- Respected members of the committee, institute leader, dear colleagues and friends.
- I will now present to you my doctoral project “Disease and ageing biomarker identification from multimodal magnetic resonance imaging”

Presentation Structure

- Background
- Methods
  - eXtreme Gradient Boosting (XGBoost)
  - Data
    - T1-weighted magnetic resonance imaging (MRI)
    - Diffusion-weighted MRI
    - Pheno- and genotypes
  - Project Overview
- Main Findings
  - White Matter Ageing
  - Pheno- and Genotype Associations
  - Brain Age: Considerations and Extensions
- Summary

2

- The presentation will be generally structured in
  - Background
  - Methods
  - Findings
  - Summary
- In the **methods** section I will highlight a **machine learning technique** which I used across my work, **extreme gradient boosting**
- In the **data** setion I will mainly focus on **magnetic resonance imaging**
- The main **findings section** will provide a general **overview across the five publications**

Background

- The brain's developmental trajectory: from brain differentiation (development) to de-differentiation (atrophy)

Neurodevelopmental Milestones

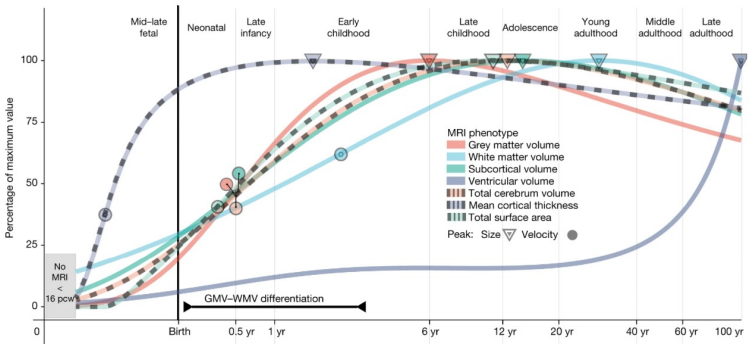

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Fig: Betlehem et al., 2022, Nature

- The brain matures and ages together with all other bodily systems as individuals grow older
- Focussing on the brain:
  - **differentiation** in **childhood to early adulthood** can be observend in **increasing cognitive abilities**;
  - these **decrease during ageing together** with the occurance of **brain atrophy**
- As an example here, we could look at different tissue types and examine the described development

Background

- The brain's developmental trajectory: from brain differentiation (development) to de-differentiation (atrophy)

- Deviations along this trajectory can signify pathology and disorders

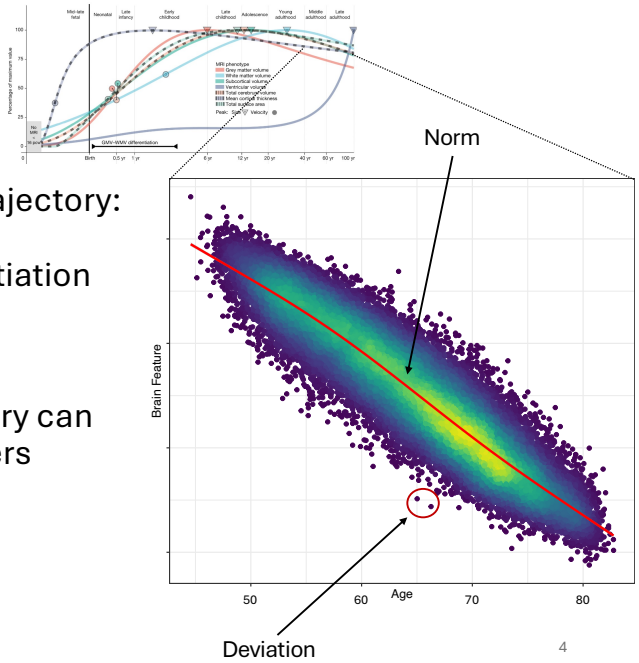

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Fig: Korbmacher et al. (in prep)

