Het Puberbrein onder de Loep

On influences of genes and environment on changes in brain health and mental health

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Questions

- How do individual differences in genes and environment influence brain health and mental health?
- What biological mechanisms are underlying?
- Is brain plasticity the key?
- *What is the role of self-regulation?*

Brain plasticity implies that the brain is capable of changing neurons, *reorganizing networks* and changing their function via new experiences

- Occurs throughout the lifetime
- Age dependent
- Brain region dependent
- Involves a variety of processes
- and can happen with different experiences

Steele and Zatorre, Review, Nat Neurosci 2018

Optimizing brain health across the life course
WHO Position Paper, 2022

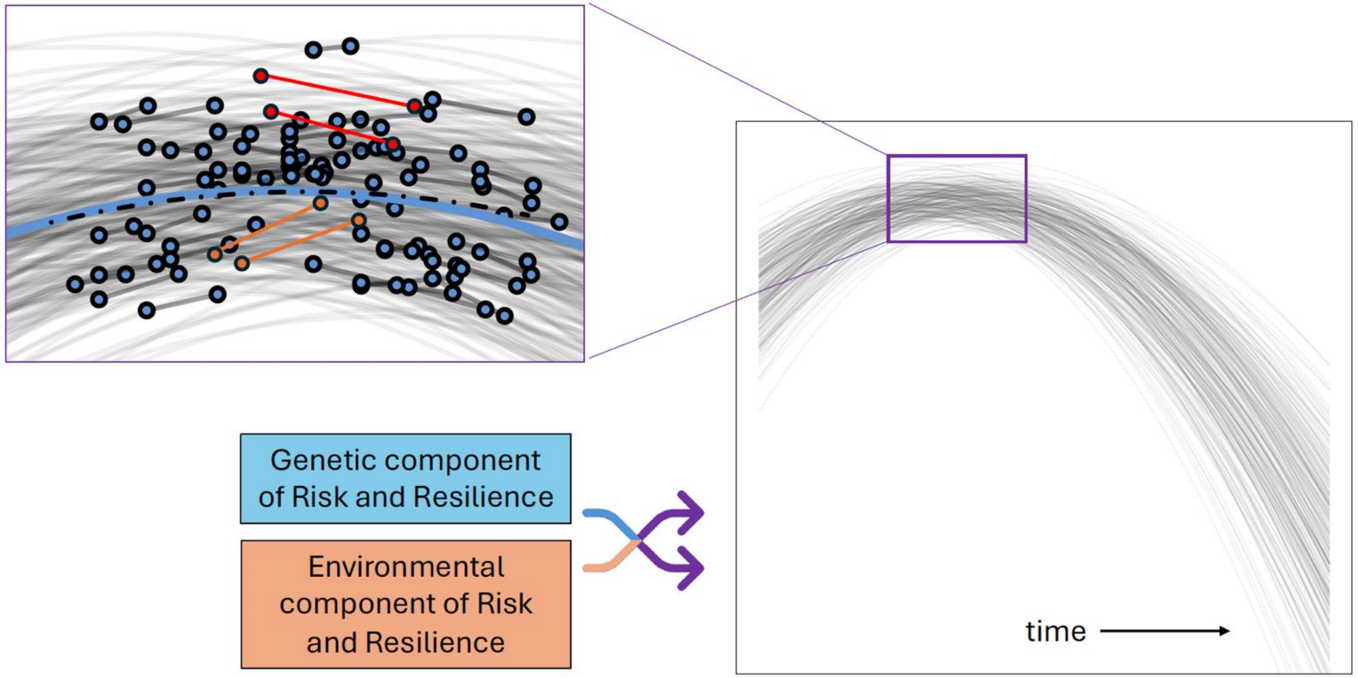
- **Brain health** defined as the state of brain functioning across cognitive, sensory, social-emotional, behavioral, and motor domains, allowing a person to realize their full potential over the life course, irrespective of the presence or absence of disorders

- **Mental health** defined as a state of well-being in which an individual realizes his or her own abilities, is able to cope with the normal stresses of life, can work productively, and is able to contribute to his or her community

- WHO acknowledges that **many of the risk and protective factors** that impact mental health (e.g., social adversities, air pollution, physical activity) are likely **mediated through changes in brain structure and/or function**

In: Hulshoff Pol and Brouwer, Neuron 2025

Brain health and mental health ***change*** throughout life, during development and aging



Hulshoff Pol and Brouwer, Neuron 2025

Unique opportunities and challenges of longitudinal approaches in studying brain health and mental health

Box 1. Opportunities and challenges of the longitudinal setup

OPPORTUNITIES

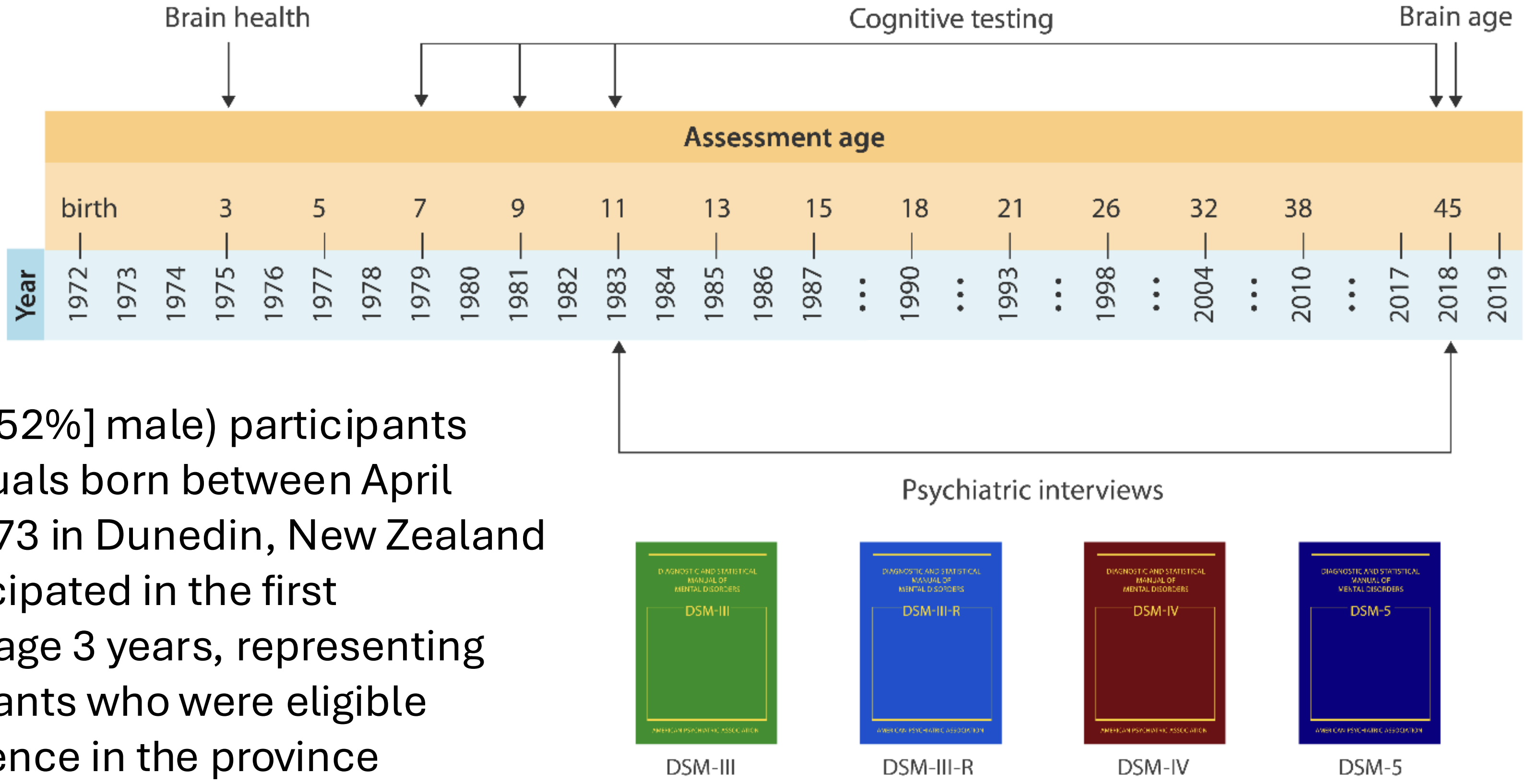
Unlock unique information on intra-individual variation during development and aging
Establish factors that can predict health outcome in the future, e.g., through mediation
Disentangle stable from varying factors of development and aging
Improve signal to noise of both stable and varying factors

CHALLENGES

Maintain high data quality over time when individuals miss out on waves (attrition rate) with risk of inclusion bias
Ensure high stability of measurements while equipment ages, updates are installed, and new advances are made
Consider economic costs and longer duration of the study
Choose the optimal model, with appropriate number of waves and length of time intervals

Hulshoff Pol and Brouwer, Neuron 2025

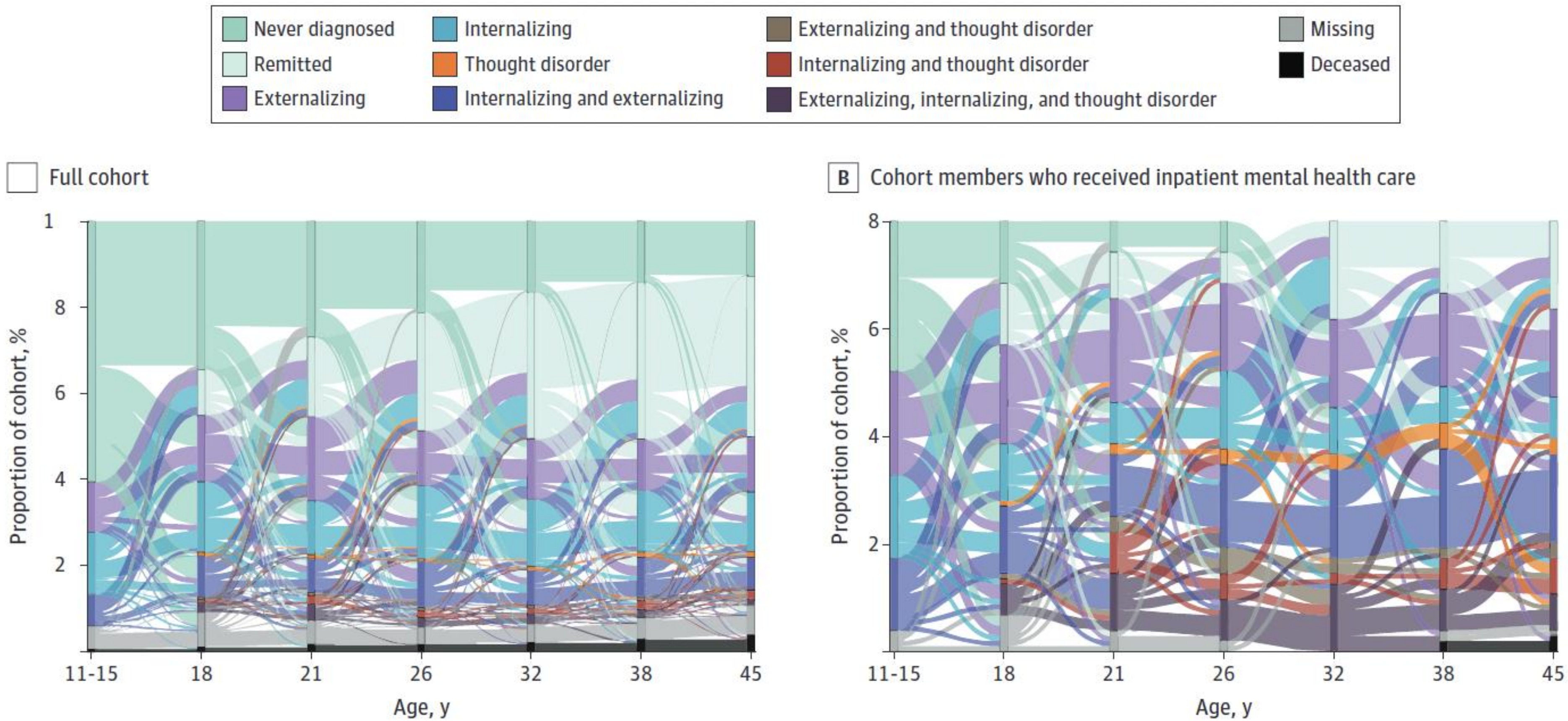
The population-representative Dunedin Cohort



The 1,037 (535[52%] male) participants were all individuals born between April 1972-March 1973 in Dunedin, New Zealand (NZ), who participated in the first assessment at age 3 years, representing 91% of participants who were eligible based on residence in the province

Caspi et al, JAMA Network Open, 2020

Brain health and mental health ***change*** throughout life, during development and aging

