MANCHESTER 1824

The University of Manchester

Cognitive Genetics

(with a side of virtual reality)

12th Jan 2024

Dr Tony Payton

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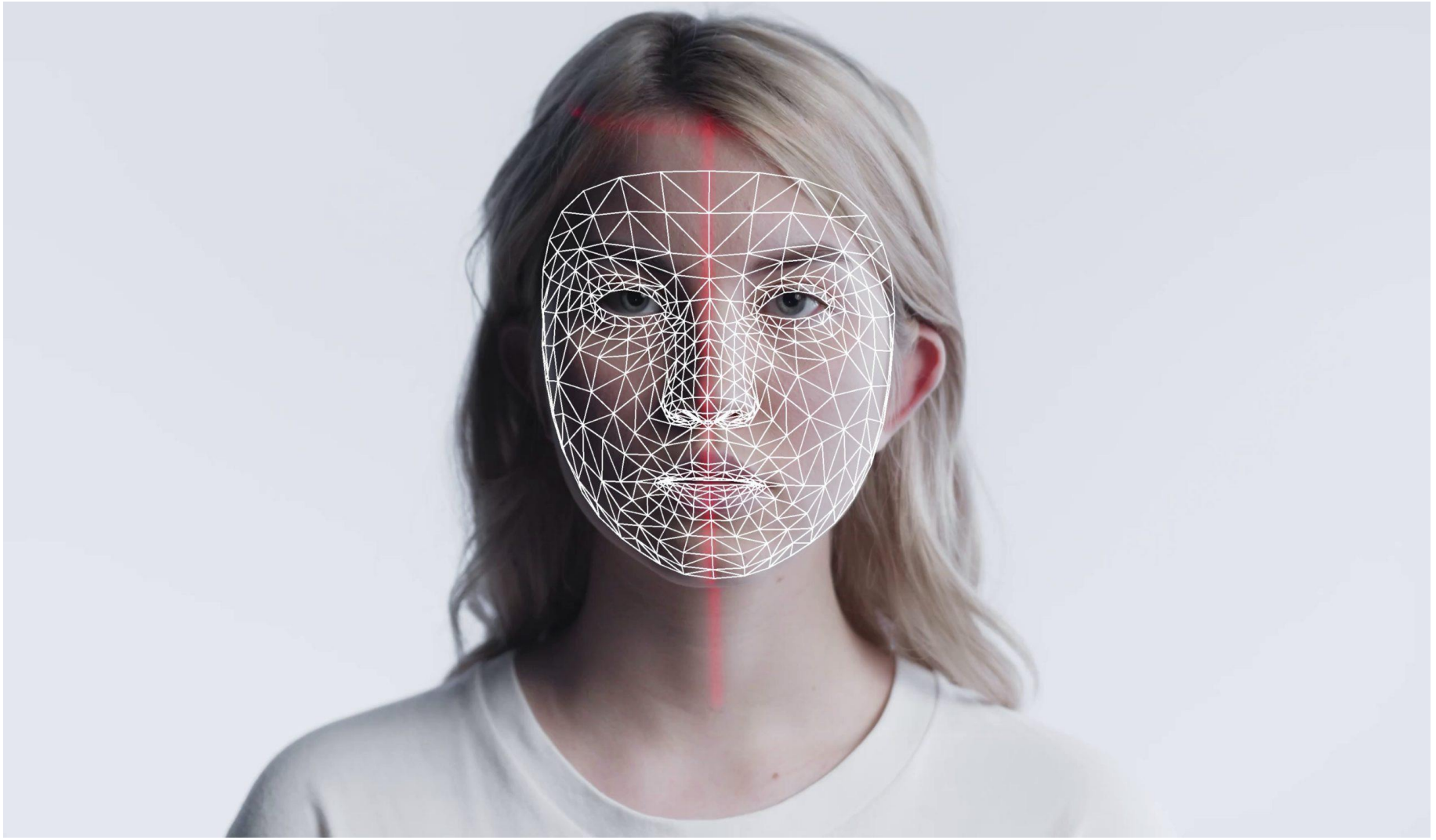
Avatar Creation: Volunteer

Facial Motion Capture



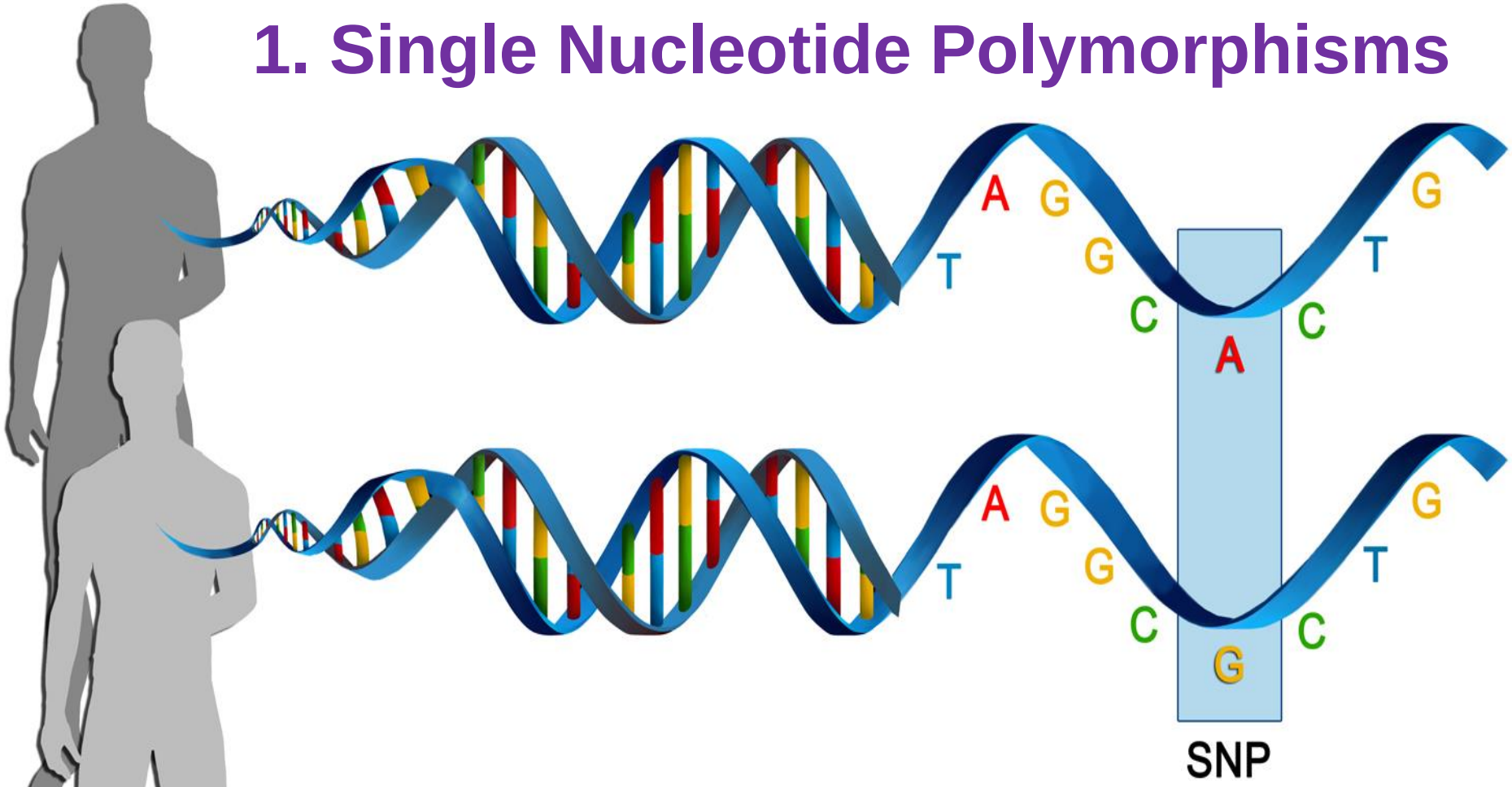
1. Single Nucleotide Polymorphisms

2. Cognitive Genetics

3. Manchester Cognitive Ageing Cohort

4. Virtual Reality/AI and Healthcare

1. Single Nucleotide Polymorphisms



>600 million SNPs in humans

>130,000 identified as pathogenic

Why are variants important?