- One can estimate normative trends or trajectories from large samples
- In the figure,
  - we focus on the **second half of life**, and take grey matter thickness as an example metric
  - the closer to the **normative line**, the closer to the **sample average**

- **Deviations** from these trajectories can **signify disorders, disorder states or health outcomes in general**
  - This connects the aspects of ageing and disease
  - The third part we touch on in this project are biomarkers, which I losely define here as
    - **measurable units which have correlational or causal value in describing health and/or ageing processes**

Background

- Knowledge of brain ageing is limited
  - Both in normal & abnormal ageing

- Project goal:
  Benchmarking brain ageing processes.
  - How does the brain age in the absence of disorders?
  - Which structures are affected mostly by healthy ageing?
  - What are useful markers of ageing?

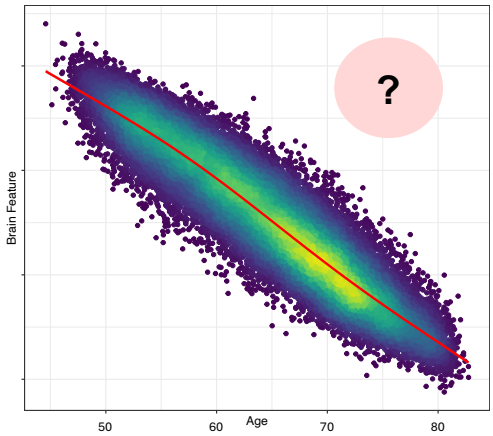

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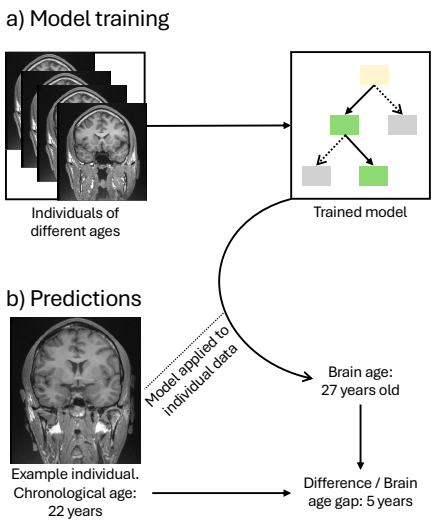
Fig: Korbmacher et al. (in prep)

- **Limited knowledge of ageing trajectories** both in healthy and diseased in sufficiently large samples
- Hence, here we **start with healthy participants**' data to establish a baseline
- These **findings** can then be **extended to clinical samples**.
- So, the **project goal** is to **benchmark ageing processes**
- That translates to different research questions such as how healthy ageing and degeneration processes look like
  - and which brain regions and markers are especially age sensitive

Background

- Brain age
  1. Training model
  2. Predicting age with that model
  3. Differences between brain age and chronological age



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- Besides classical age-associations, one can use brain age
  - For that one **trains a model**, usually using machine learning on **magnetic resonance images of many** individuals
  - This model is then used to **make individual predictions**, "a best guess" about the age of a person based on their brain
  - This can be done using different brain features and scales, from the **voxel/pixel level to reconstructed features** such as grey matter thickness in a brain region
  - Multiple studies indicate that the difference between chronological and brain age (the **brain age gap**) indicates **multiple health outcomes and diseases**
  - Schematic on the right presents this process from a) training process to b) individual level predictions

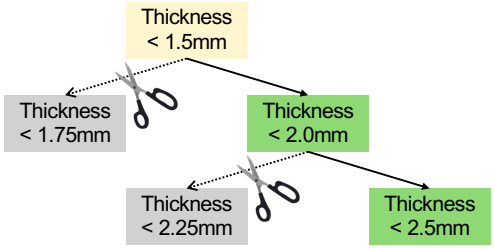
Methods: XGBoost

- Gradient boosting: generally good performance on tabular data (better than deep learning)
- Uses decision tree
  - Arbitrary splitting of the data, e.g. cortical thickness < 2mm
  - "Prune tree" at lower performance