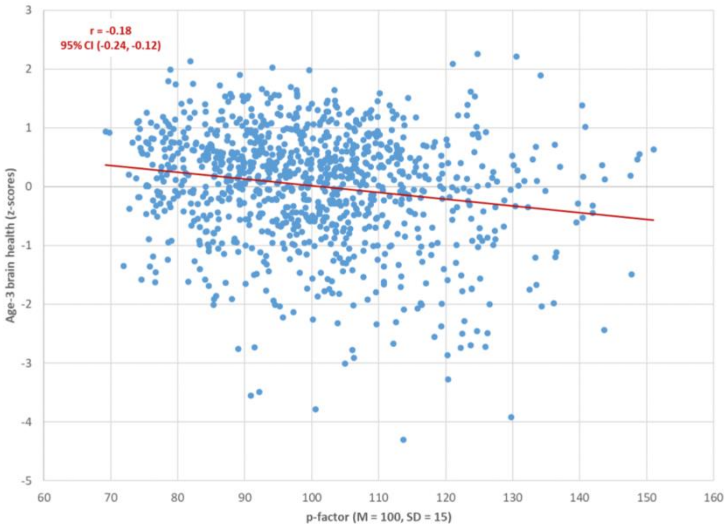


Ebb and Flow of mental health – Sankey diagrams

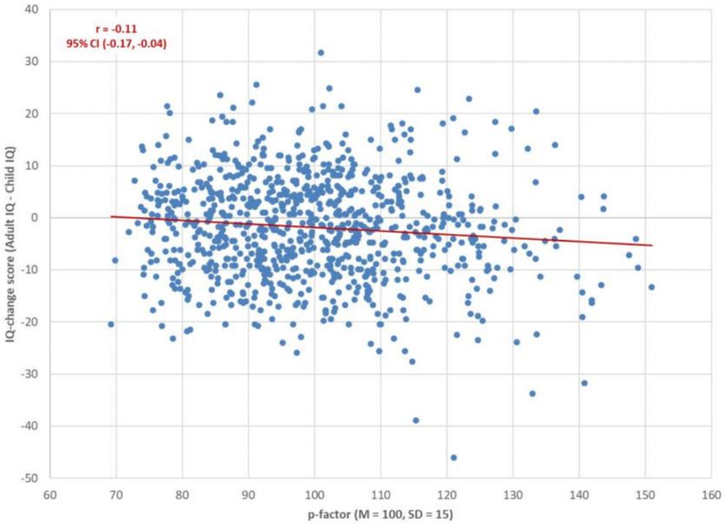
Caspi et al, JAMA Network Open, 2020

Origins and Sequelae of the P-factor

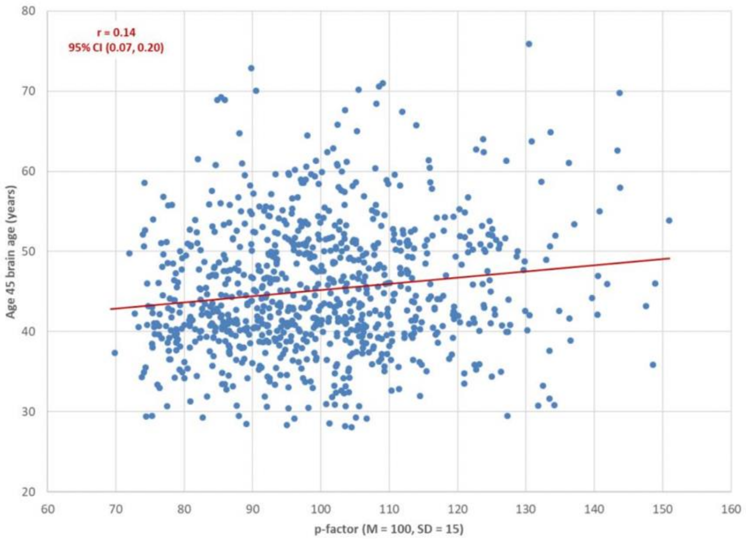
Brain Health at age 3 years (z-score)



IQ-change score (adult-child)



Brain Age at 45 years (MRI)



P-factor (Mean=100; SD=15)

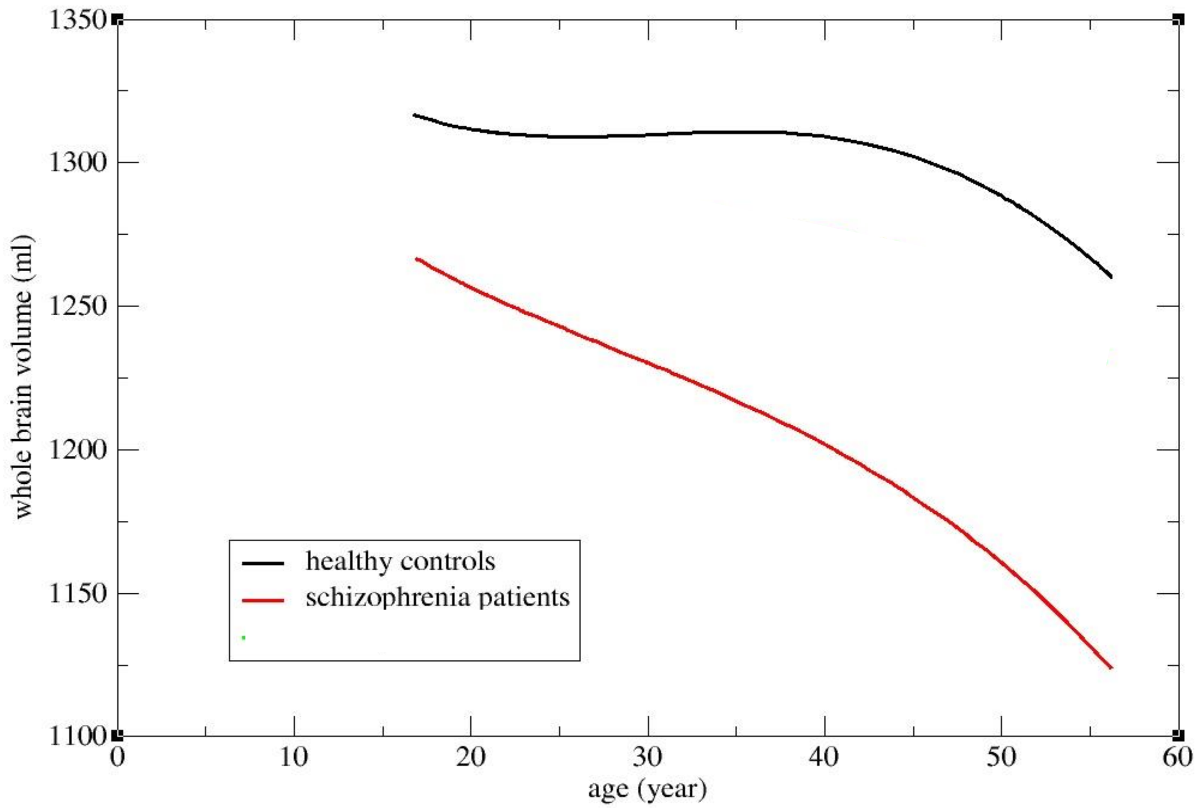
	p-factor	Thought Disorders factor	Internalizing Factor	Externalizing factor
Child Brain Health	-0.18 (-0.24, -0.12)	-0.17 (-0.23, -0.11)	-0.14 (-0.20, -0.07)	-0.10 (-0.16, -0.04)
Child IQ	-0.19 (-0.25, -0.13)	-0.17 (-0.23, -0.11)	-0.16 (-0.22, -0.10)	-0.08 (-0.14, -0.02)
Adult IQ	-0.24 (-0.30, -0.18)	-0.23 (-0.29, -0.17)	-0.18 (-0.24, -0.12)	-0.20 (-0.26, -0.14)
IQ Decline	-0.11 (-0.17, -0.04)	-0.11 (-0.17, -0.05)	-0.05 (-0.12, 0.01)	-0.18 (-0.24, -0.11)
Brain Age	0.14 (0.04, 0.20)	0.16 (0.10, 0.23)	0.17 (0.10, 0.23)	0.14 (0.07, 0.20)

Note: Numbers represent Pearson r's and 95% confidence intervals.

