchymal small vessel disease damage mediate the relation.

The results suggest that in older people, associations between aortic stiffness and memory are mediated by pathways that include cerebral microvascular remodeling and microvascular parenchymal damage.


Important papers on genetics from Iceland
Research by the DECODE company

Whole Genome Sequencing by DeCode- A revolution

- Purpose: The whole-genome sequencing; WGS); of up to 3700 Icelanders
- Allows genetic variance to be detected with >0.1% prevalence
- With the use of genealogy of the Icelandic people and so called long-range phasing of haplotypes (bit´s of the genome) one can impute the genomic sequence of a large proportion of the nation
- With this method one can find:
  - Common genetic variance which has not been identified with other methods
  - Rare genetic variance associated with great increase in risk
- Has already shown results for ovarian cancer, glioma, sick sinus syndrome and gout
  - Sulem *et al.* Nat Genet 2011 Oct 9 Epub, Rafnar *et al.* Nat Genet 2011 Oct 2 Epub,
  - Stacey *et al.* Nat Genet 2011 Sept 25 Epub, Holm *et al.* Nat Genet 43(4):316-20 (2011)

Identification of a protective variant in APP

LETTER

doi:10.1038/nature11283

A mutation in *APP* protects against Alzheimer's disease and age-related cognitive decline

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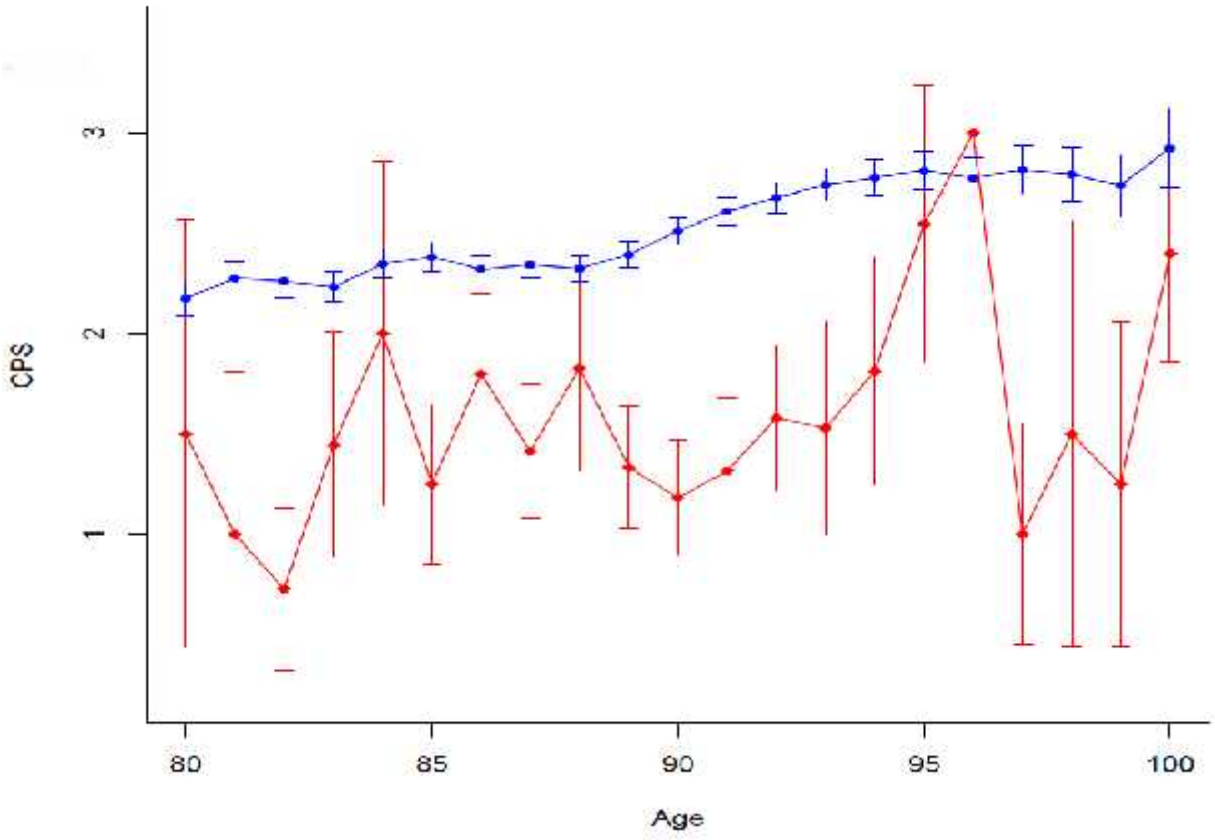
Nature. 2012 Aug 2;488(7409):96-9

A673T (instead of V) promotes intact cognition in the elderly without AD



A673T carriers (N=42; in red)
A673T non-carriers (N=3,673; in blue)
AD cases not included

Δ = -1.03
P = 0.0021

A673T in APP - Summary

- A673T protects significantly against AD
- Promotes healthy cognition in the elderly in the absence of AD
- *in vitro* studies show that A673T alters APP processing:
  - Less cleavage by β-secretase (BACE1)
  - More cleavage by α-secretase
  - Less cleavage by recombinant BACE1 in cleavage assays

Coding variant in TREM2 confers risk of AD

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Variant of *TREM2* Associated with the Risk of Alzheimer's Disease