Objective function of XGBoost

$$obj(\theta) = \underbrace{\sum_i^n l(y_i, \hat{y}_i)}_{\text{Loss function}} + \underbrace{\sum_{k=1}^K \Omega(f_k)}_{\text{Regularisation parameter}}$$

Single decision tree predicting age from cortical thickness



XGB: Chen et al., 2016, SIGKDD Int.
by maninder (cleanpng.com)

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- We used extreme gradient boosting (**XGBoost**) as this algorithm **performs very well on tabular data**
- Simply said, XGBoost is a **function of functions**, entailing a **loss function and regularisation**, to **sum up optimized decision trees towards a best prediction**
- Practically speaking,
  1. Start with a prediction, then estimate prediction error (or residuals)
     - Then clusters similar residuals into two groups, e.g. resulting in our group of people with different cortical thicknesses in the first box

Methods: XGBoost

- Gradient boosting: generally good performance on tabular data (better than deep learning)
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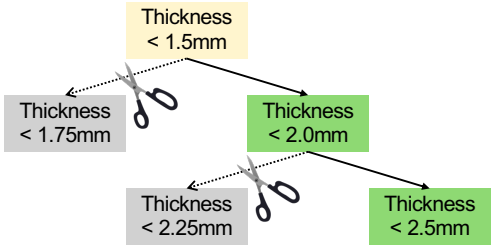


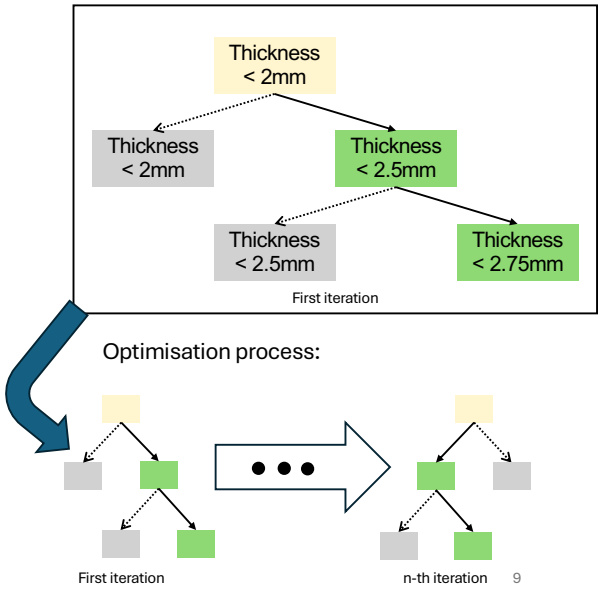
XGB: Chen et al., 2016, SIGKDD Int. 8

by maninder (cleanpng.com)

- This process is aided by **regularisation parameters to reduce** the model's **sensitivity to individual observations** (*overfitting*)
  - This is the extreme in XGBoost (compared to regular gradient boosting)
- The model uses **hyperparameters** which impose flexibility or constraints on the model
  - e.g. the **iterations** the model is allowed to **"learn"** > "short or longer learning period"
- This process is repeated, forming the decision tree
- Here, this means **splitting the sample** further and further **towards the average population cortical thickness**, as 1.5mm is a relatively thin cortex, 2.5mm a good estimate of the average cortical thickness
- During this process, groupings which improve model performance will be used, others discarded = "pruning"

Methods: XGBoost

- Gradient boosting: generally better performance than deep learning on tabular data
- Uses decision tree
  - Arbitrary splitting of the data, e.g. cortical thickness < 2mm
  - Prune at lower performance