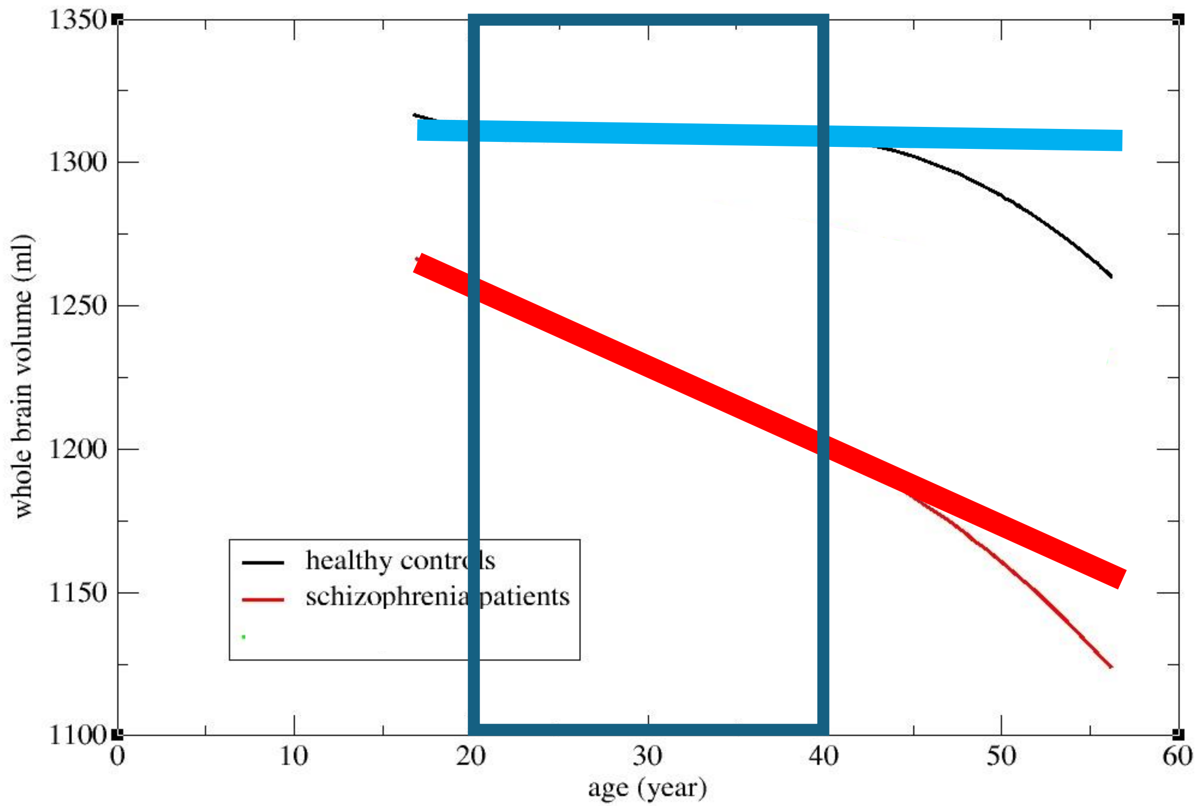
Caspi et al, JAMA Network Open, 2020

Brain Changes: phenotypic associations

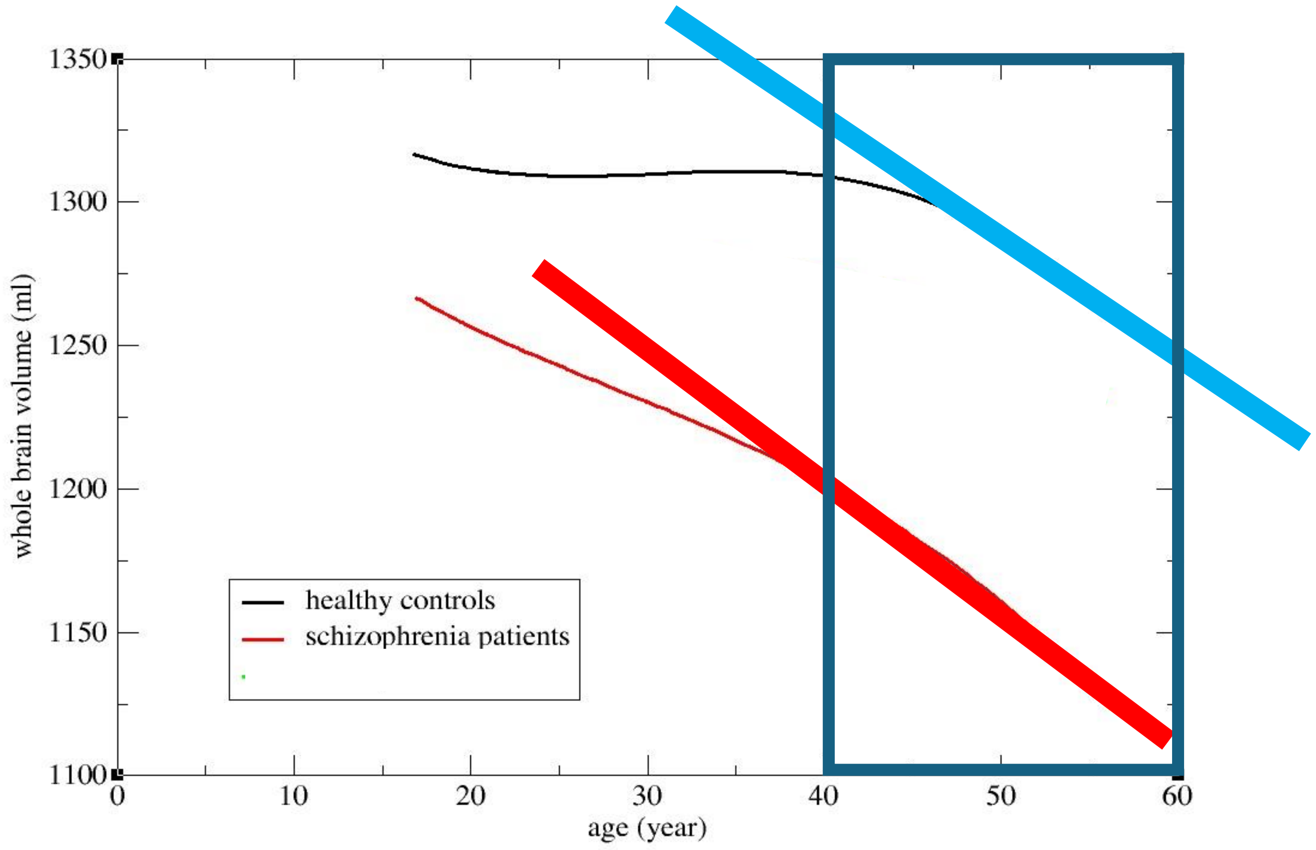
Longitudinal brain *changes in SZ*



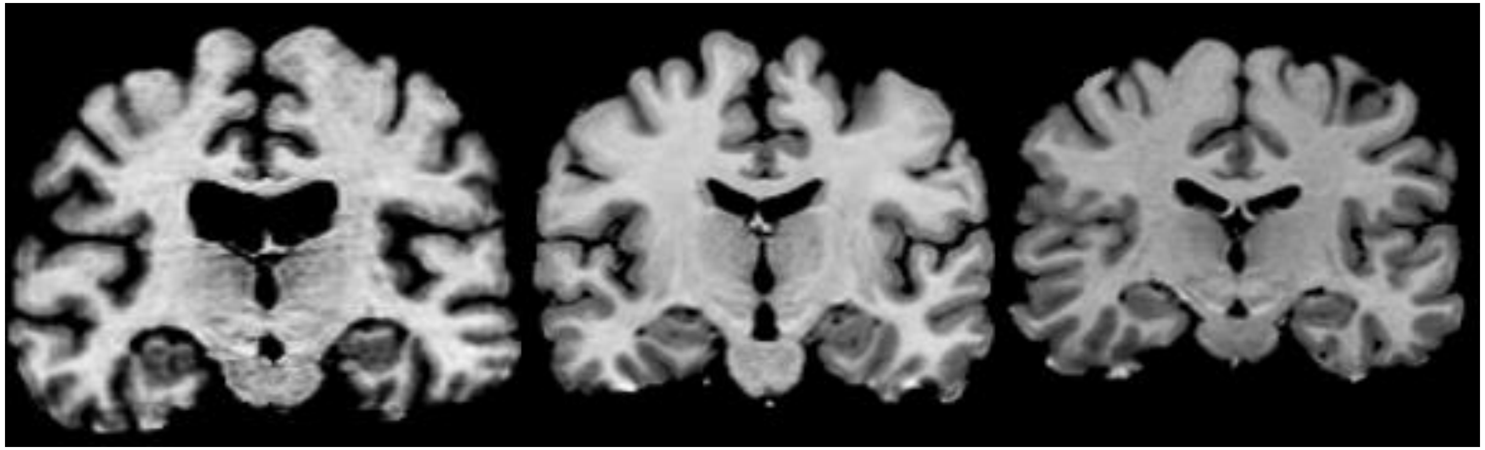
Longitudinal brain *changes in SZ*



Longitudinal brain *changes in SZ*



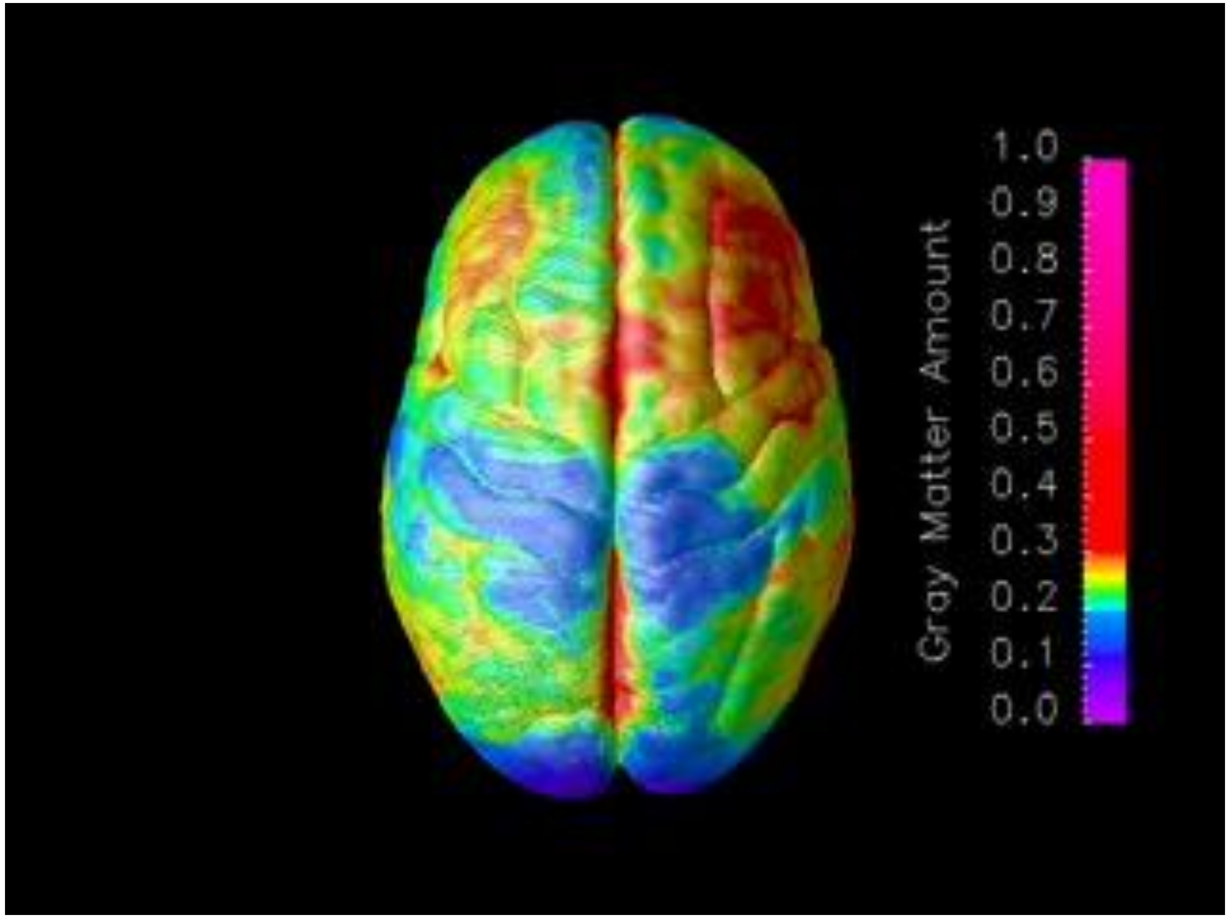
Individual differences in brain tissue loss in schizophrenia