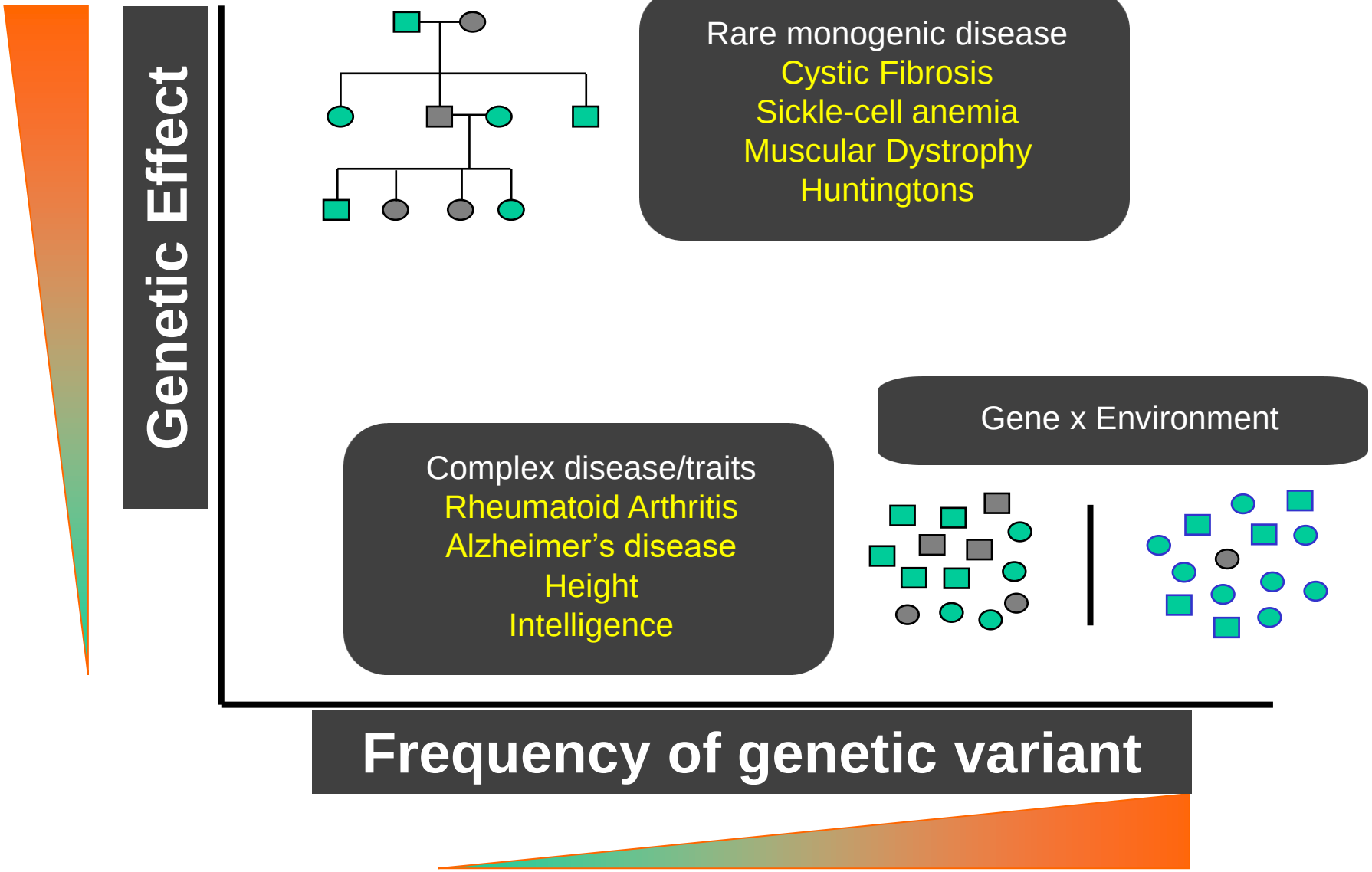
Normal variation
Height
Eye Colour
Intelligence

Differences in response to medication
Antidepressants or cancer treatment

Directly result in a genetic condition
Monogenic Disease/Trait

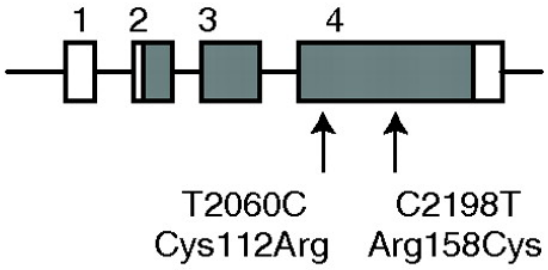
May contribute towards risk of a genetic condition
Complex Disease/Trait

Monogenic (Mendelian) vs Complex Disease/Traits



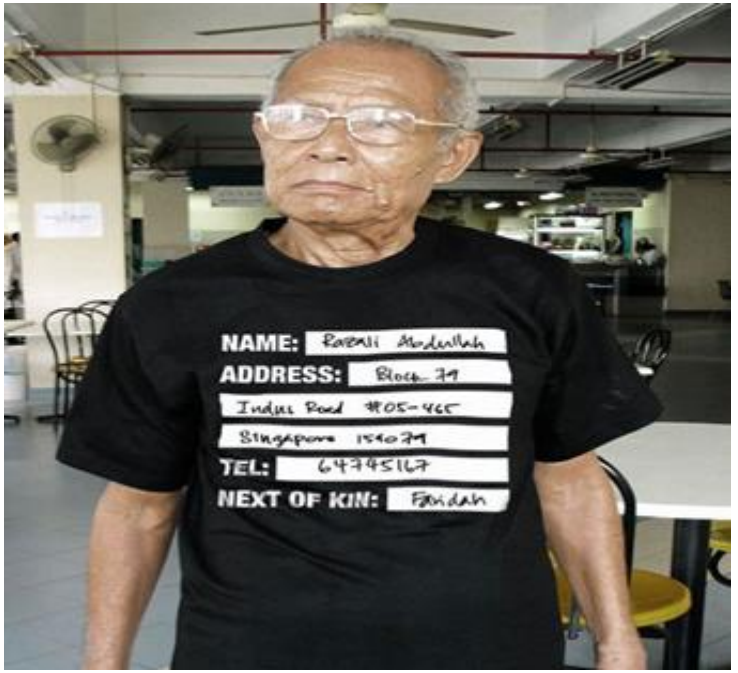
Apolipoprotein E and Alzheimer's disease

A



B

Isotype	aa Position 112	158
ε2	TGC (Cys)	TGC (Cys)
ε3	TGC (Cys)	CGC (Arg)
ε4	CGC (Arg)	CGC (Arg)



Risk of developing AD

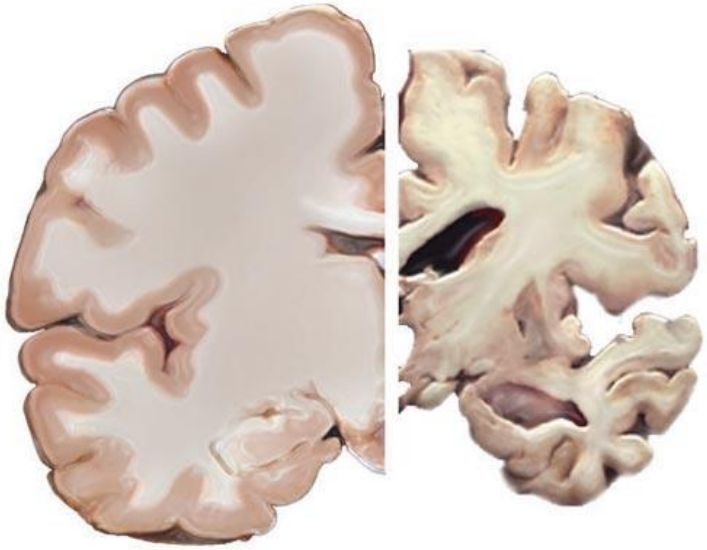
20% no ε4 mean age onset 84yrs

47% one ε4 mean age onset 75yrs

91% two ε4 mean age onset 68yrs

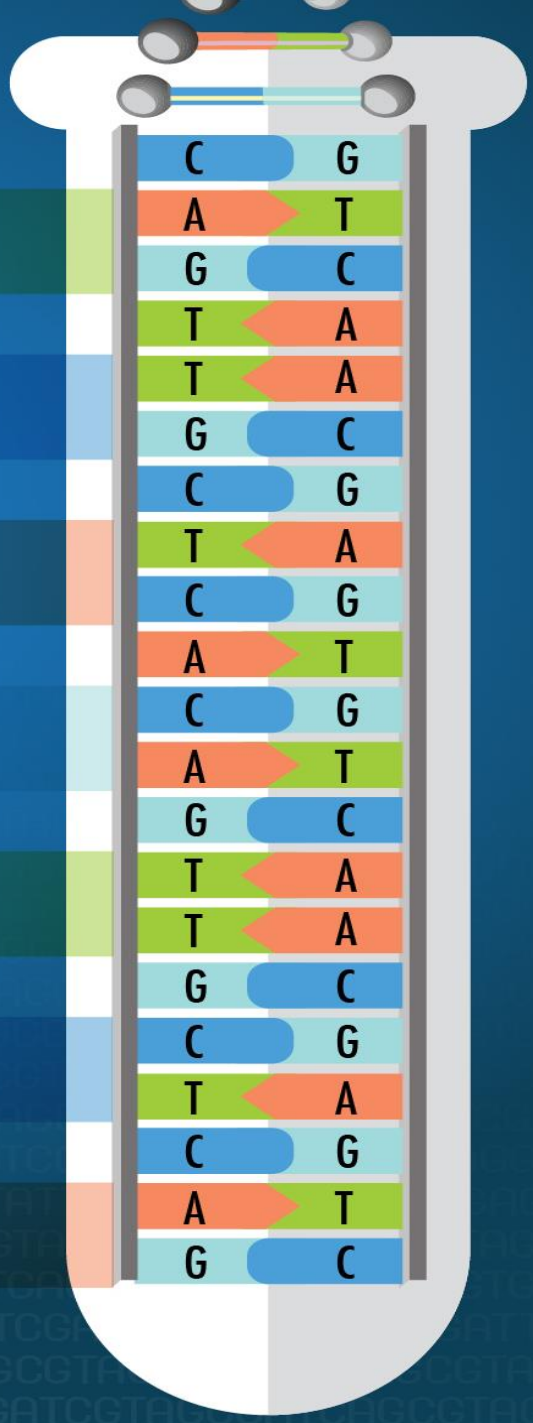
ε4 allele frequency: 14%

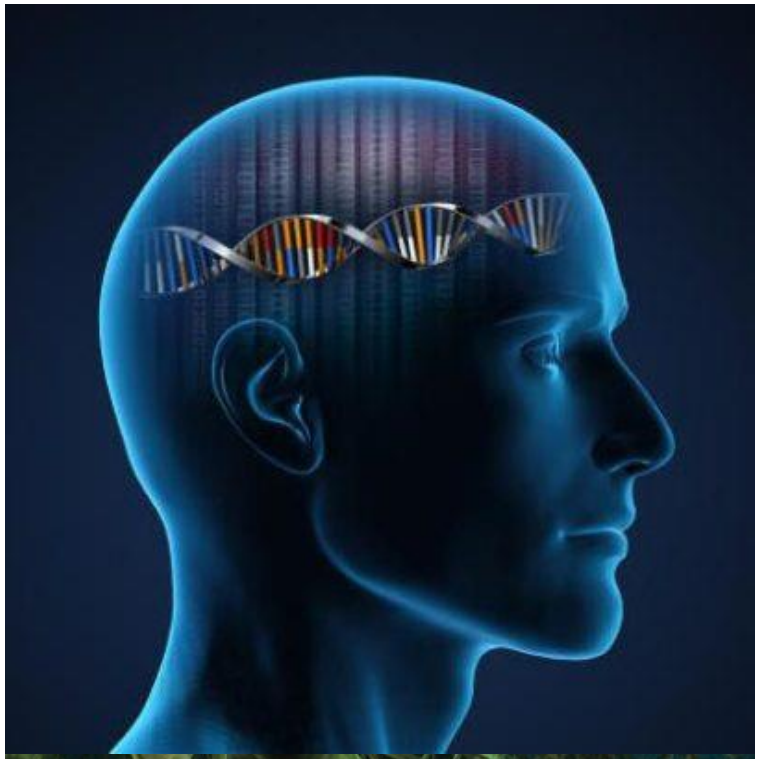
Healthy Brain Severe AD



Genetic Tests Can Help to:

- Diagnose Your Disease
- Pinpoint Genetic Factors That Caused Your Disease
- Predict How Severe Your Disease Might Be
- Choose the Best Medicine and Correct Dose
- Discover Genetic Factors That Increase Your Disease Risk
- Find Genetic Factors That Could Be Passed to Your Children
- Screen Newborns for Certain Treatable Conditions

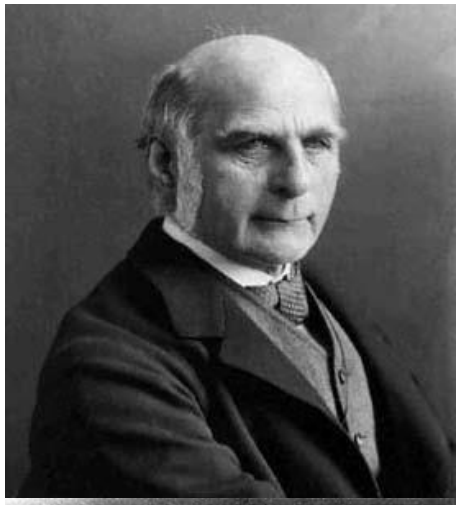


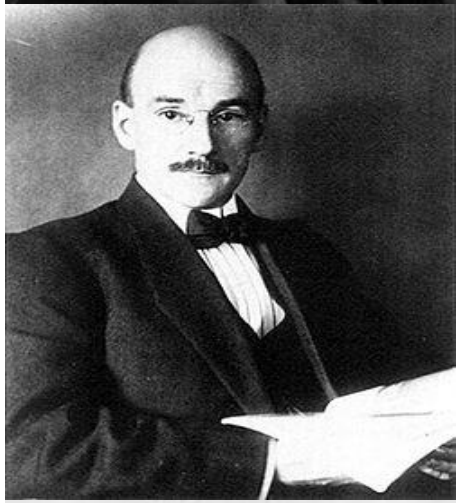


2. Cognitive Genetics

Identification of genetic variants which regulate the level of cognitive ability/decline with age

Memory
Novel Problem Solving
Vocabulary Ability
Processing Speed





A Controversial Past

1883 - Francis Galton

"supplanting inefficient human stock by better strains, by such efforts as may be reasonable, to further the ends of evolution more rapidly"

Galton F. (1883). Inquires into human faculty. Macmillan. London

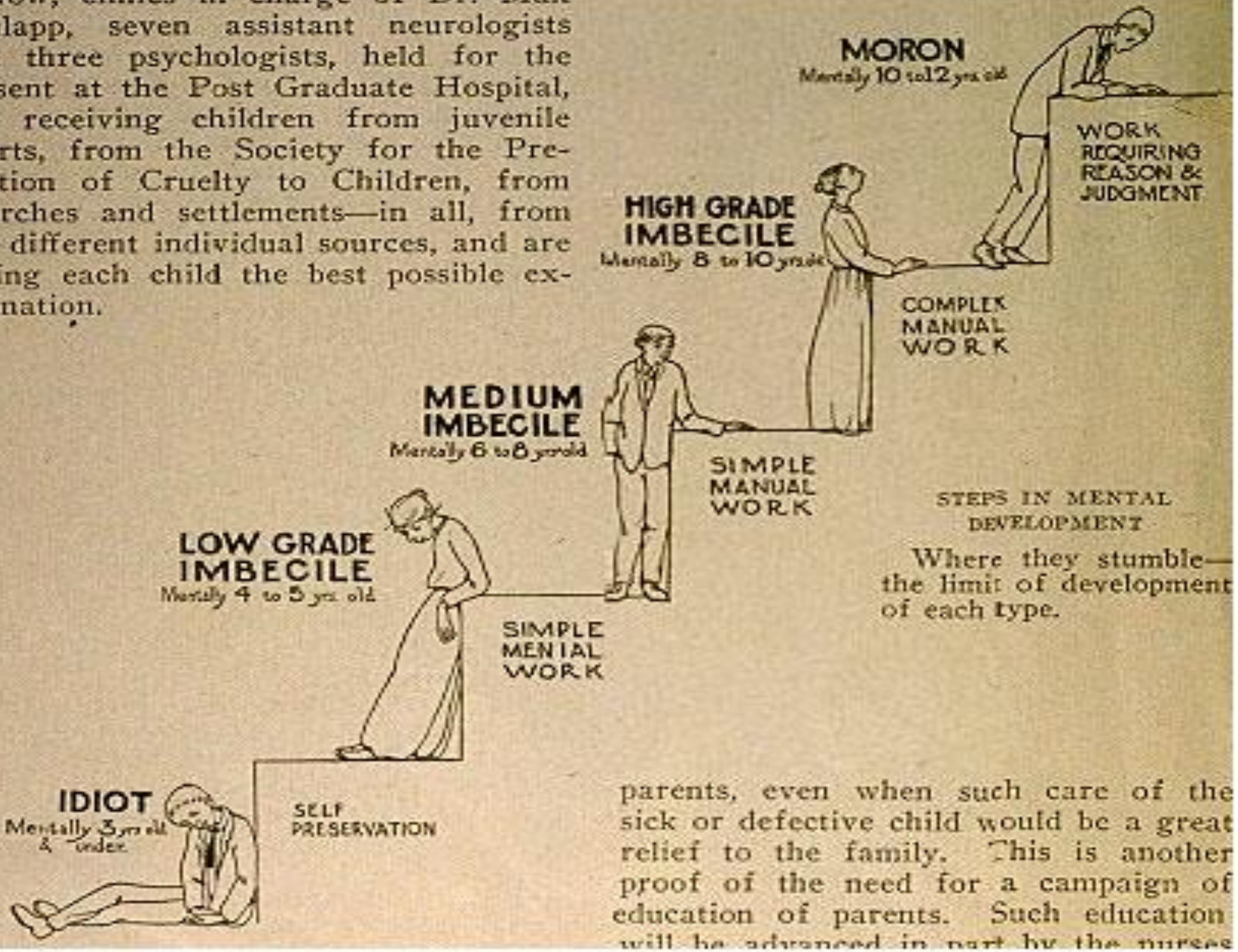
1900 - Henry Goddard

IQ test rankings: "idiots, imbeciles, and morons"

1912 - Tests used at Ellis Island

Discovered that large percentages of the new immigrants were "feeble-minded".

Now, clinics in charge of Dr. Max Schlapp, seven assistant neurologists and three psychologists, held for the present at the Post Graduate Hospital, are receiving children from juvenile courts, from the Society for the Prevention of Cruelty to Children, from churches and settlements—in all, from 47 different individual sources, and are giving each child the best possible examination.



STEPS IN MENTAL DEVELOPMENT

Where they stumble—the limit of development of each type.

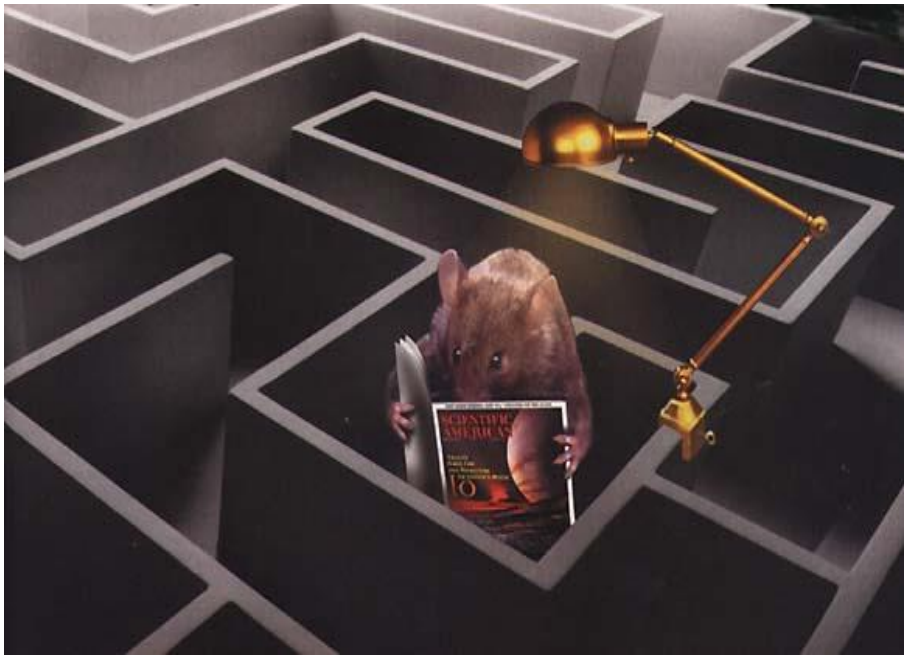
parents, even when such care of the sick or defective child would be a great relief to the family. This is another proof of the need for a campaign of education of parents. Such education will be advanced in part by the nurses

A Controversial Future?