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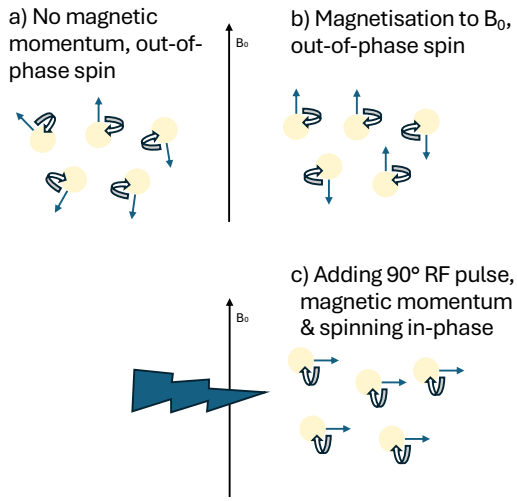
2. Use the **previous tree's or first iteration's residuals** and **build trees** until **hyperparameter restrictions** stop the procedure or the **optimum** is found

- Beyond the machine learning part, we used more classical statistical approaches such as mixed and regular linear models.

Methods: Data

- Magnetic resonance imaging (MRI)
  - T1-weighted MRI
    - Clear contrasts between grey and white matter
  - Diffusion MRI
    - Diffusion restricted by tissue, hence useful for white matter mapping
- Pheno- & genotypes



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- The **data** we use for XGBoost and other age-associations is extracted from magnetic resonance imaging (MRI)
- Magnetic resonance imaging
  - A strong magnet serves to provide the body's protons with a magnetic momentum [from a) to b)]
    - a) protons possess spin and magnetisation (arrow) more or less at random in body
    - b) when added to strong magnetic field the protons gain become micro-dipolar magnets and spin faster
    - c) add radio frequency pulse (resonant with the protons of interest) > sets protons in high energy state
  - When protons return into their equilibrium, they collectively emit energy which can be used to form the MRI signal

Methods: Data

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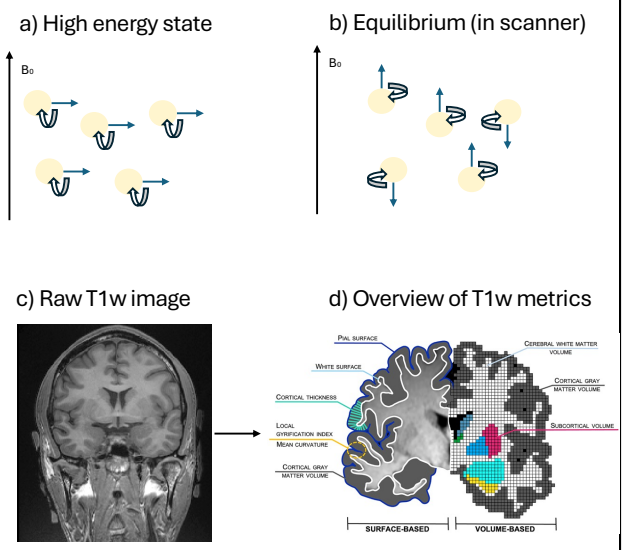

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Backhausen et al. (2021), Neuropsy Rev, 32 (2)

- Different sequences for provoking these energy states, containing radio frequencies with different configurations
- Here we used:
  - T1w & dMRI
- T1w: presents differences in longitudinal tissue relaxation rate (as shown in a and b, as an extension of the previous slide)
- The resulting images shows good contrast between tissue types c)
- In panel d) we then see different possibilities to use these contrast differences to estimate further metrics, GM thickness, volume, surface area

Methods: Data

- Magnetic resonance imaging (MRI)
  - T1-weighted MRI
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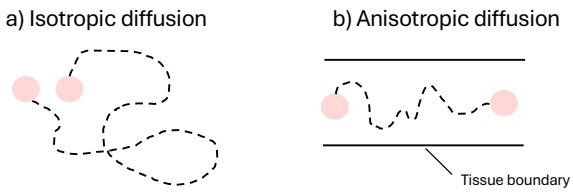

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- Diffusion: random movement of molecules, e.g.
  - a) in water (*unrestricted*)
  - B) *restricted* by tissue in the brain