Poor outcome | Good outcome | Control individual

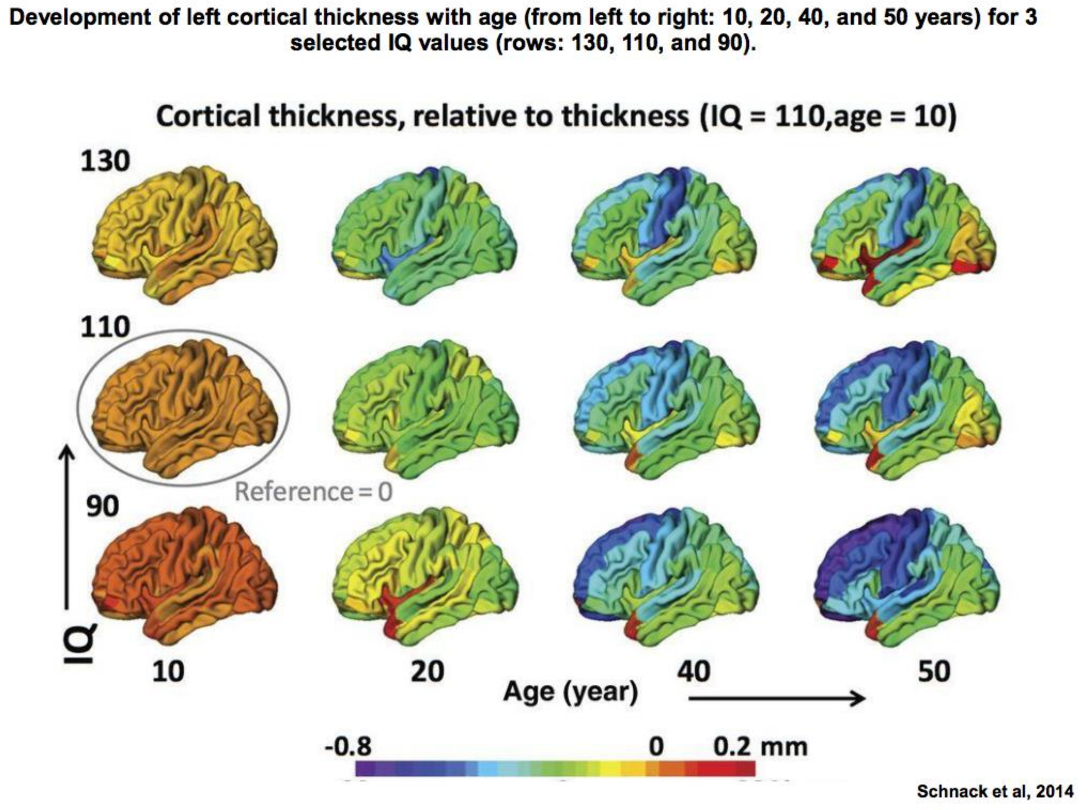
Staal et al, Am J Psychiatry 2001

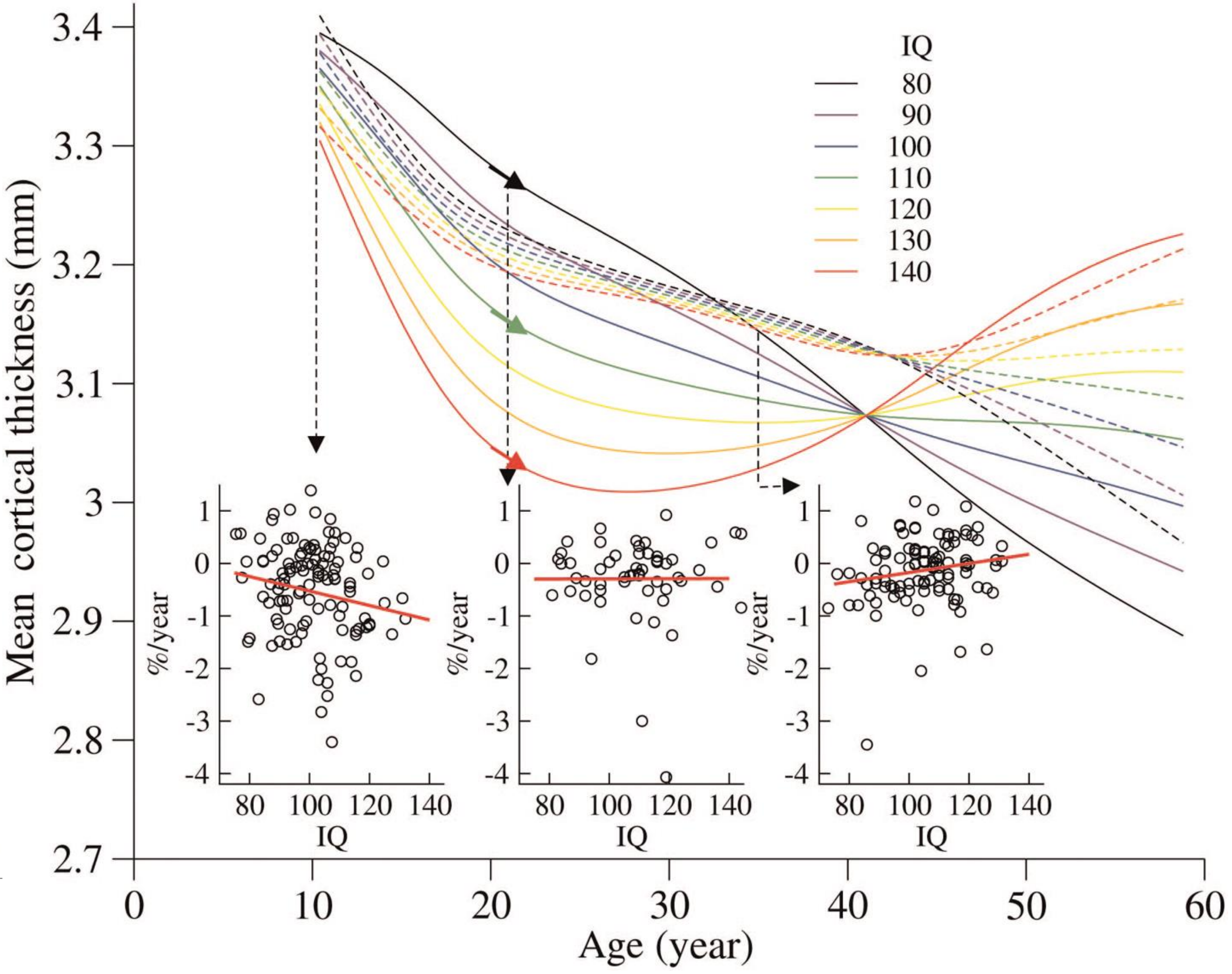
Human Brain Development



Gogtay et al, PNAS 2004

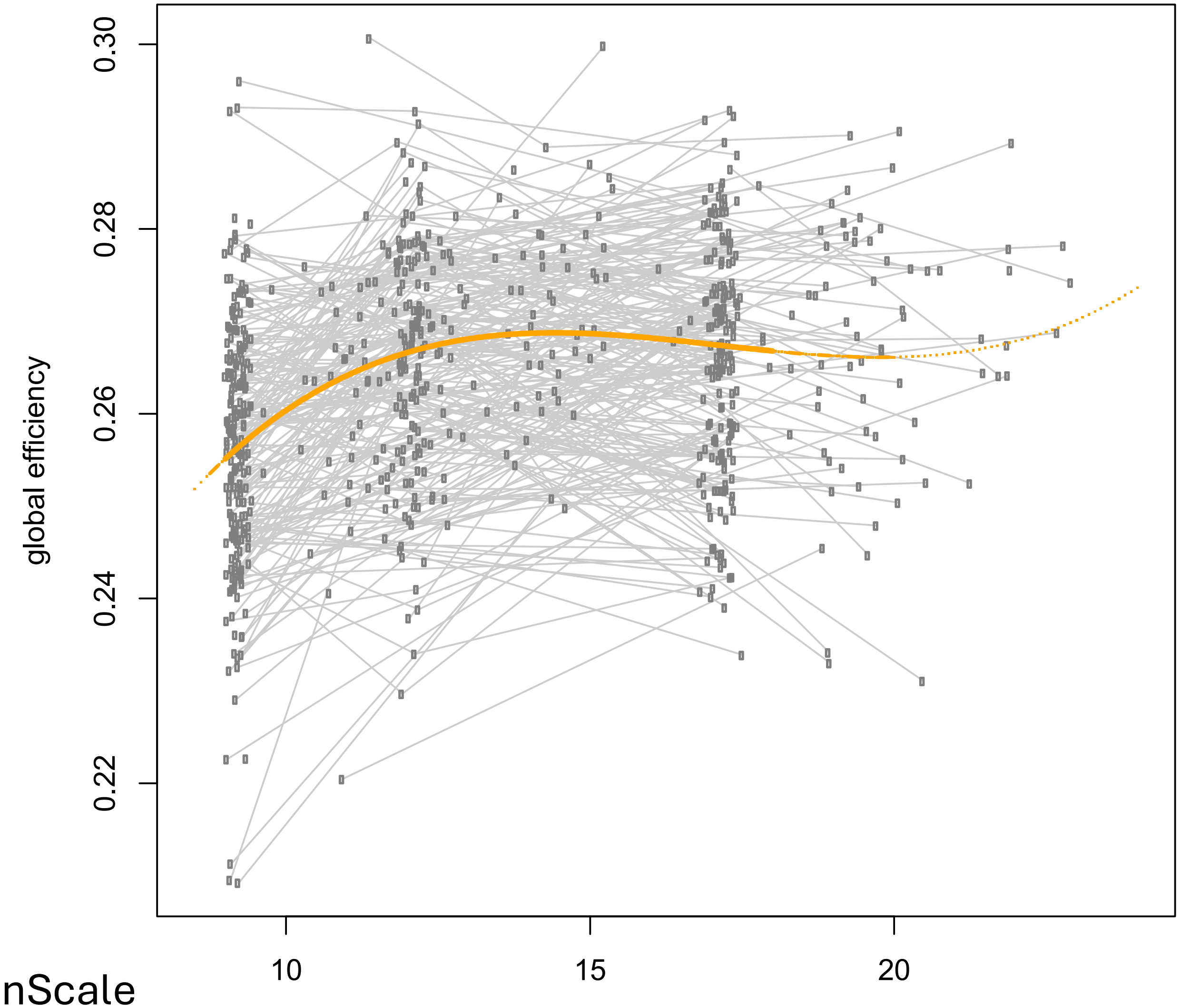
Cortical thickness change and general cognitive functioning