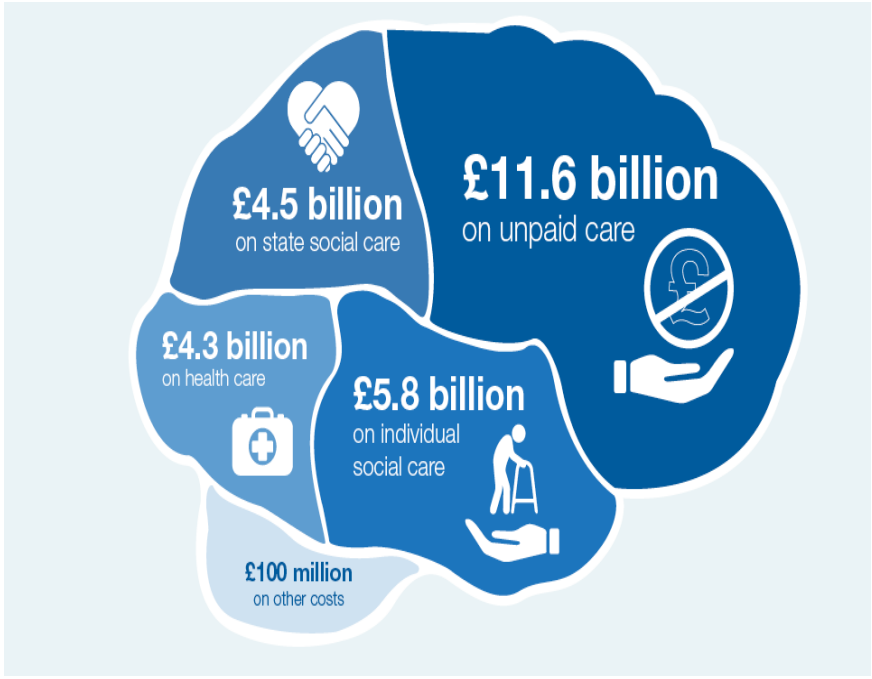
Ethical to develop “super-human” intellect?

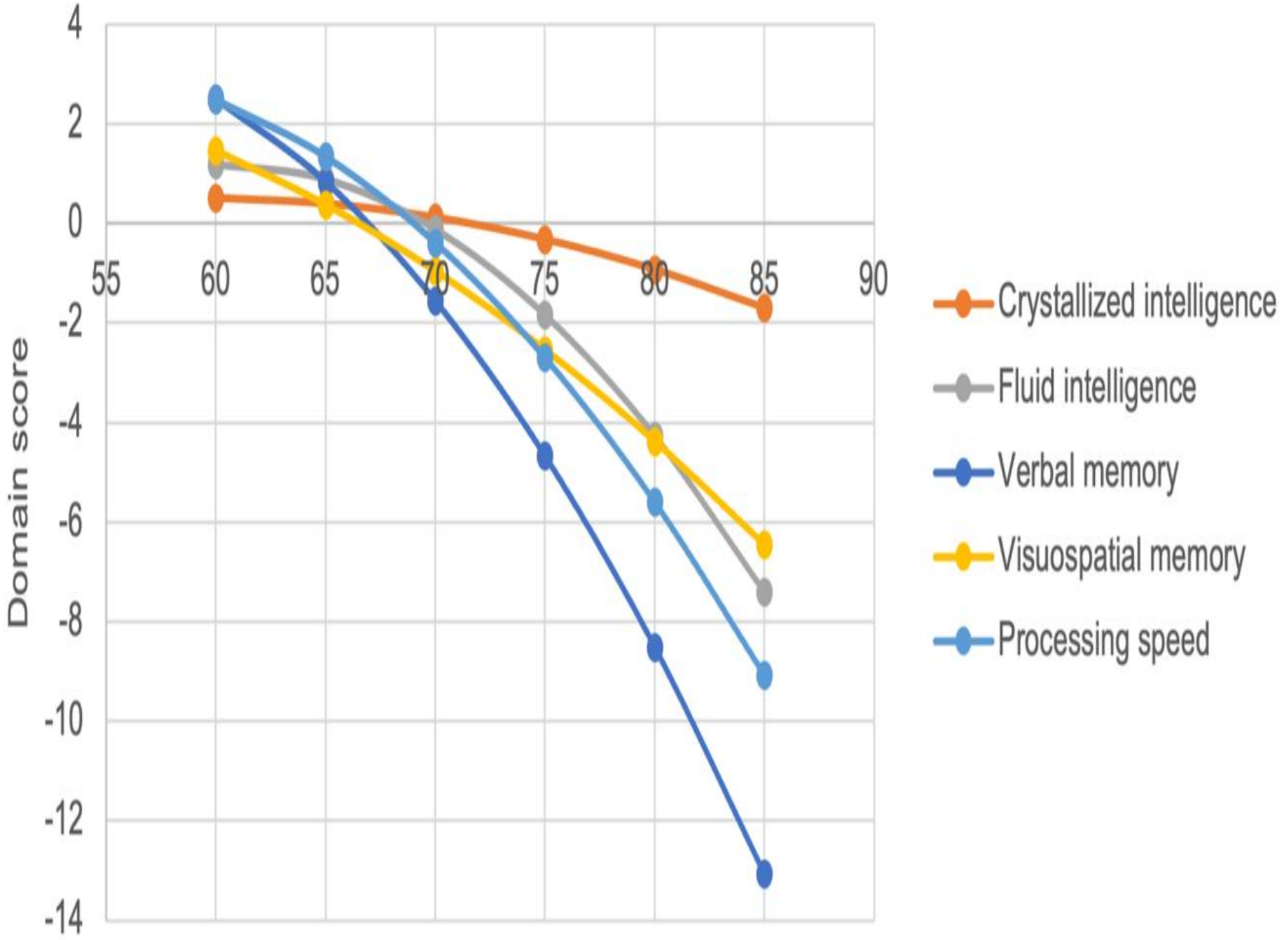
Will only the very rich have access to new drugs/tech?

Should we screen embryos to select for intelligence?



Cognitive impairment UK: >£26 bill




4
2
0
-2
-4
-6
-8
-10
-12
-14
55
60
65
70
75
80
85
90
Domain score
Crystallized intelligence
Fluid intelligence
Verbal memory
Visuospatial memory
Processing speed

3. UoM Cognitive Ageing Cohort (1982)

>6500 volunteers aged 50yrs +
Manchester and Newcastle
66% female
Almost all Caucasian
Dementia was exclusion criteria

Follow-up of up to ~36 yrs

95% of volunteers now deceased

Data

Sociodemographic

PDQ (159 employment, health/medication, daily activity, hobbies, family members)

Cognition (28)

Fluid, memory, processing, speed, vocabulary

Mental Health

Depression, personality, life-events, life satisfaction, dementia status

General Health

Cornell Medical Index (263)

Clinical Measures

Balance, BP, BMI, Lung Volume, MRI (brain region volumes), Cortisol, Pain, Dysphagia, Hearing loss

Sleep

Pittsburgh Sleep Quality index
Sleep Timing Questionnaire
Sleep efficiency measures

~1000 unique measures

Biological Material

Manchester Brain Bank
Prof Federico Roncaroli
Andy Robinson
Yvonne Davidson

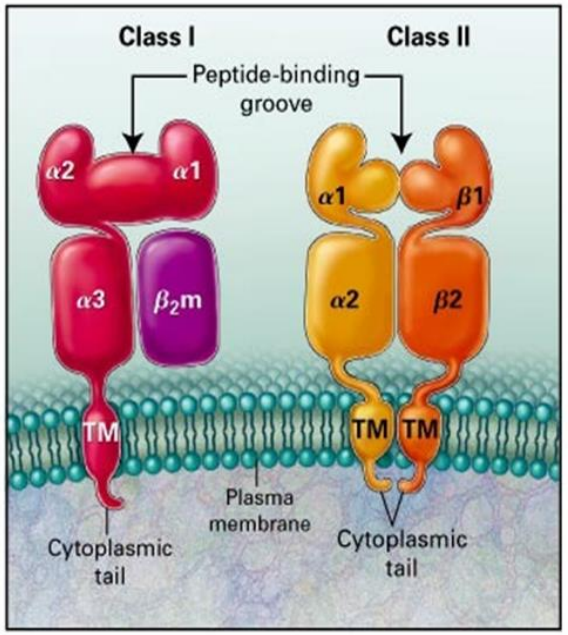
Brains (~140)
Brain Weight
Braak Stage
CERAD Score
Primary age-related tauopathy
Clinical diagnosis
WMH
Cerebral blood flow

Biological Material

1563 DNA samples (minimum of 17 years follow-up)

GWAS imputed to 1000 genomes, HRC, HLA (Impute 2)
Epigenetic, CNVs, Transcriptomic

Plasma, Serum (600)



>100 publications with ~75 genetic

Cognition, Dementia, Pain, Dysphagia, Depression, Longevity

1. Manchester-Edinburgh Collaboration

GWAS cognitive ability and non-pathological decline

BBSRC £1.3 mill, 2008

3500 volunteers (≥ 50 years)

MANCHESTER 1824

The University of Manchester

BBSRC

bioscience for the future

LBC 1936

THE UNIVERSITY of EDINBURGH

Intelligence (h^2 =51%)

GWAS unrelated individuals

Consistent with twin studies

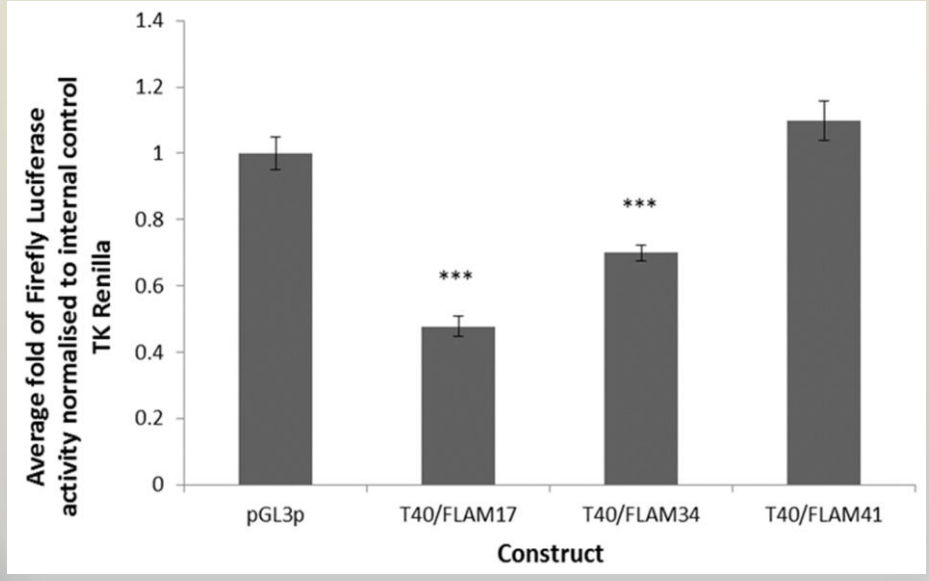
Davies et al. Mol Psych. 2011. 16: 996-1005