Methods: Data

- Magnetic resonance imaging (MRI)
  - T1-weighted MRI
    - Clear contrasts between grey and white matter
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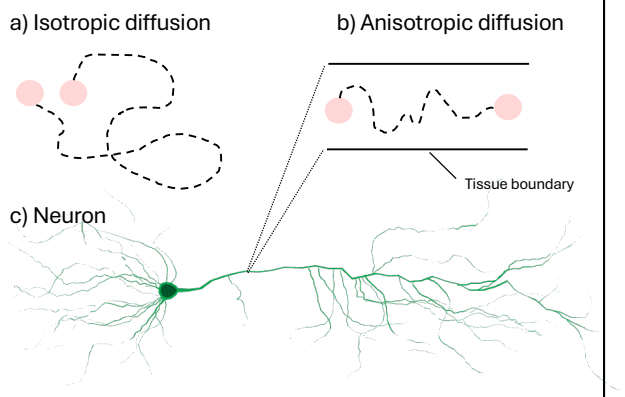

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- White matter, defined by bundles/tracts of axons
  - c) axons - part of neurons

Methods: Data

- Magnetic resonance imaging (MRI)
  - T1-weighted MRI
    - Clear contrasts between grey and white matter
  - Diffusion MRI
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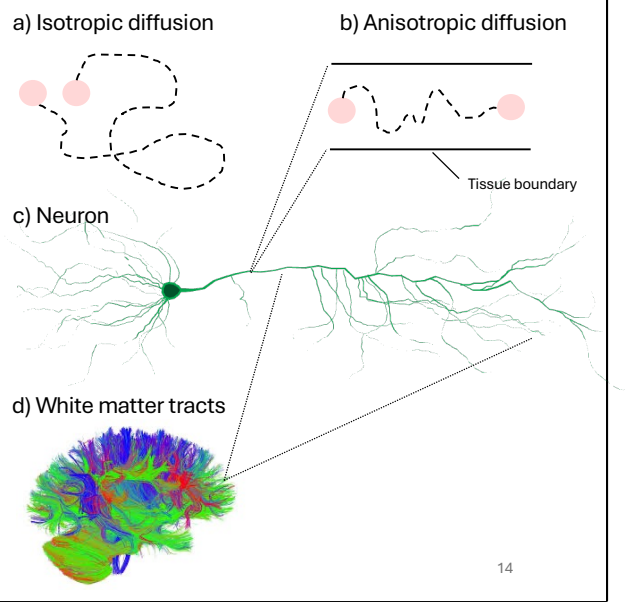

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- The diffusion coefficient will vary in different tissue types allowing to image white matter
  - d) whole brain tracts [colour indicates direction]
- The clearly restricted motion of molecules in white matter bundles is why diffusion MRI has often been used for white matter mapping

Methods: Data

- Magnetic resonance imaging (MRI)
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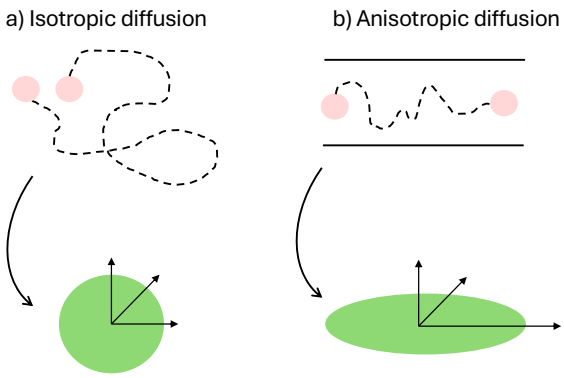

Most common approach: Diffusion Tensor Imaging (DTI)

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DTI: Basser et al., 1994, Biophys. J.