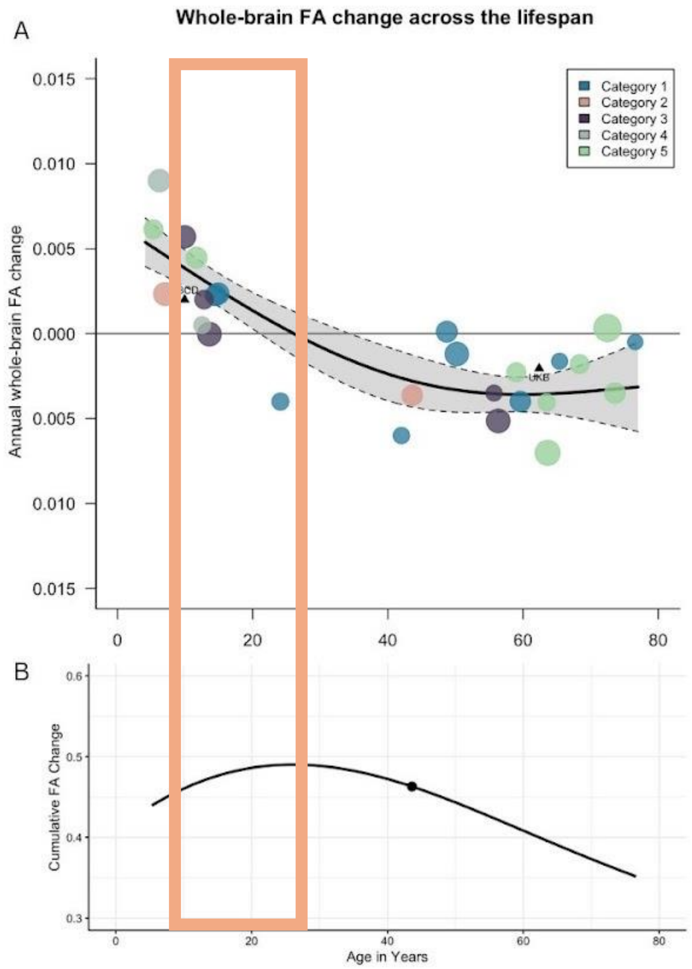
Schnack et al, Cerebral Cortex 2015

White matter integrity measured using DTI increases up to at least age 20 years



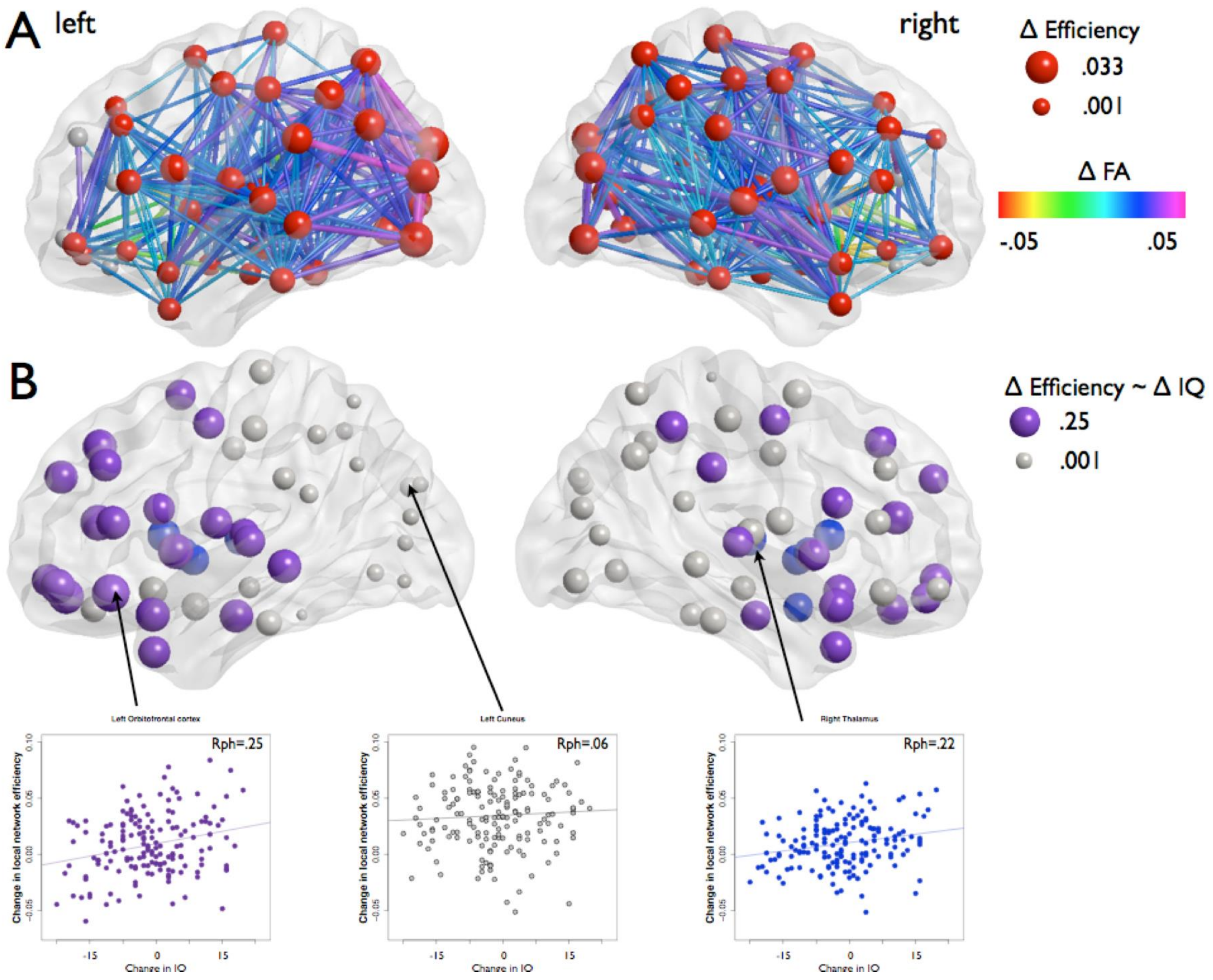
BrainScale

Koenis et al., HBM 2015, 2018



Colyer-Patel et al, BioRxiv 2025

Higher efficient brain, more IQ gain



BrainScale

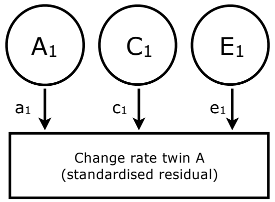
Koenis et al, HBM 2015

Conclusions I

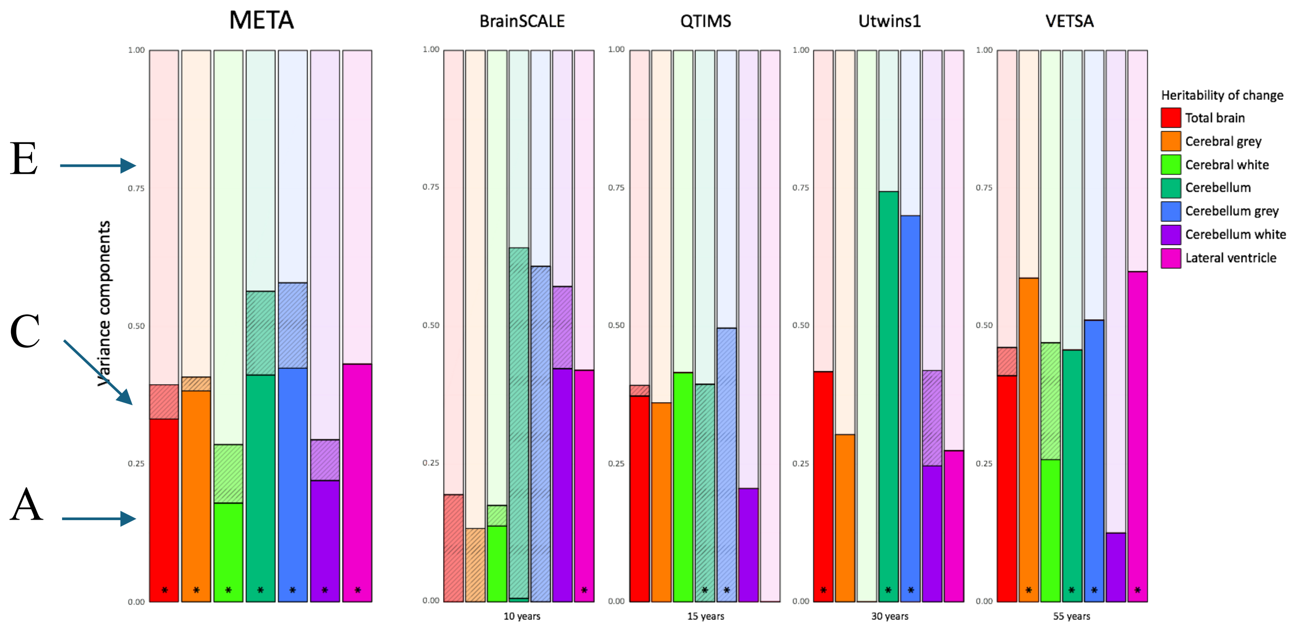
- Human brain structure changes throughout life and these brain changes are associated with functioning

Brain Changes: influences of genes

Brain changes are heritable in a meta-analysis of longitudinal twin studies



Univariate model change rate



Brouwer et al, Human Brain Mapping 2017

Main findings:

"Simple" annual change rates carry detectable genetic signal

Significant heritability of annual change rates (up to 60%)

For some phenotypes, genetic factors implicated in change are different from those influencing the baseline volumes:
indicating the existence of genetic variants that are specific for (long term) brain changes

nature neuroscience
ARTICLES
https://doi.org/10.1038/s41593-022-01042-4
Check for updates

Genetic variants associated with longitudinal changes in brain structure across the lifespan

Human brain structure changes throughout the lifespan. Altered brain growth or rates of decline are implicated in a vast range of psychiatric, developmental and neurodegenerative diseases. In this study, we identified common genetic variants that affect rates of brain growth or atrophy in what is, to our knowledge, the first genome-wide association meta-analysis of changes in brain morphology across the lifespan. Longitudinal magnetic resonance imaging data from 15,640 individuals were used to compute rates of change for 15 brain structures. The most robustly identified genes *GPR139*, *DACH1* and *APOE* are associated with metabolic processes. We demonstrate global genetic overlap with depression, schizophrenia, cognitive functioning, insomnia, height, body mass index and smoking. Gene set findings implicate both early brain development and neurodegenerative processes in the rates of brain changes. Identifying variants involved in structural brain changes may help to determine biological pathways underlying optimal and dysfunctional brain development and aging.

NIH National Institutes of Health

ENIGMA
Enhancing Neuro Imaging Genetics through Meta-Analysis

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http://enigma.ini.usc.edu/ongoing/enigma-plasticity-working-group/