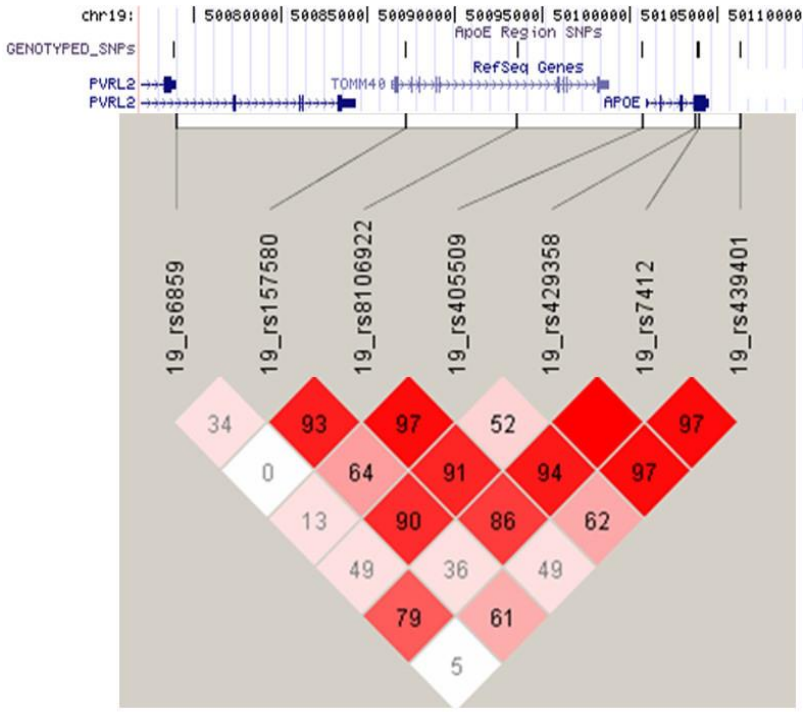
TOMM40/APOE locus

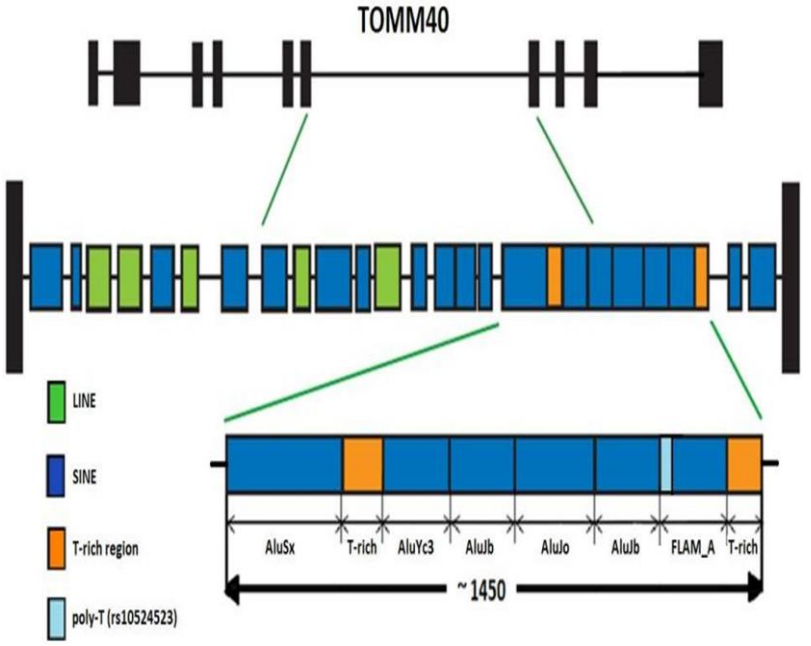
Associated with cog decline

Davies et al. Mol Psych. 2014. 19: 76-87

Payton et al. Neurobiol Aging. 2016.39:217.e1-7



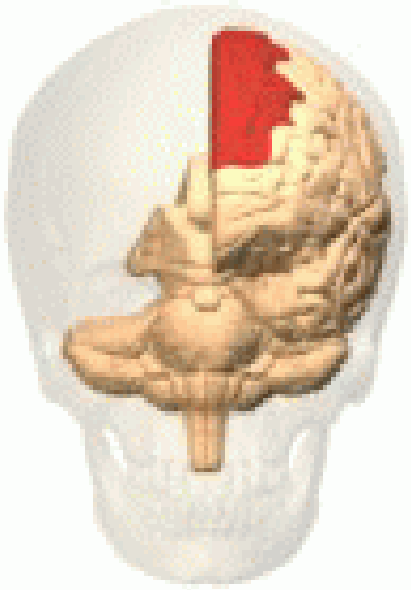


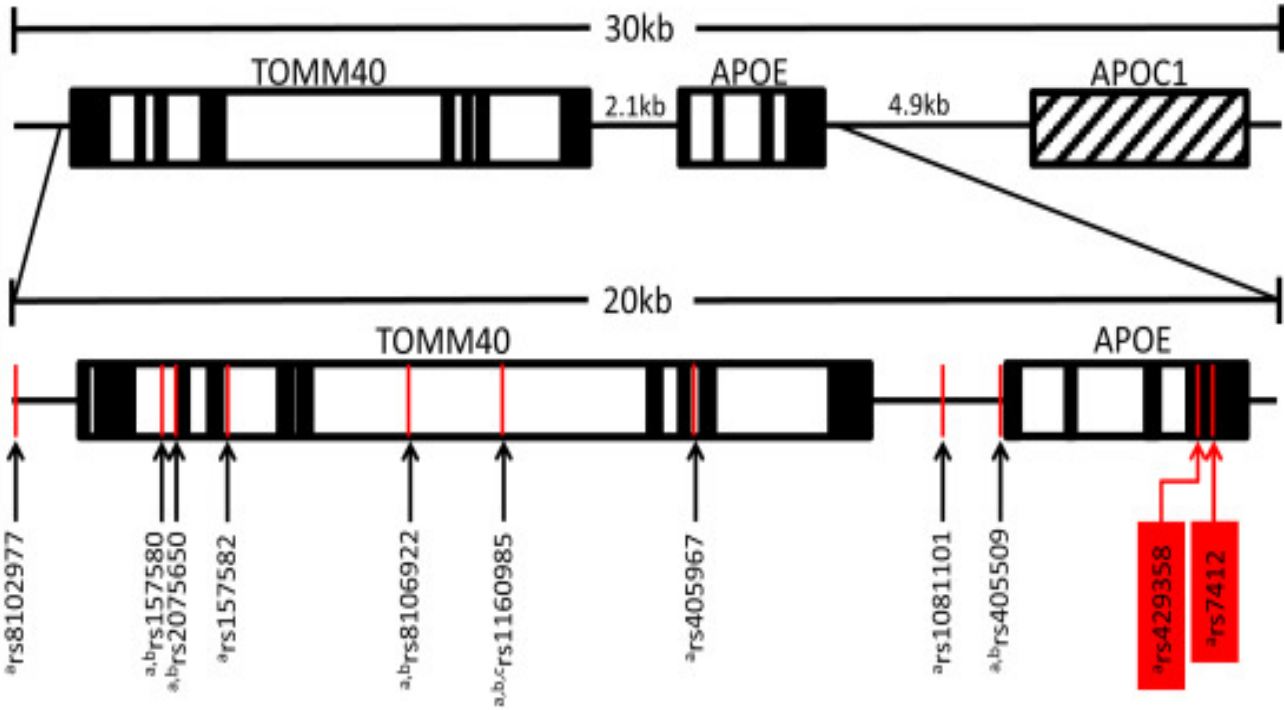


APOE levels and DNA methylation in superior frontal gyrus

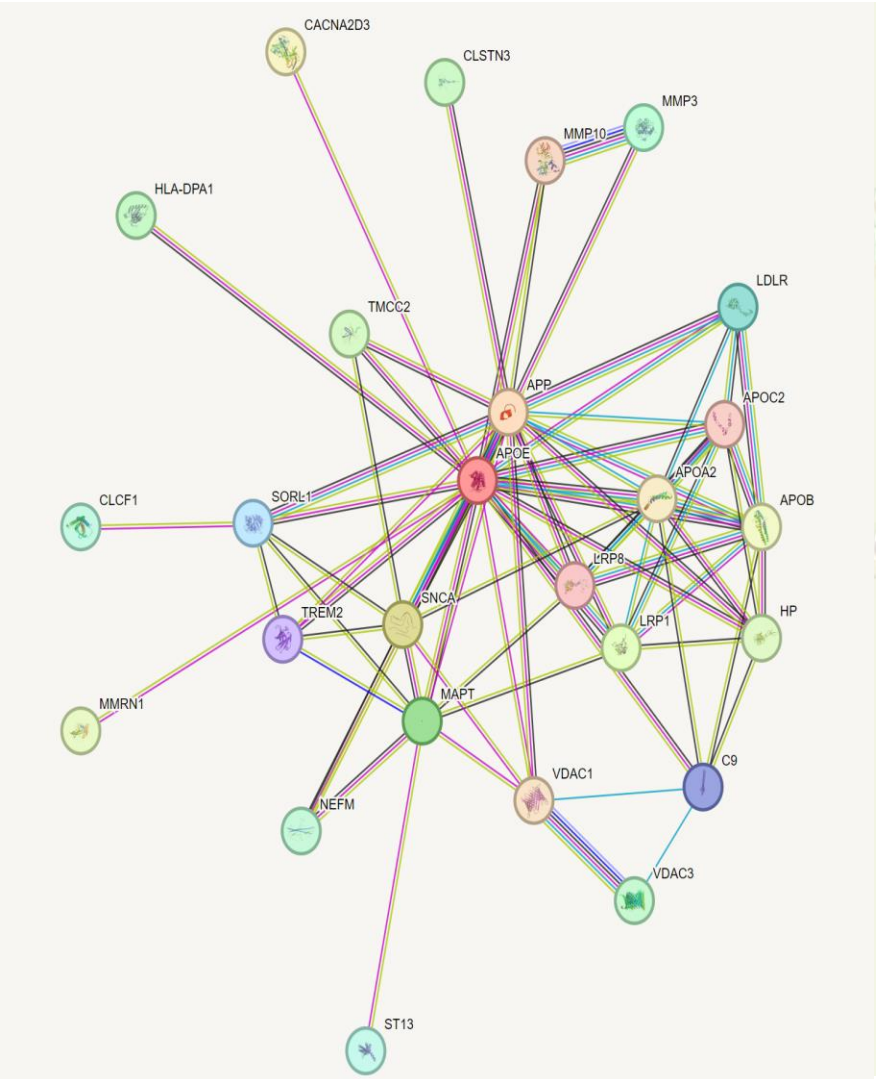
DNA methylation at TOMM40 promoter was associated with Aβ plaques and rate of cognitive decline