- We can use tensors consisting of three vectors to establish simple visualisations of diffusion
- For isotropic diffusion, the tensor is ball shaped (a)
- For anisotropic diffusion, the tensor is cigar shaped

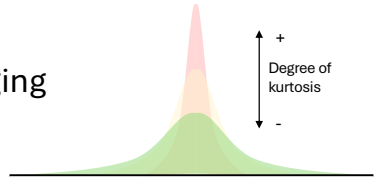
- OFTEN Using Gaussian tensors to model the diffusion direction is called diffusion tensor imaging
- IMPORTANT: NOT MICROSTRUCTURE MODELLING

- Problem: in most voxels, the organisation of tissue is complex, including crossing fibres and different tissue types
- In these cases, we might need other diffusion approaches providing similar or different metrics

Methods: Data

- Magnetic resonance imaging (MRI)
  - T1-weighted MRI
    - Clear contrasts between grey and white matter
  - Diffusion MRI
    - Diffusion restricted by tissue, hence useful for white matter mapping
- Pheno- & genotypes

a) Diffusion Kurtosis Imaging



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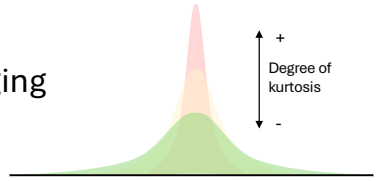
Kurtosis: Jensen et al., 2005, MR Med. 53 (6)

- For example, we can assume that water in biological tissue does not always behave Gaussian
  - We deviate from the isotropic function and describe diffusion with kurtosis (influences distribution shape)
  - The idea is that different levels of kurtosis allow to describe different tissue types or compartments

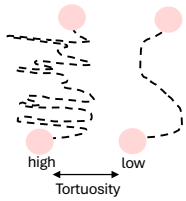
Methods: Data

- Magnetic resonance imaging (MRI)
  - T1-weighted MRI
    - Clear contrasts between grey and white matter
  - Diffusion MRI
    - Diffusion restricted by tissue, hence useful for white matter mapping
- Pheno- & genotypes

a) Diffusion Kurtosis Imaging



b) Spherical Mean Technique



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Spherical Mean Technique: Kaden et al., 2016, MR Med. 75 (4)

- We can also extend the DTI model by attempting to model the path length travelled by protons, instead of the linear distance (Spherical Mean Technique)

Methods: Data

- Magnetic resonance imaging (MRI)
  - T1-weighted MRI
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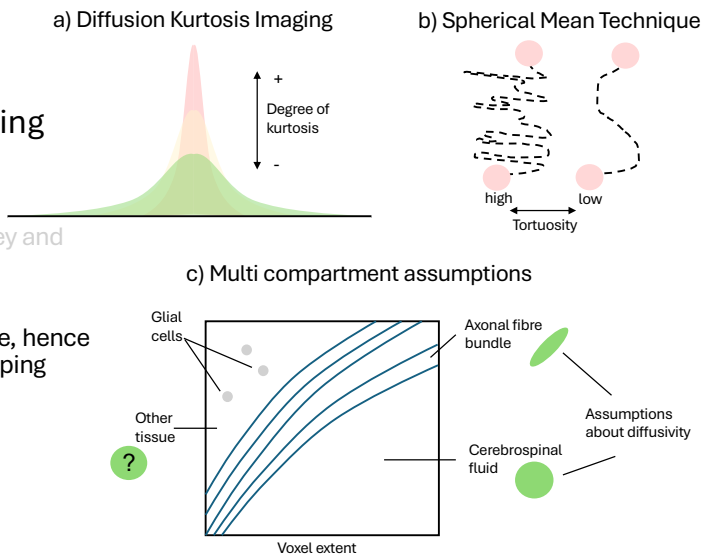
- Pheno- & genotypes



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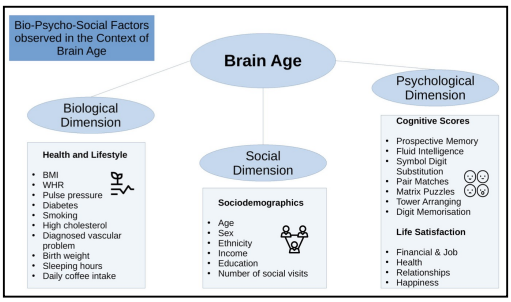
- Finally, we know that there are rarely only axons in a voxel
- Hence, different tissue compartments should be addressed differentially
- We can do so by making assumptions about differential diffusivity. Some approaches:
  - We can give a machine learning model the freedom to learn different orientation distribution functions (BRIA)
  - Or we make more static assumptions about diffusivity in different directions based on different compartments
    - E.g., thinking back the tensor, being different or similar tensor shapes in different tissue compartments
- **THERE IS NO CONSENSUS TO WHICH APPROACH IMAGES WM BEST**
- **SO WE USED SEVERAL DIFFUSION APPROACHES TO VALIDATE THESE**
- **We did not invent new approaches but tested their age associations in different ways**