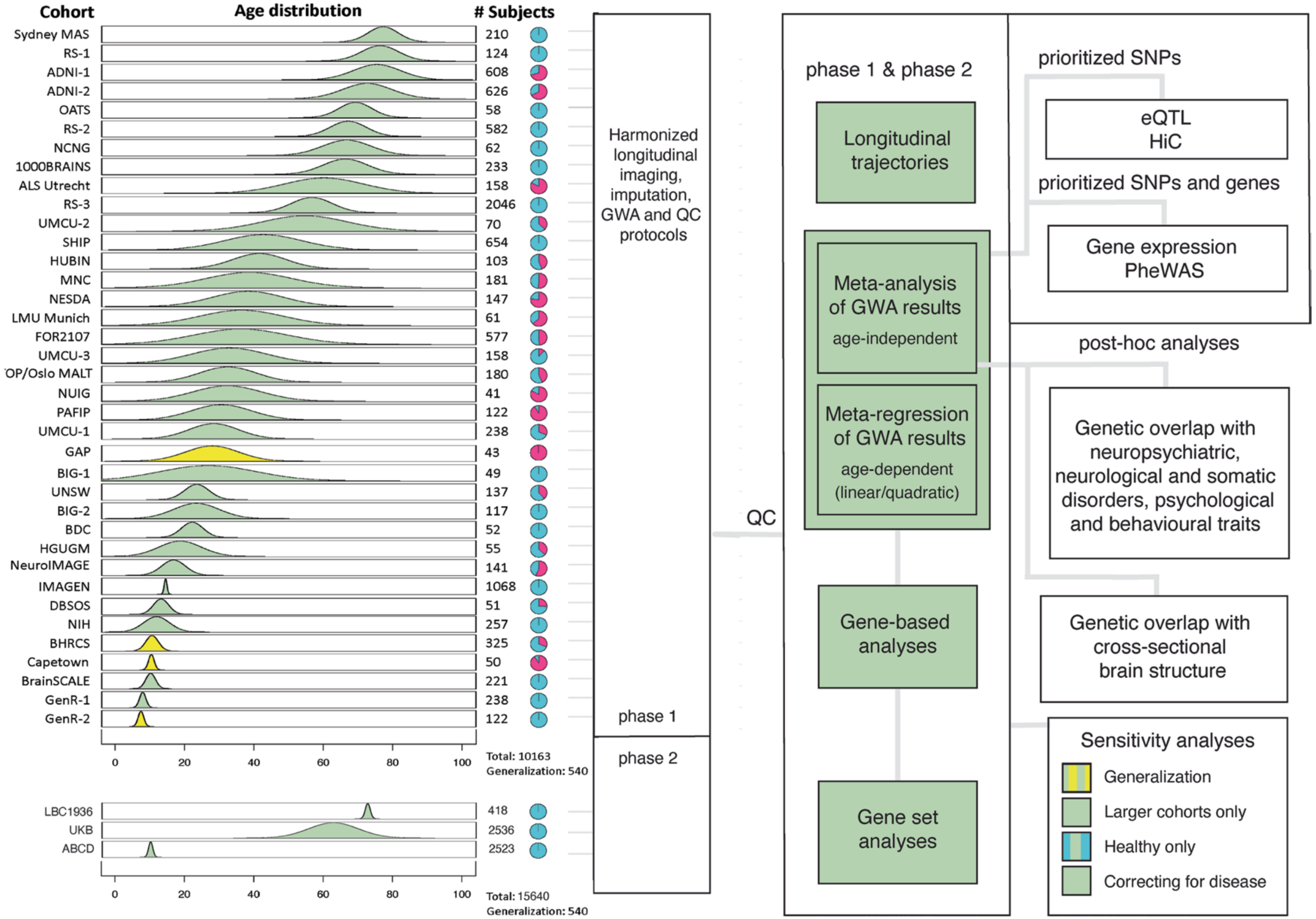
Brouwer et al Nat Neurosci 2022

Demographics and analysis

ENIGMA plasticity GWAS of longitudinal brain changes

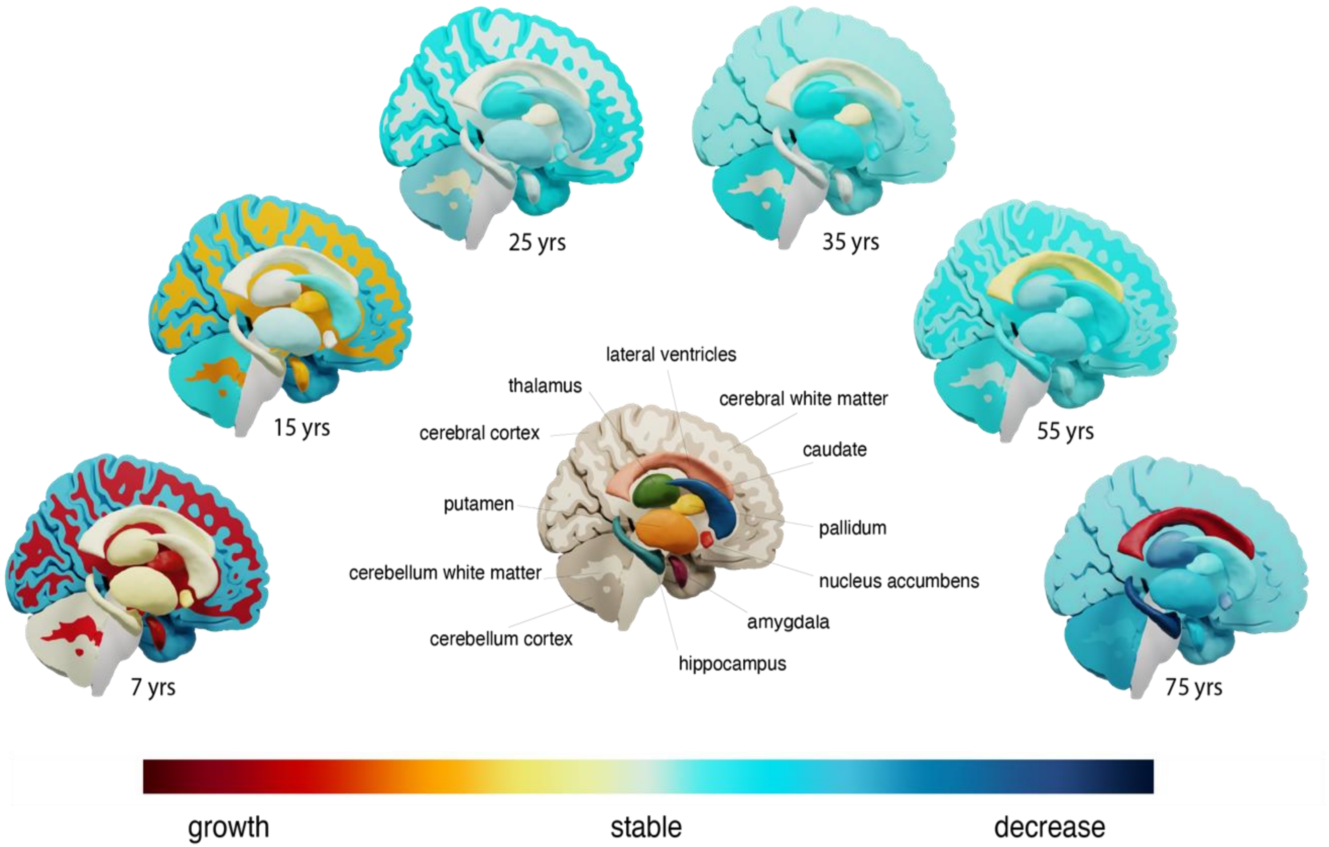
N: 15640 Total

Age span: 4-99 years



Brouwer et al, Nat Neurosci 2022

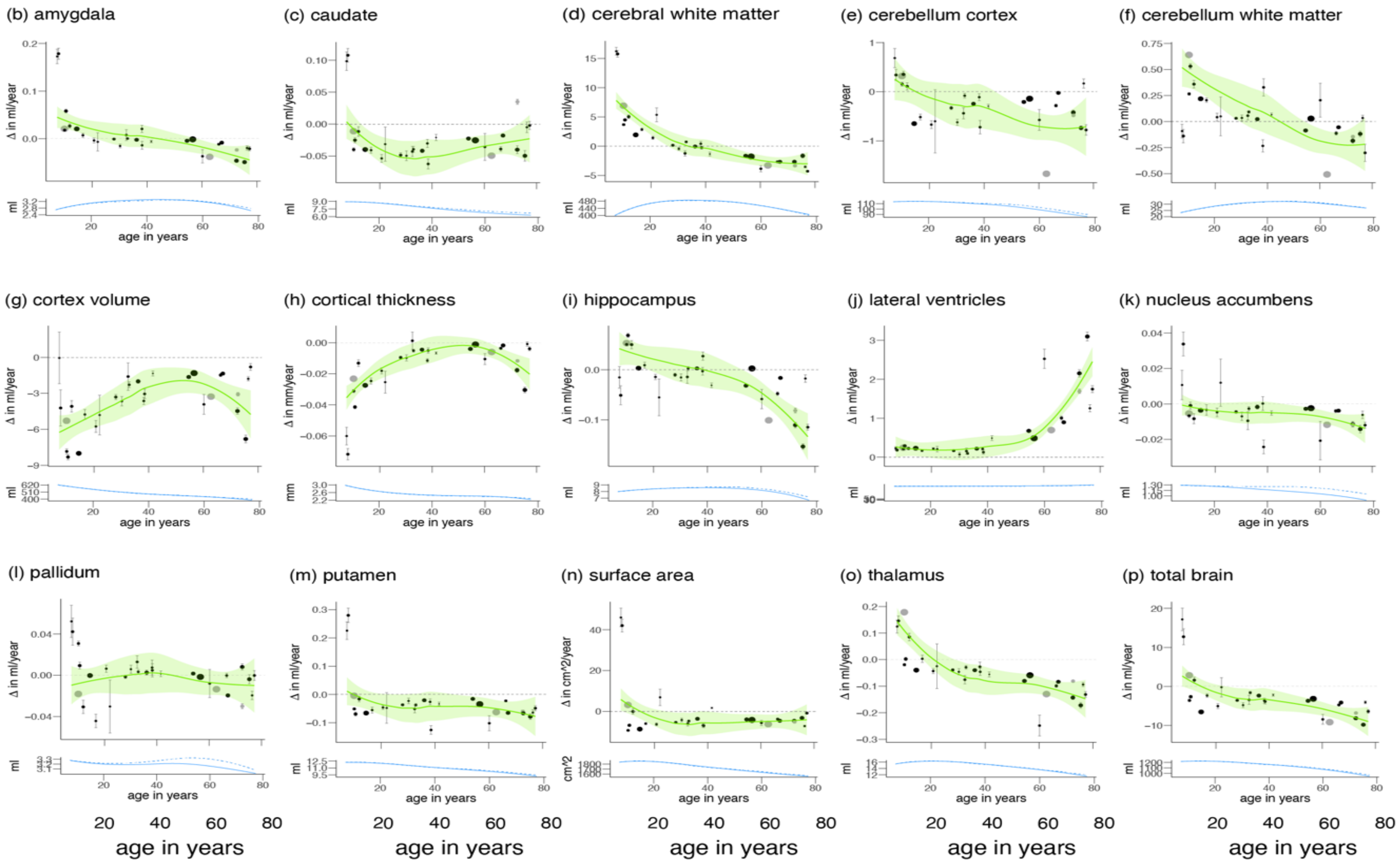
Phenotypic brain changes throughout the lifespan



ENGIMA-Plasticity

Brouwer et al, Nat Neurosci 2022

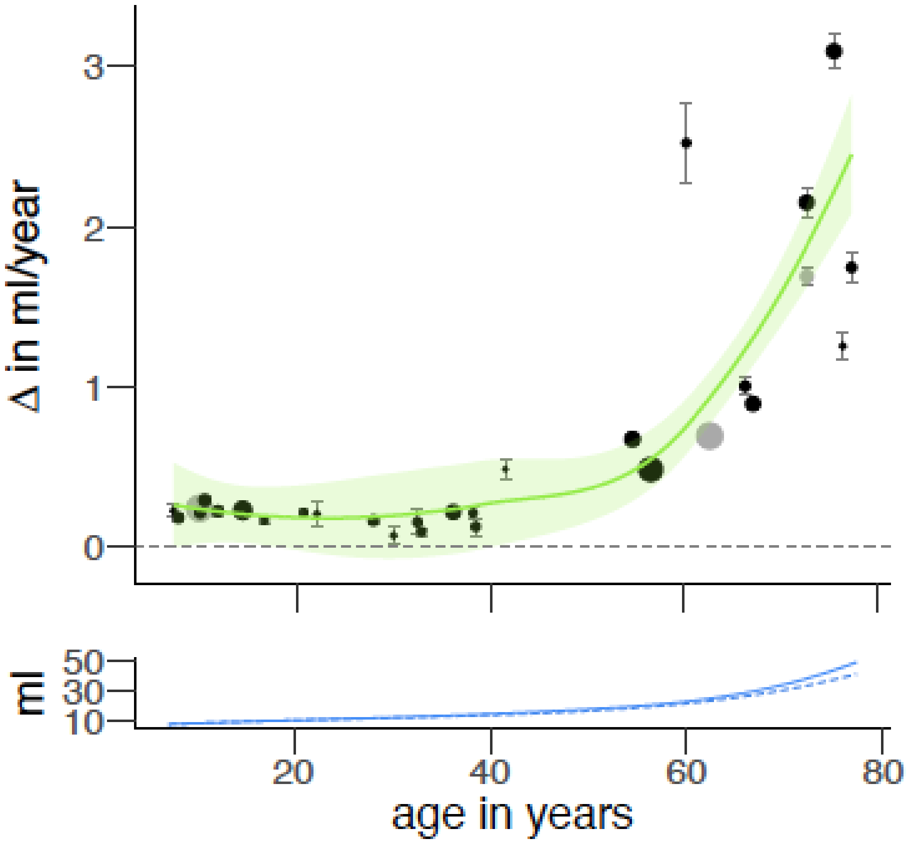
Annual rates of change Δ per cohort for each structure



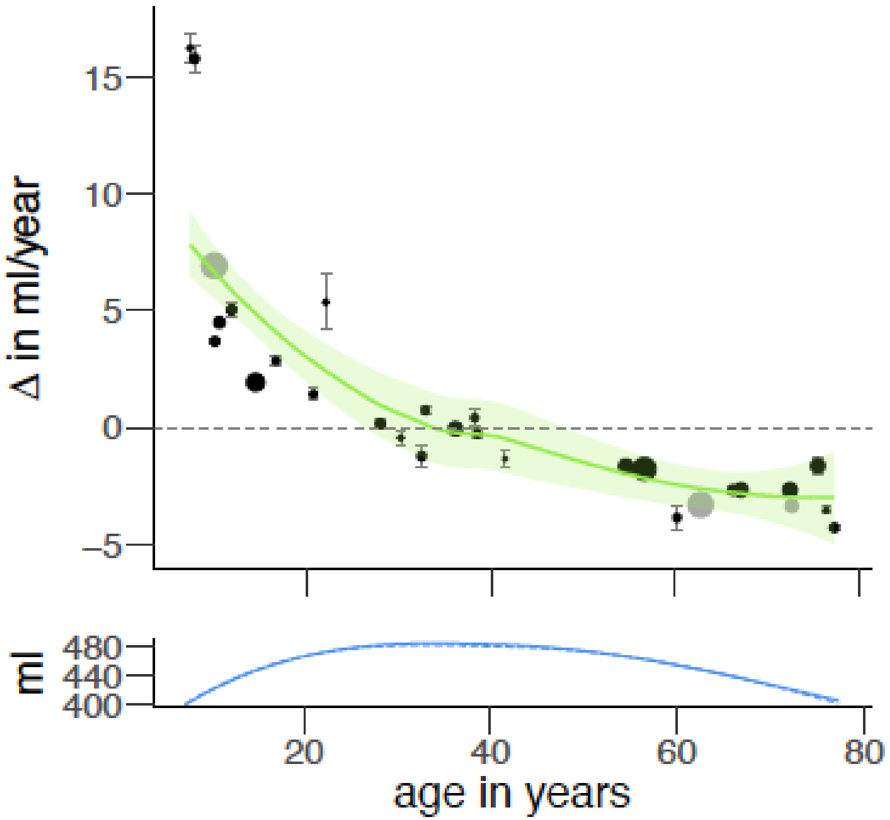
Brouwer et al, Nat Neurosci 2022

Annual rates of change Δ per cohort for each structure

Lateral ventricle change

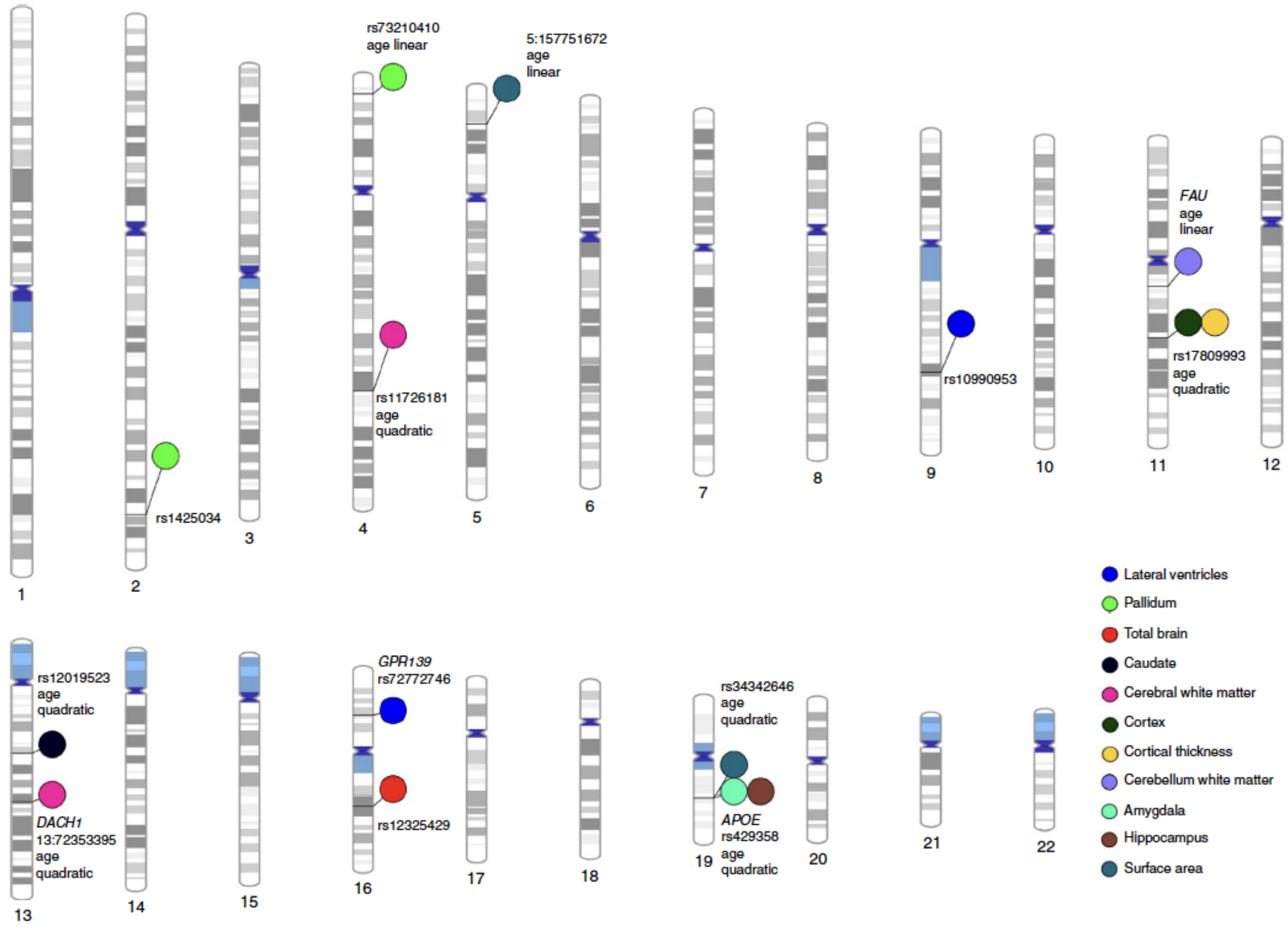


White matter change



Brouwer et al, Nat Neurosci 2022

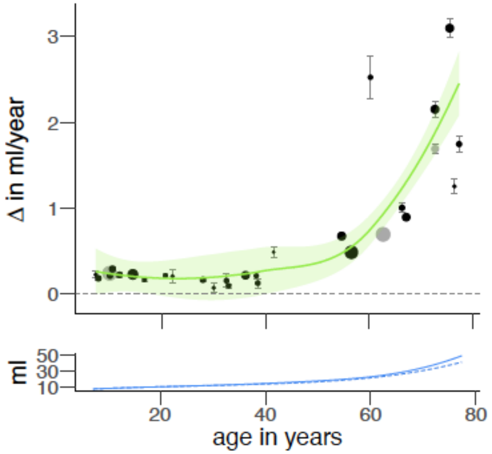
Genome-wide significant SNPs and genes with effects on brain changes at their respective loci across the human genome