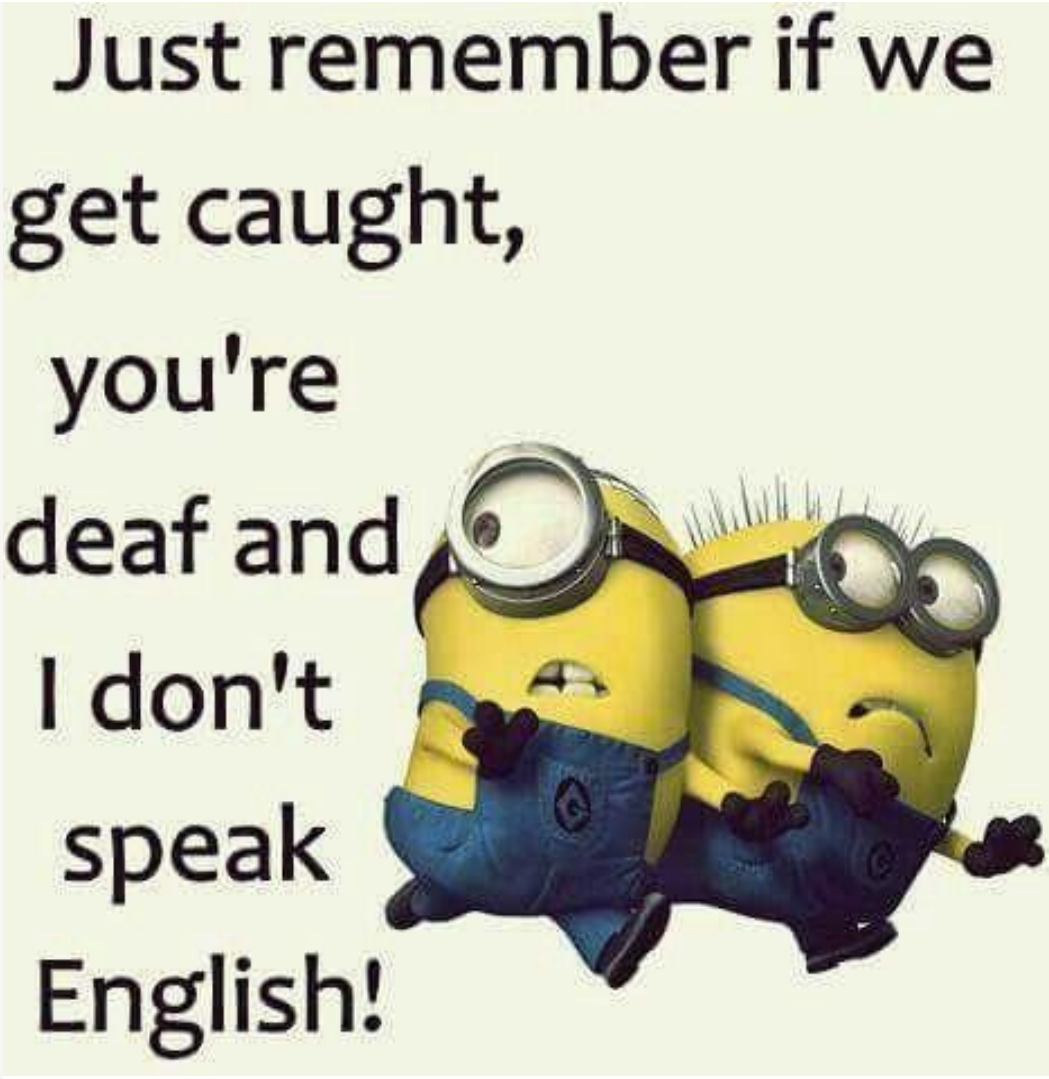
APOE ε4 carriers had significantly higher methylation in the promoter region compared to non-ε4 carriers





THM-1: Genetic variants are likely to have partners in crime



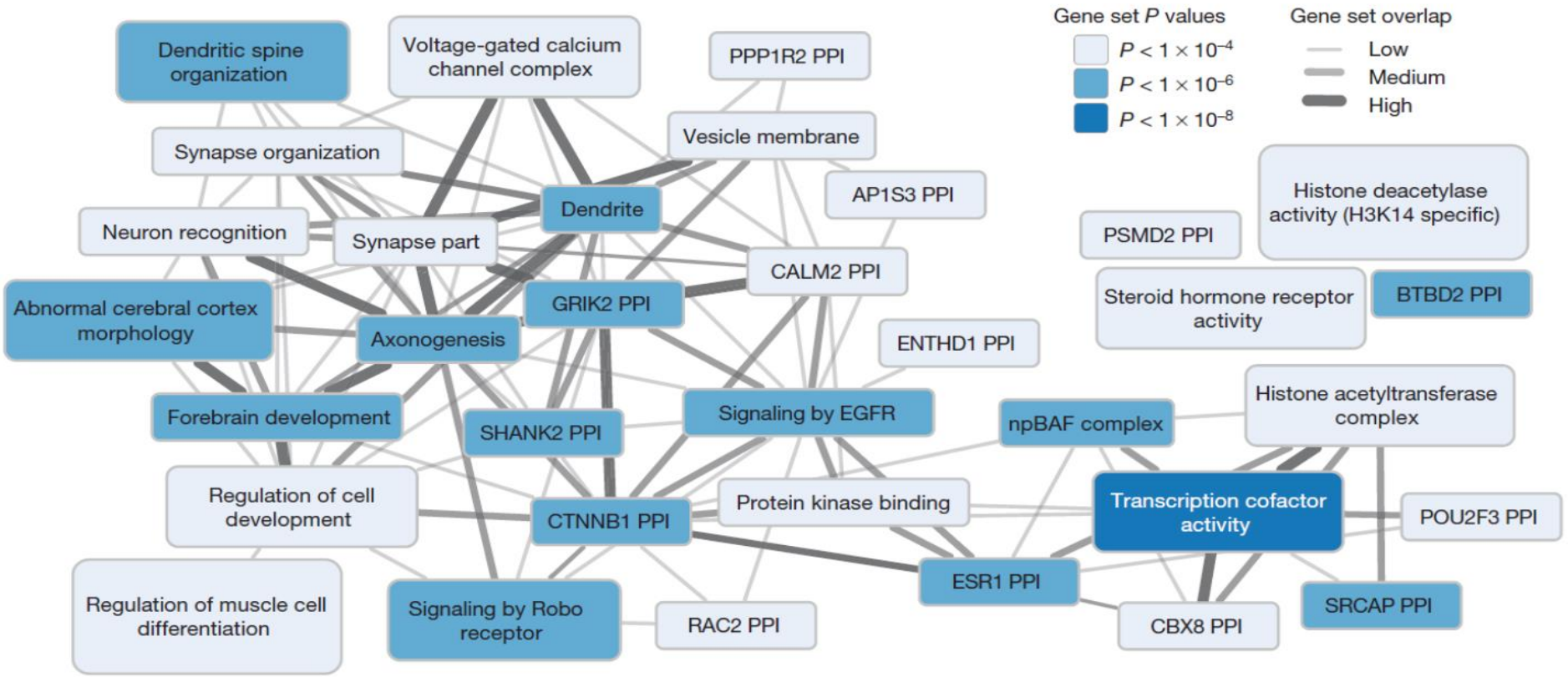


2. Educational Attainment (COGENT consortium)

293,723 individuals, 30+ yrs, European decent, ~9.3M SNPs

74 independent genome-wide significant ($5x10^{-8}$) loci identified
Okbay et al. 2016. Nature. 533: 539-42.

3 million individuals; 3952 independent SNPs identified
Okbay et al. 2022. Nature Genetics. 54(4):437-449