Methods: Data

- Magnetic resonance imaging (MRI)
  - Diffusion MRI
    - Diffusion restricted by tissue, hence useful for white matter mapping
  - T1-weighted MRI
    - Clear contrasts between grey and white matter
- Pheno- & genotypes

Phenotypes (bio-psycho-social factors)



Genotypes (polygenic risk)

Alzheimer's Disease			Neuro-degenerative
Anxiety	Autism spectrum	Attention deficit hyperactivity	Psychiatric
Depression (uni-& bipolar)	Obsessive-compulsive	Schizophrenia	

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- Finally, we used both pheno- and genotypes
- Phenotypes: bio-psycho-social factors, being health and lifestyle factors, demographics, cognitive abilities
  - All measured as numerics
- Genotypes: polygenic risk scores, which indicate the genetic propensity to develop a certain disorder
  - For disorders *classically* described as neurodegenerative and psychiatric
  - Also a numeric propensity score, which is higher at a higher likelihood.

Methods: Datasets

Data: UKB, TOP, NCNG, BBSC, FTHP

- UK Biobank (UKB)
  - ~ 500k total participants, ~ 50k imaging participants, ~5k scanned twice
  - Geno- and phenotyping biobank, linked with hospital records
  - Largest MRI data base
- Tematisk Område Psykose (TOP) & Norwegian cognitive and neurogenetics study (NCNG)
  - Psychosis, neurodegeneration in focus
  - Healthy participant portion used: N = 1,065
- Bergen Breakfast Scanning Club (BBSC) & Frequently Travelling Human Phantom (FTHP)
  - Estimates of reliability of MRI data
  - N_{BBSC} = 3, number of scans = 25-40
  - N_{FTHP} = 1, number of scans = 557

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UK Biobank (UKB)