Brouwer et al, Nat Neurosci 2022

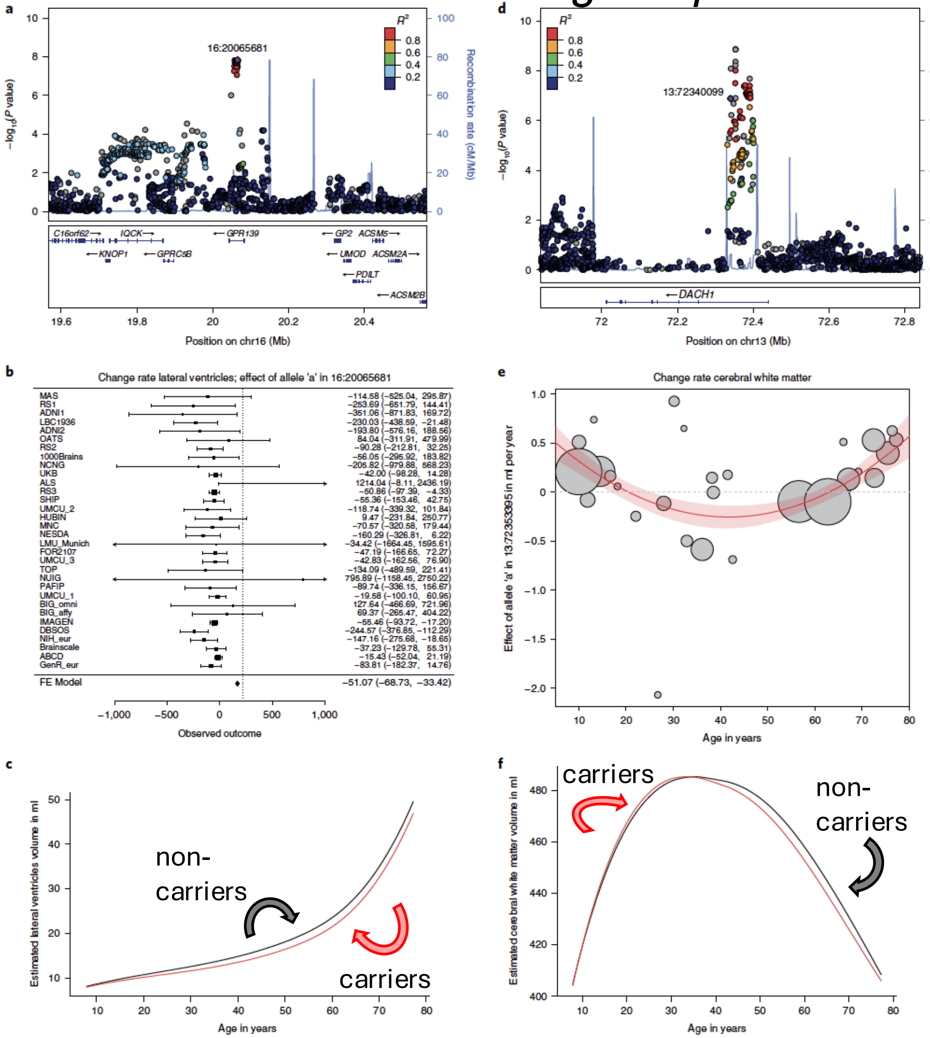
Summary of findings for two top SNPs

Lateral ventricle change

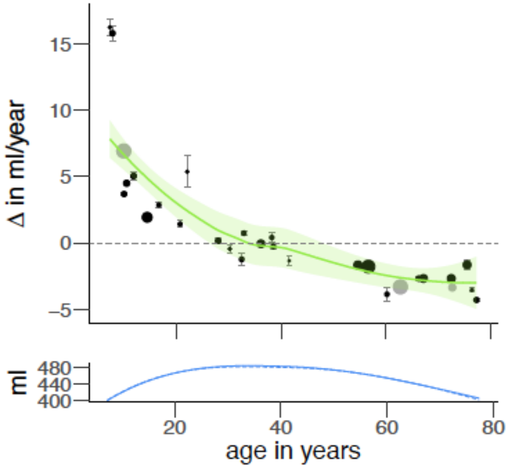


*age-**in**dependent*

quadratic age-dependent



White matter change

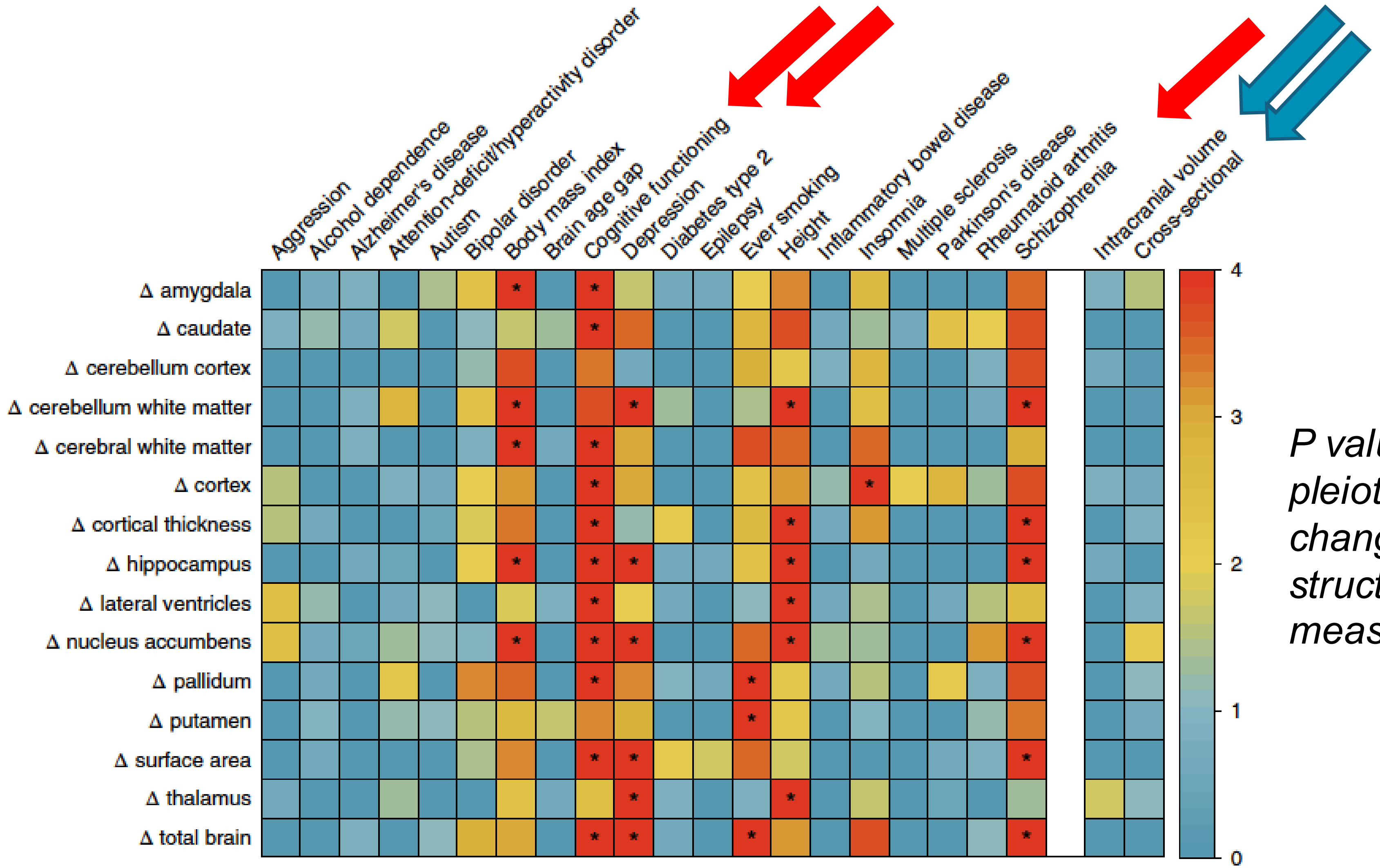


G-protein-coupling receptor gene 139 (GPR139)

Dachshund family transcription factor 1 (DACH1)

Brouwer et al, Nat Neurosci 2022

Genetic overlap with other phenotypes



P values for pleiotropy between change rates of structural brain measures

Brouwer et al, Nat Neurosci 2022

Conclusions II

- Common genetic variants affect rates of brain growth and atrophy
- There is a global genetic overlap with depression, schizophrenia, cognitive functioning, insomnia, height, body mass index, smoking
- Identifying variants involved in structural brain changes may help to determine biological pathways underlying optimal and dysfunctional brain development and aging

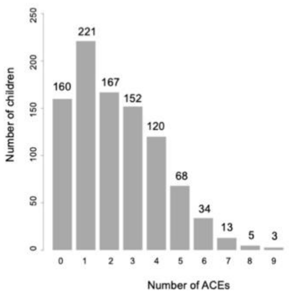
Brain Changes: influences of environment

YOUth cohort

Onland et al, Developmental Cognitive Neuroscience 2020

Number, prevalence and overlap for the exposure to Adverse Childhood Experiences (ACEs) and brain structures per child

Number of ACEs per child

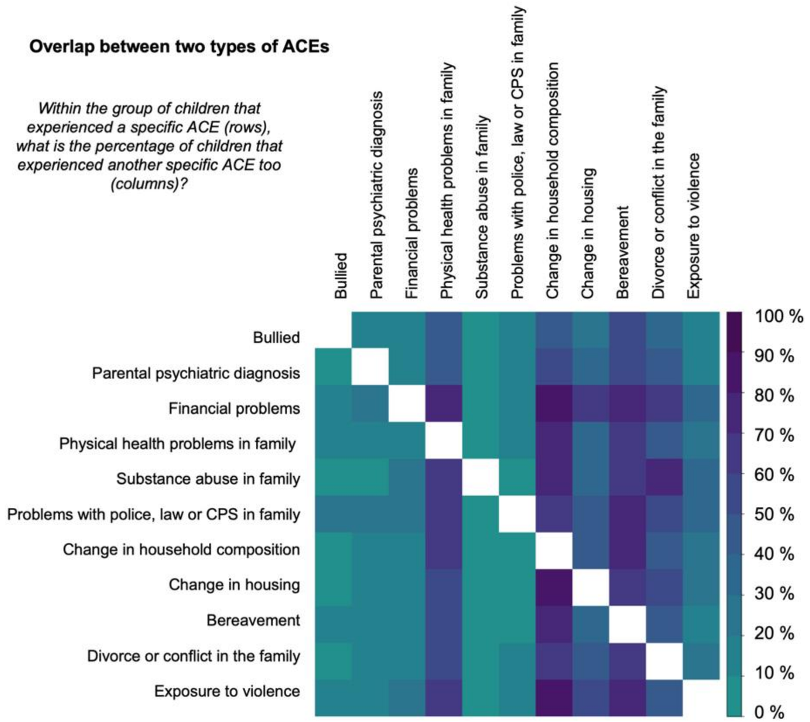


Prevalence of ACEs

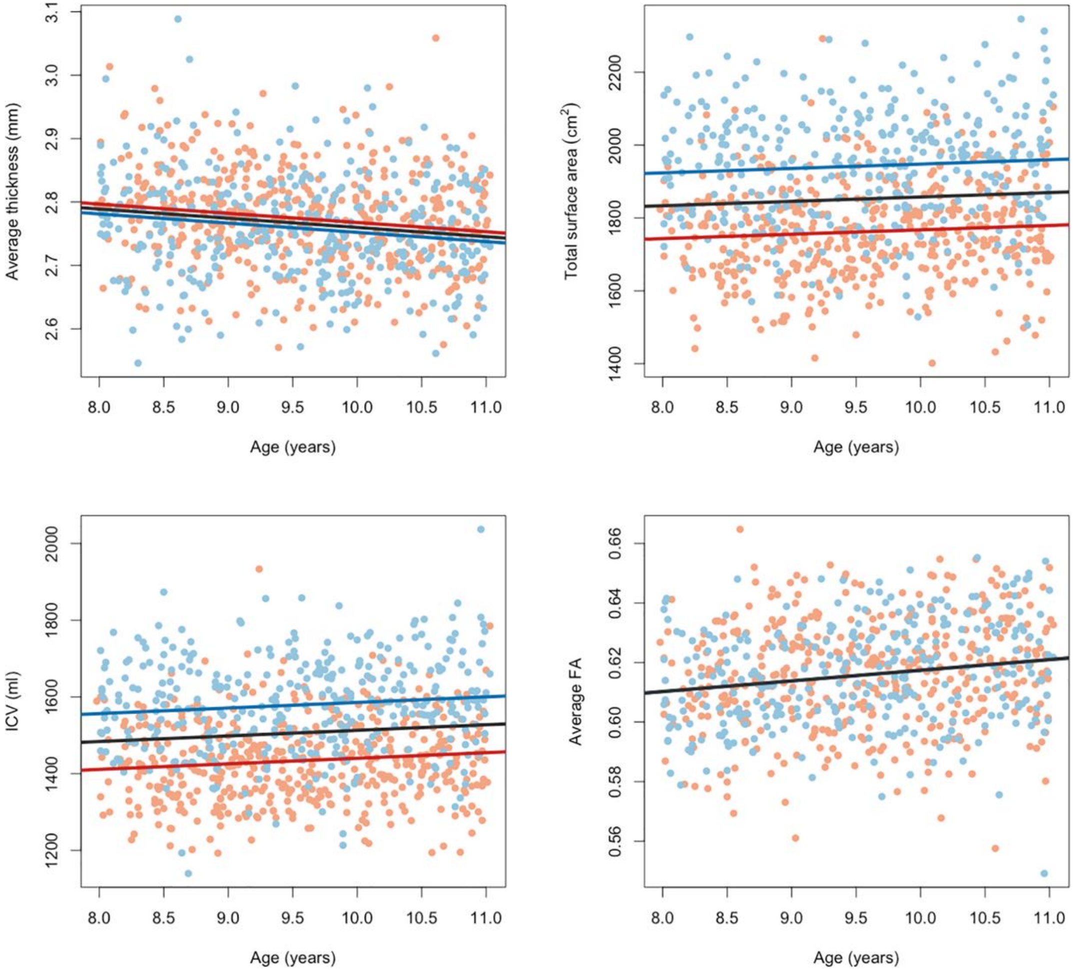
ACEs	ACE (%)	N	N T1w	N DWI
Financial problems	8			
Physical health problems in the family	41			
Substance abuse in the family	2			
Problems with police, law or child protection services	3			
Change in household composition	47	1046	785	702
Change in housing	26			
Bereavement	50			
Divorce or conflict in the family	31			
Exposure to violence	11			
Bullied	6	948	707	631
Parental psychiatric diagnosis	11	1056	791	708
Any ACE	83	943	704	628

Overlap between two types of ACEs

Within the group of children that experienced a specific ACE (rows), what is the percentage of children that experienced another specific ACE too (columns)?