THM-2: Seek collaborators

Increase statistical power

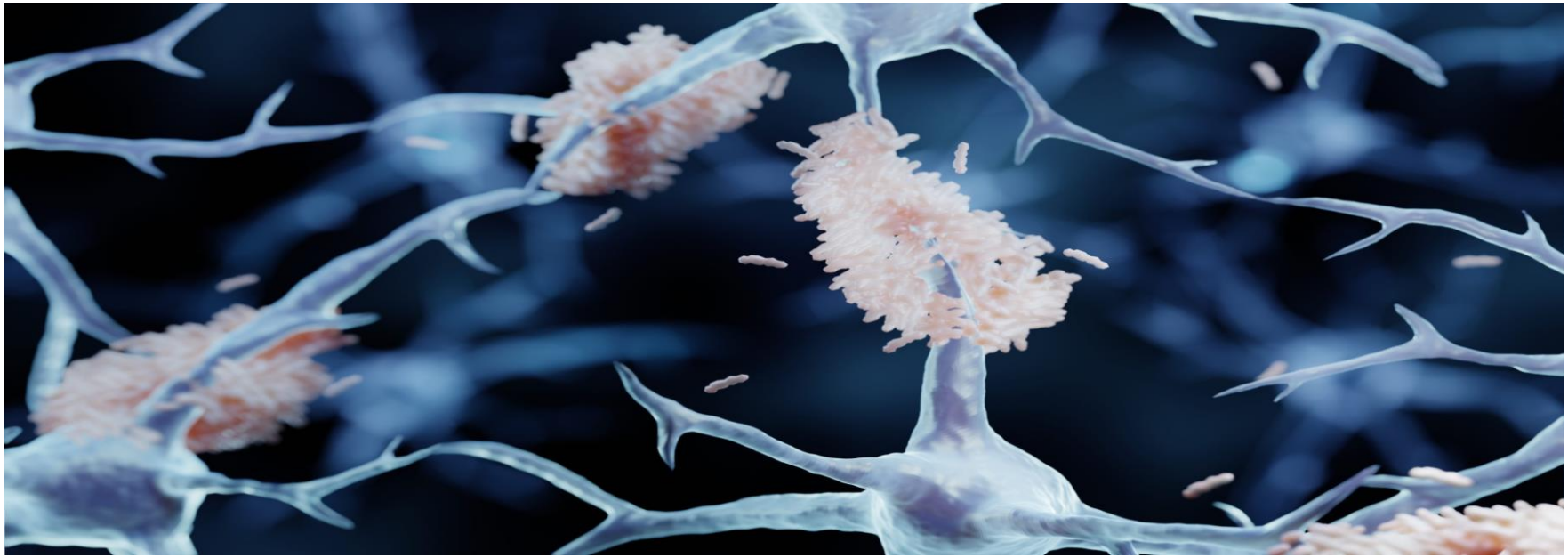
Learn from one another

3. Effect of hypertension on AD pathology

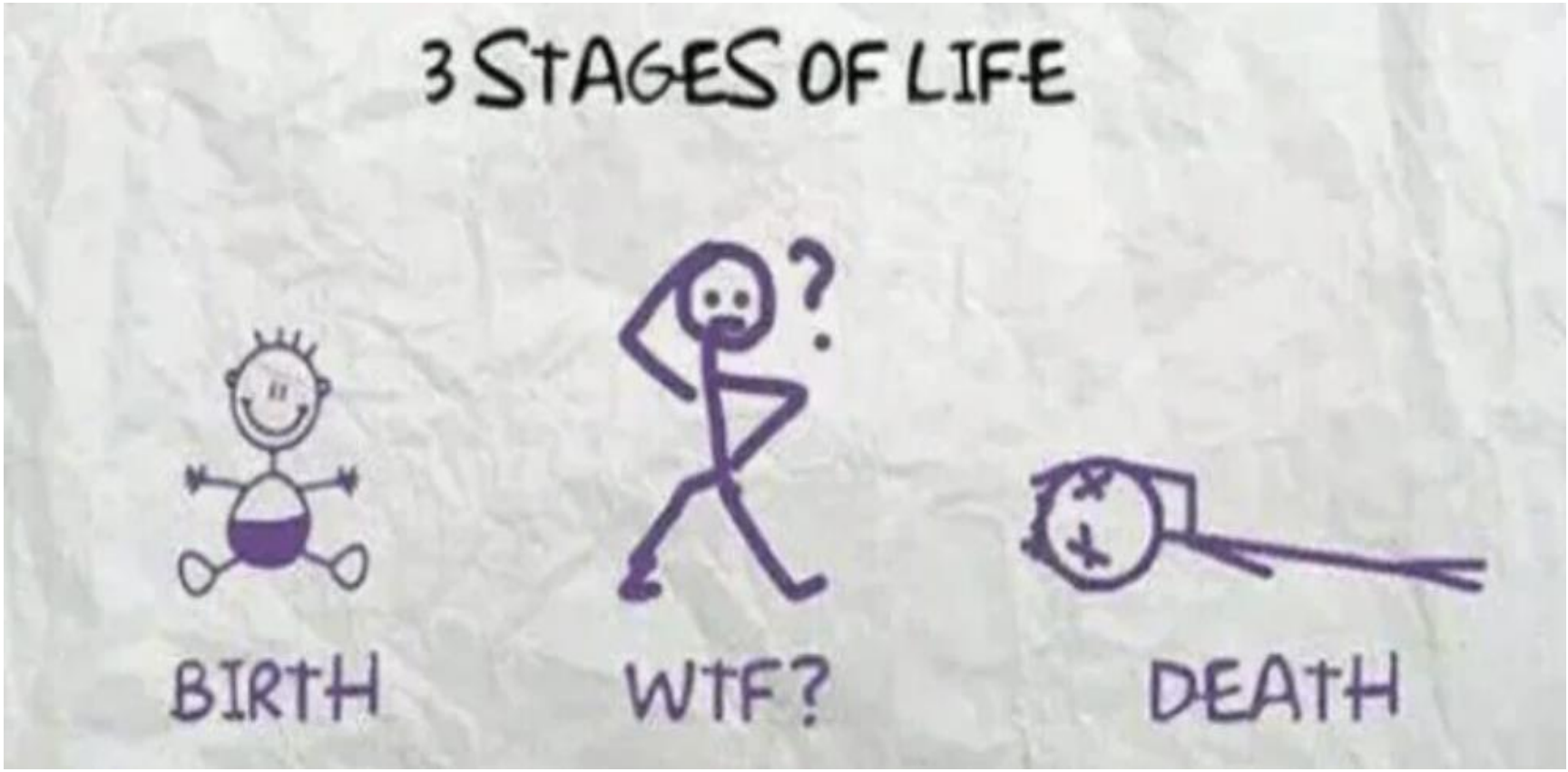
Mid-life (40-65 years) hypertension is a significant risk for vascular dementia and AD.

Late-life (>65 years) is more complex with some studies suggesting that hypertension may be protective against cognitive decline and dementia.

Late-life hypertension reduces AD pathology, possibly mediated by increasing blood flow to brain and helping Aβ clearance.



THM-3: Risk factors may change throughout life



Future studies

Most of the research has used cognitive measures, but there's a lot of data that hasn't been investigated in detail:

Life-long learning
Pollution
Depression
Personality
General Health
Imaging (WMH, brain volumes)

Summary not itemised data used; 25% data still not entered

NGS, other OMICs

Phenotype	Measures	Longitudinal	Time Points	Years	Number of Volunteers	Number of measures
01_Sociodemograpic	Karasek Job Content Questionnaire	N			3788	2
	Personal Details Questionnaire	Y	7	24	6372	159
02_Cognition	Multiple tests for memory, processing speed, fluid intelligence and vocabulary (inc. TICS)	Y	11	35	6356	26
	Cognitive Failures Questionnaire	N			4071	1
	Telephone Interview for Cognitive Status (TICS)	Y	5	13	865	1
03_General Health	Cornell Medical Index	Y	4	12	2809	263
	Hearing Loss	N			265	3
04_Mental Health	Beck, Yesavage and Geriatric Depression Tests	Y	11	29	5482	3
	Eysenck Personality Questionnaire	N			3523	4
	Negative Life Events	Y	4	19	3510	2
	Personality Intellectual Ageing Contexts	Y	2	11	1881	3
	Satisfaction with Life Scale	N			549	6
	Self Awareness Questionnaire	N			3719	4
05_Clinical	Various (inc. balance, blood pressure, BMI, lung volume)	N			580	33
	Heamoglobin A1C and Cortisol	N			580	10
	Pain	N			751	67
	Dysphagia	N			627	18
06_Sleep	Loughborough Sleep Diary	Y	7	1	465	92
	Personal Details Questionnaire: Sleep	Y	4	25	6000	21
	Pittsburgh Sleep Quality Index	N			477	34
	Sleep Study Health Questionnaire	N			477	92
	Sleep Timing Questionnaire	N			467	25
07_Death Registrations	Date of death and dementia status	N			6000	8
08_Brain/Neuopathology	Brain weight, neuropathology diagnosis, clinical diagnosis, CERAD, Thal, Braak, Synaptic Density	N			126	12

4. Virtual Reality/AI and Healthcare

What is Virtual Reality?

Computer-generated simulation of a 3D image or environment that can be interacted with in a seemingly real or physical way.

AI/VR: STAKEHOLDER BENEFITS

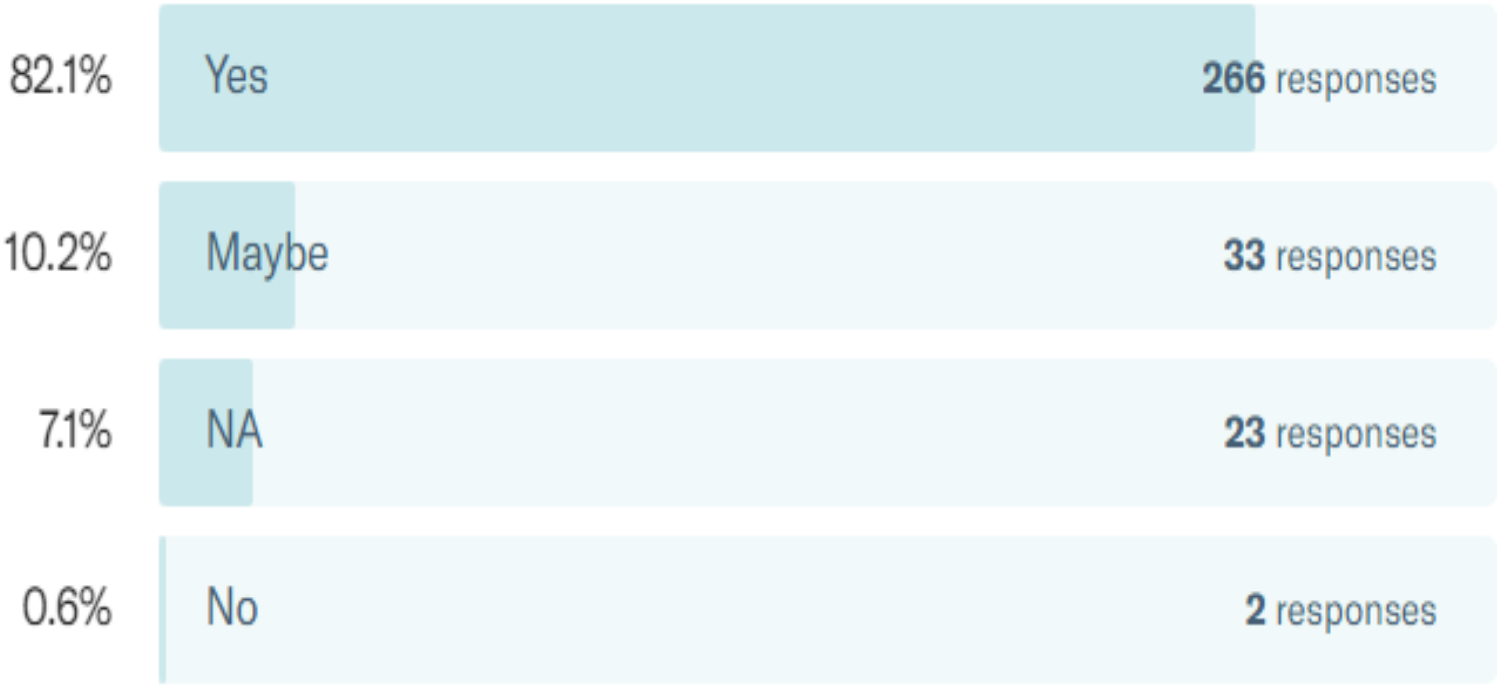
TEACHING STAFF	STUDENTS	HEALTHCARE INDUSTRY
Remove need for repeated training (time and cost saving)	Ability to practice Immediate performance related feedback	Better trained professionals Improved patient safety