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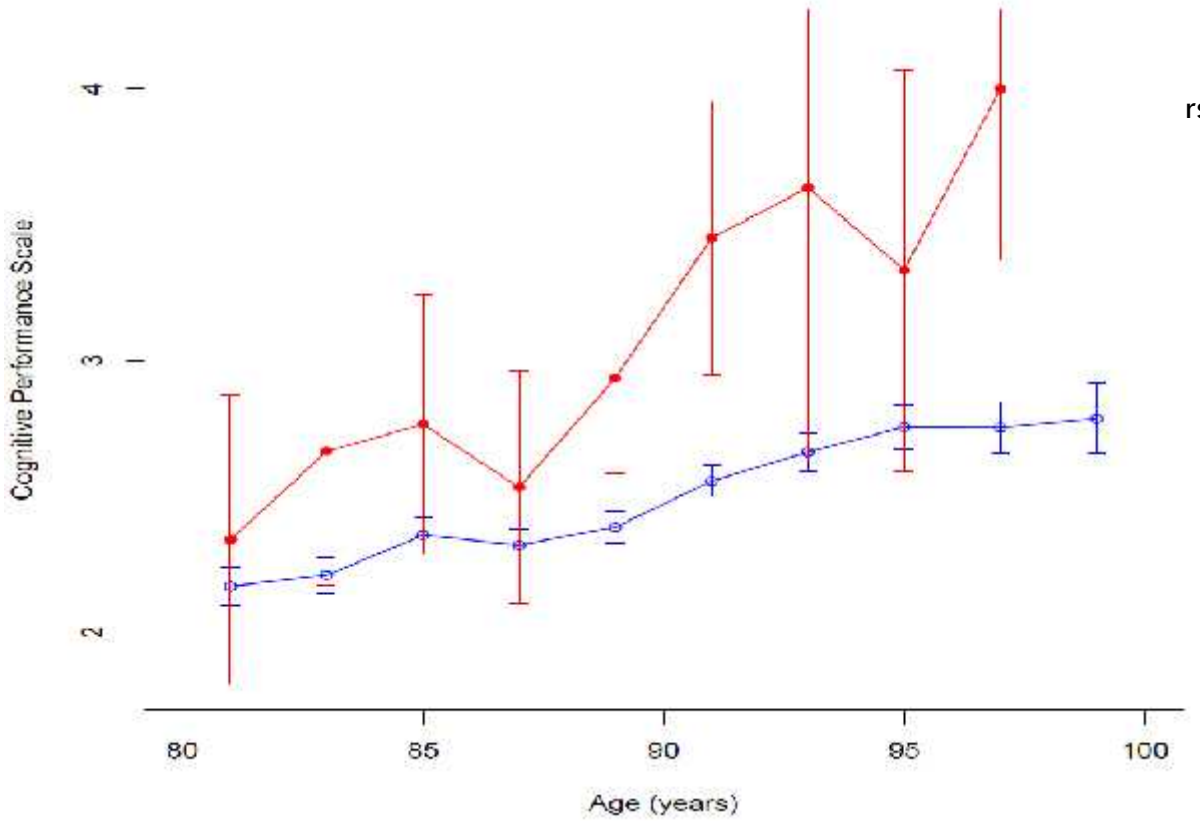
rs75932628-T is also predictive of loss of cognitive function in the elderly in the absence of AD



rs75932628-T carriers

rs75932628-T non-carriers

rs75932628-T lowers age at onset of AD

- Each copy of rs75932628-T lowers age at onset of AD by 3.18 years in Iceland ($P = 0.20$)
- Comparable to the effect of ApoE ε4 (3.22 years)
- Similar result obtained in Dutch data (3.65 years/allele of rs75932628-T)

ELSEVIER

Alzheimer's & Dementia

Convergent genetic and expression data implicate immunity in Alzheimer's disease

International Genomics of Alzheimer's Disease Consortium (IGAP)

This study uses the largest genome-wide association study (GWAS) sample yet assembled for late-onset AD [4] and is the first to combine GWAS and expression data in a systematic search for the biological pathways underlying the genetic susceptibility to this disorder.

RESEARCH IN CONTEXT

1. Systematic review: As **the main motivation for genetic analysis of complex traits is to understand the biology of disease and inform the search for treatments, interpretation of genetic signals in a biologically meaningful way is essential. Pathway analyses** that integrate multiple dense sources of data provide a means of starting to do this. Identifying strong susceptibility targets also highlights potential drug targets.

1. Interpretation: This study implicates regulation of endocytosis and protein ubiquitination, in addition to cholesterol metabolism, as potential therapeutic targets in Alzheimer's disease (AD). It strongly reinforces the critical role of the immune system in conferring AD susceptibility.

Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk

Alzheimer's disease (AD) is highly heritable and recent studies have identified over **20 disease-associated genomic loci.** Yet these only explain a small proportion of the genetic variance, indicating that undiscovered loci remain.

Here, we performed a large genome-wide association study of **clinically diagnosed AD and AD-by-proxy** (71,880 cases, 383,378 controls). AD-by-proxy, based on parental diagnoses, showed strong genetic correlation with AD ($r_g = 0.81$).

Meta-analysis **identified 29 risk loci, implicating 215 potential causative genes**.

Associated genes are strongly expressed in immune-related tissues and cell types (spleen, liver, and microglia).
Gene-set analyses indicate biological mechanisms involved in lipid-related processes and degradation of amyloid precursor proteins.

We show strong genetic correlations with multiple health-related outcomes, and Mendelian randomization results suggest a protective effect of cognitive ability on AD risk.

Iris E. Jansen et. al. *Nature Genetics* **volume 51**, 2019,pages404–413(2019)