Darker colours mean higher overlap (based on subset in a row and differs for upper and lower triangle)



YOUth

Adverse events 1 year prior

Brain structures between 8 and 11 years of age

Buimer et al, Front Psychiatry 2022

Family exposure to violence and FA

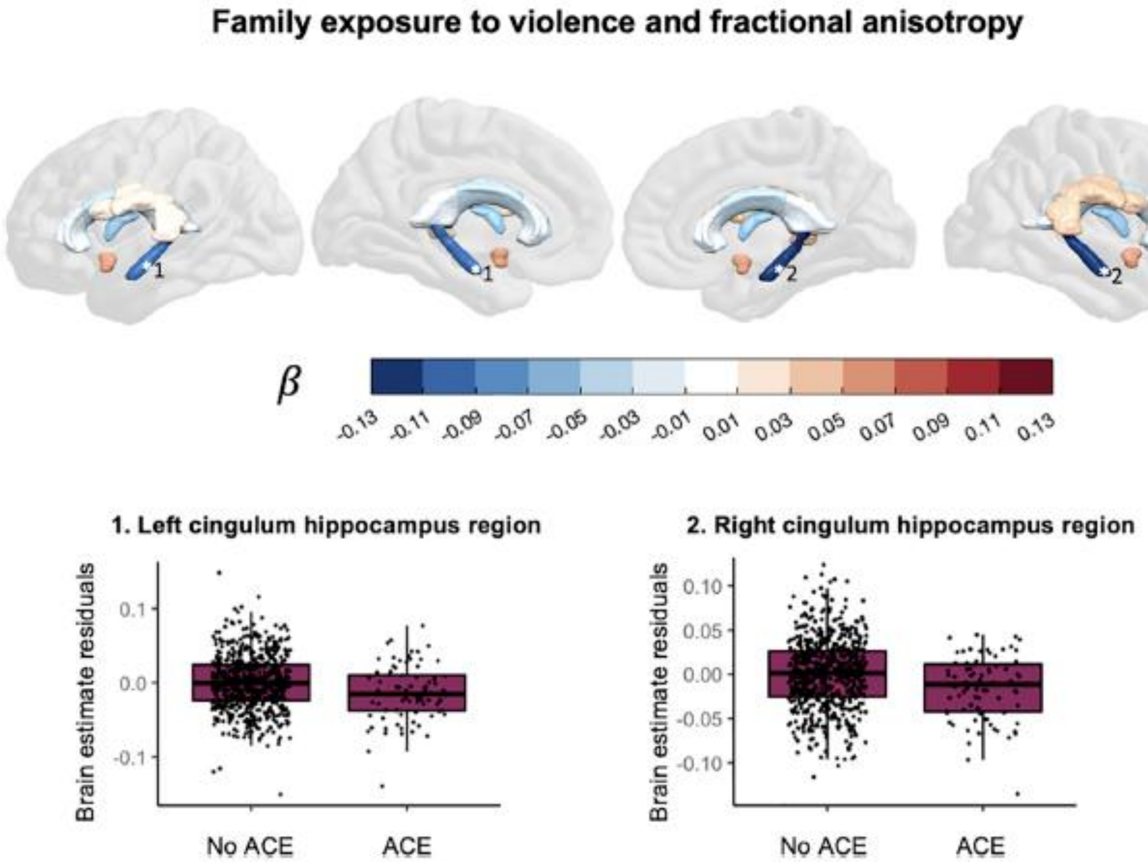


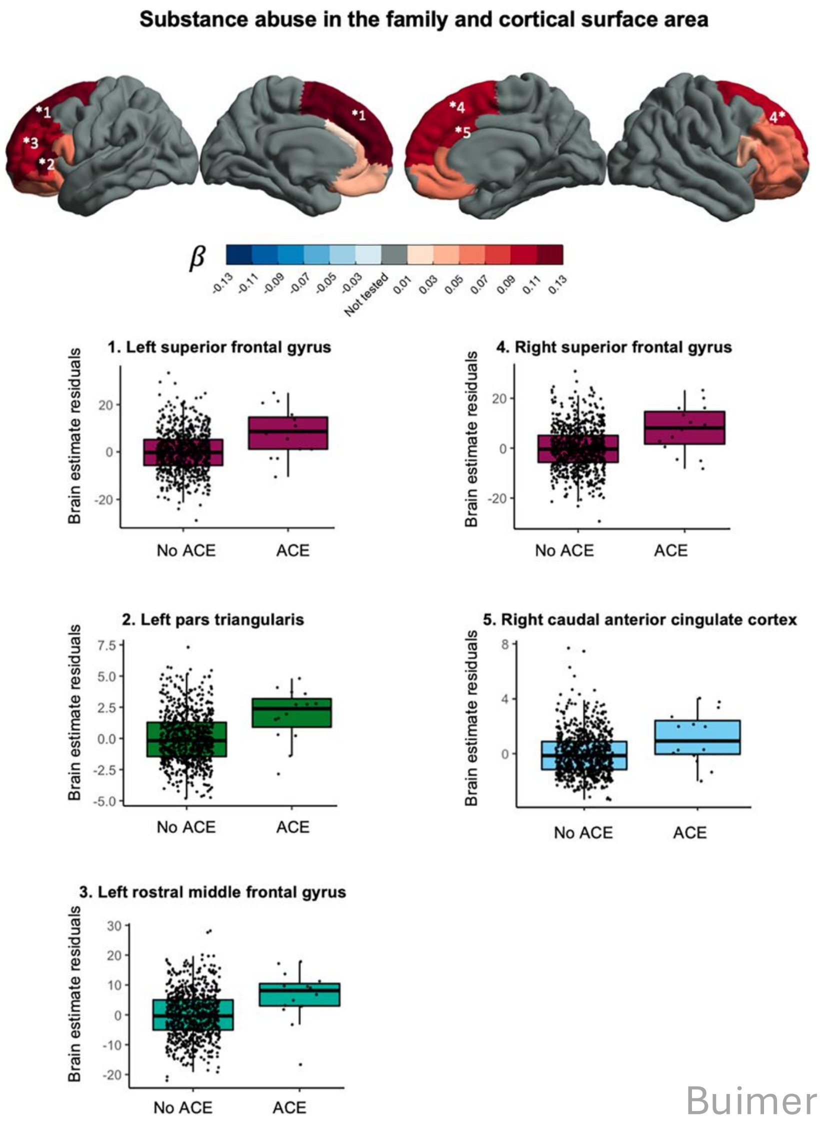
FIGURE 5
Associations between exposure to violence and fractional anisotropy.

- Household exposure to violence was associated with lower FA in the left and right cingulum bundle hippocampus region

YOUth

Buimer et al, Front Psychiatry 2022

Associations between substance abuse in the household and cortical surface area



- Growing up in a family with substance abuse problems was associated with a larger cortical surface area in the bilateral superior frontal gyrus, the left pars triangularis, the left rostral middle frontal gyrus and the right caudal anterior cingulate gyrus.

YOUth

Buimer et al, Front Psychiatry 2022

Conclusions III

- Family exposure to violence and substance abuse in the family were associated with altered brain structures in youth, but in general, small effects and no evidence for significant differences in most ACEs

- Longer intervals between adversity and brain measurements and longitudinal measurements may reveal whether more evidence for the impact of ACEs on brain development will emerge later in life

Brain Changes: influences on self-regulation

Questions

What is self-regulation? "The ability to flexibly activate, monitor, inhibit, persevere and/or adapt one's behavior, attention, emotions and cognitive strategies in response to direction from internal cues, environmental stimuli and feedback from others, in an attempt to attain personally-relevant goals" (Moilanen, 2007; Wesarg-Menzel et al., 2023)

Self-regulation abilities self-regulation outcomes

Part of an ongoing study!

Self-regulation abilities
Cognitive appraisal strategies
Cognitive control
Delay of gratification
Effortful control
Emotion Regulation
Executive function
Identity exploration
Inhibitory control
Meta-memory monitoring
Mindfulness
Planning
Processing speed
Prosocial behavior
Reaction Time
Response inhibition
Reward sensitivity
Risk-taking
Socialization pathways
Value-based learning

Self-regulation outcomes
Attention Deficit Hyperactivity Disorder (ADHD)
Agression
Antisocial behavior
Anxiety
Conduct problems/disorder
Disruptive Behavioral Disorder (DBD)
Depression
Externalizing behavior
Impulsivity
Impulsive personality traits
Internalising behavior
Irritability
Neuroticism
Rebellious behavior
Wellbeing
Worry

Ongoing NWO Zwaartekracht onderzoek GUTS – Growing Up Together in Society

- https://www.gutsproject.com/home/
- https://meedoenaanguts.nl/

GROWING UP TOGETHER IN SOCIETY

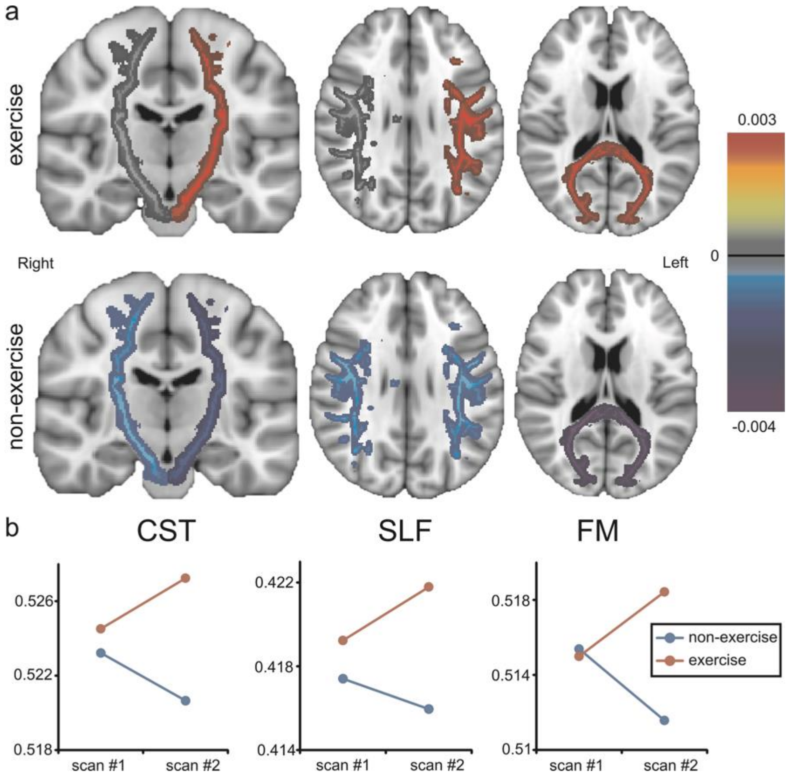
Conclusions IV

- Self-regulation for anticipation and planning of inhibitory behavior is linked to brain structure

- Brain development impacts self-regulatory capacities, but so far much is unaccounted for in the diversity of self-regulation abilities in youth

- **And how about exercise?**

Physical exercise influences white matter integrity



Svátková et al, Schiz Bulletin 2015

Conclusions overall

- Unraveling secrets of changes in human brain structure provides insight into brain health and mental health

- Knowledge of the neurobiological mechanisms involved in human brain changes can aid in finding optimal (treatment) strategies for brain health and mental health

- You can train your brain and boost your connectome by physical exercise

Thank you!