VR Evaluation 2019

✓ 16

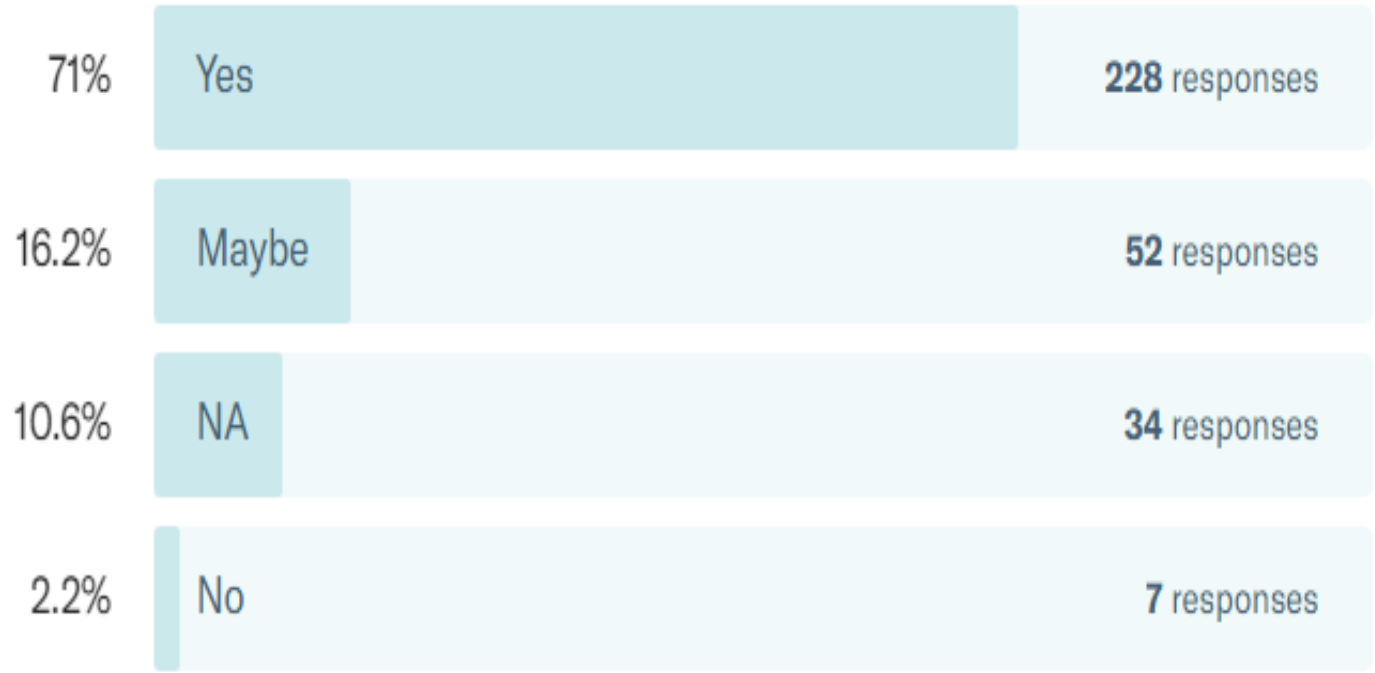
Would VR enhance your learning experience?

324 out of 333 people answered this question



✓ 17 **Would you more likely enrol on a course that includes VR as a teaching tool?**

321 out of 333 people answered this question




Sentira XR
Transforming healthcare training and improving
patient safety through Virtual Reality and
Natural Language Processing

Evolution of VR/AI technology

2019

2020

2023

2024?

Integrated with Meta AI Chatbot

Useful for HE

- Light Weight (0.5kg)
- Transportable
- Reasonably Priced
- Easy to use

Live Video-based AI Facial Mocap

Other VR/AI Functionality

Eye Tracking

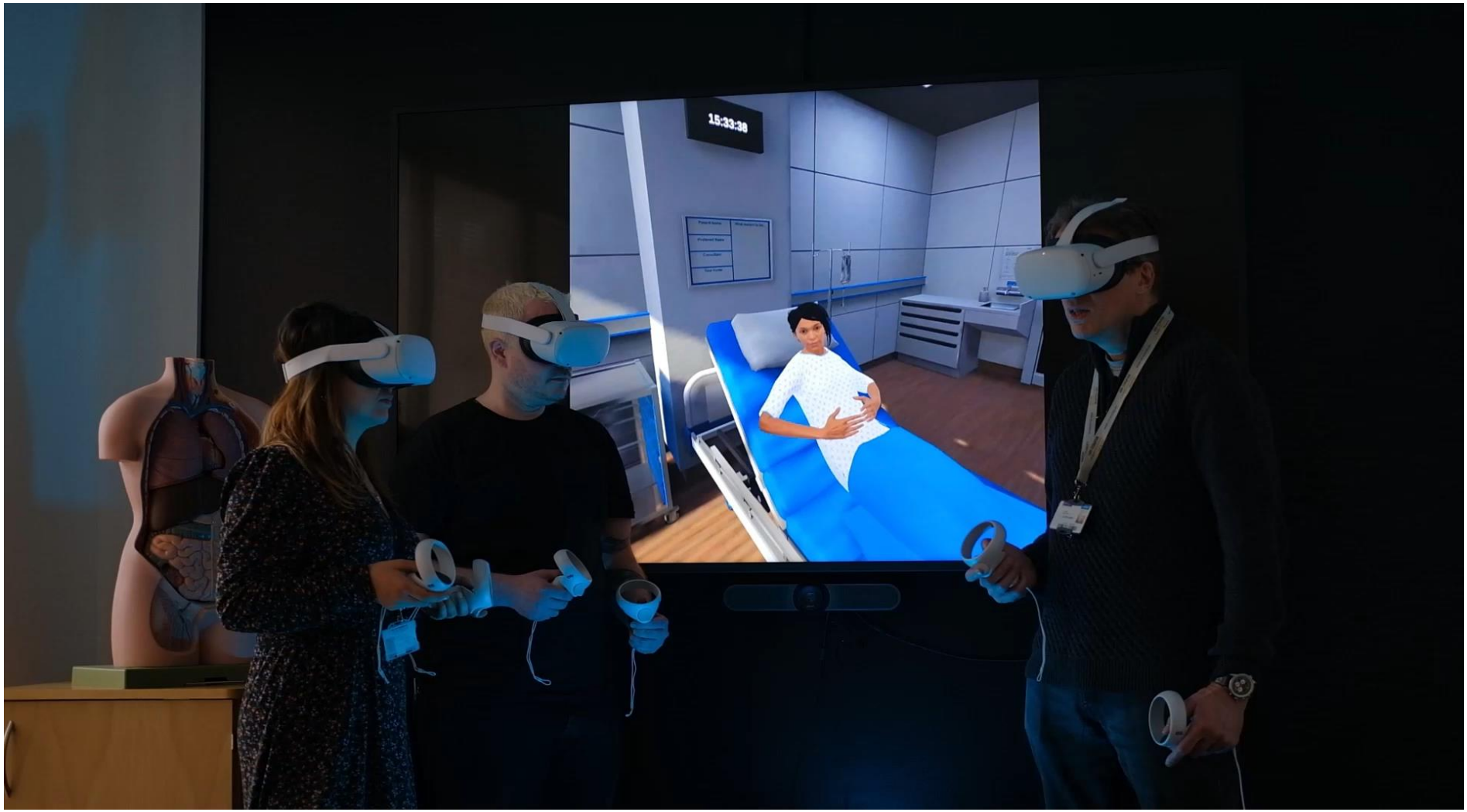
Hand Tracking

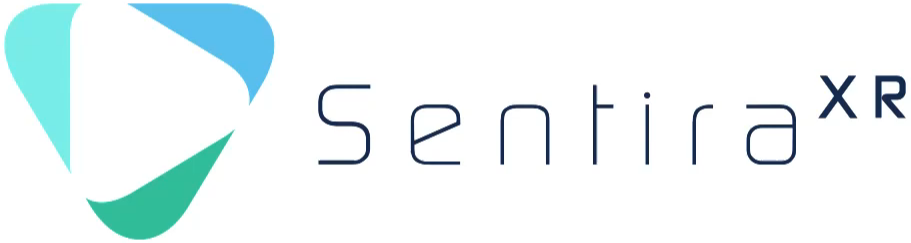
Voice Cloning

Monitoring Behaviour


“
엄마, 어디 있었어?
항상... 네 곁에...

Natural Language Processing




SentiraXR


SentiraXR

VR@Manchester

The VR@Manchester working group is bringing together people from across the University for series of VR demonstrations and to look at the current state of XR at the University. All University staff, researchers and PGRs are welcome.

Feb. 28, 2024 14:00 — 16:00

4.204 University Place

tony.payton@sentiraxr.com