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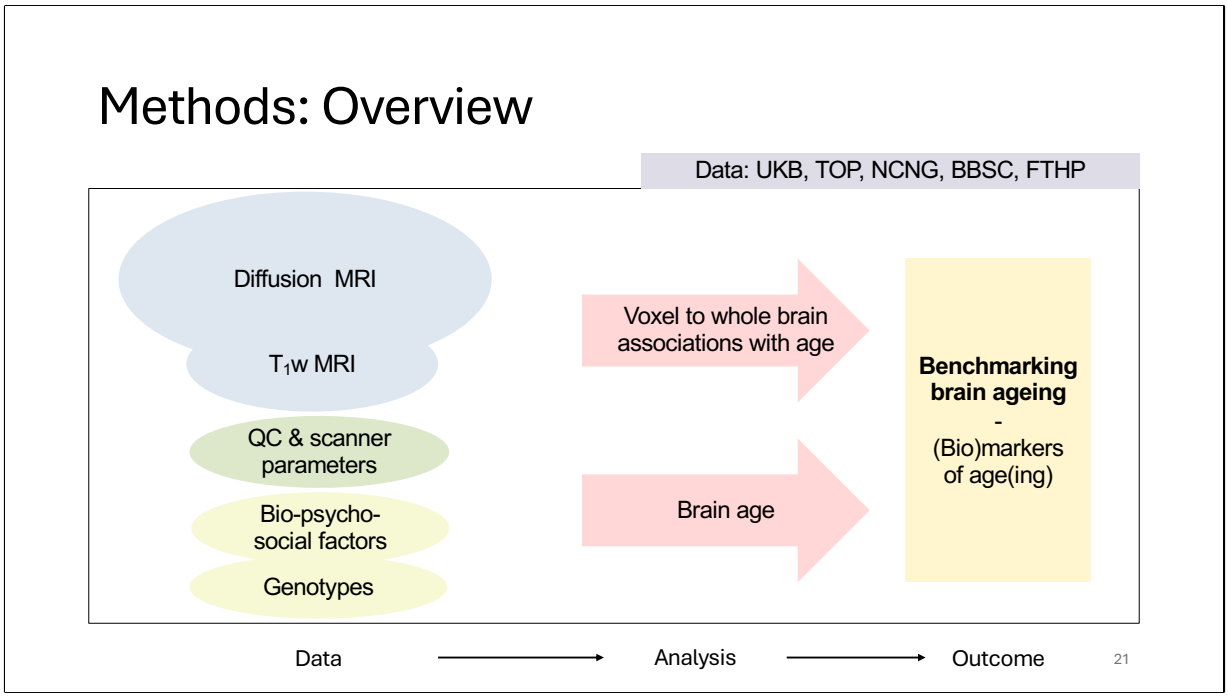
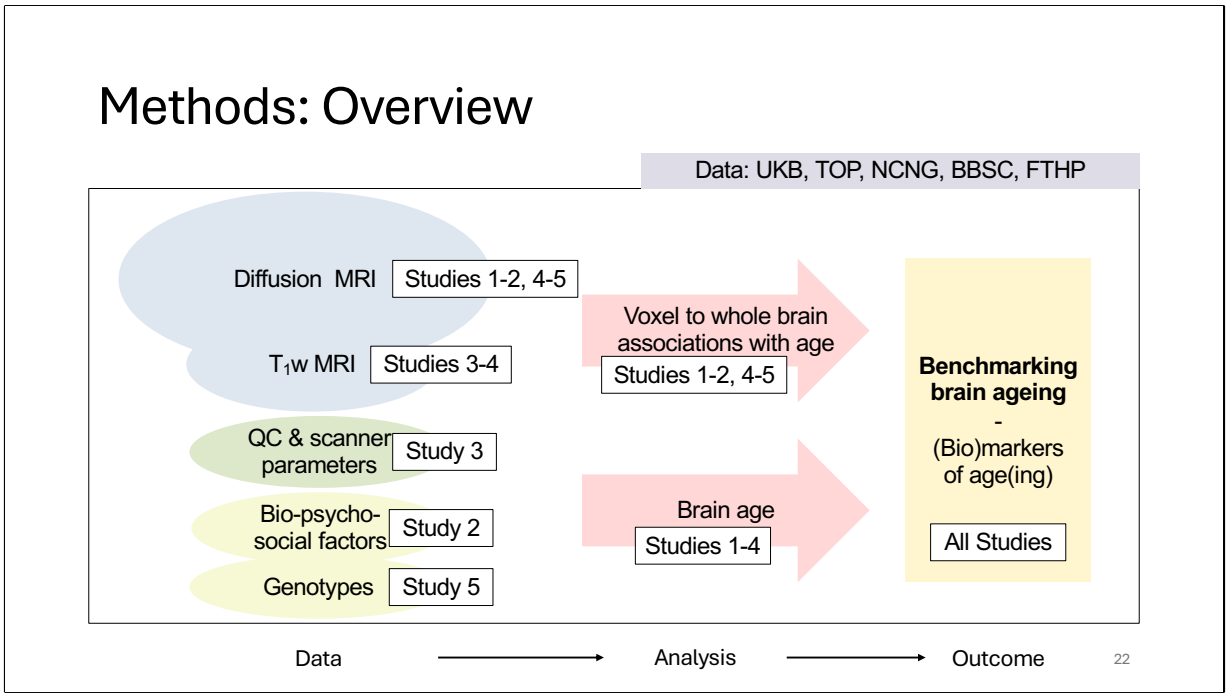
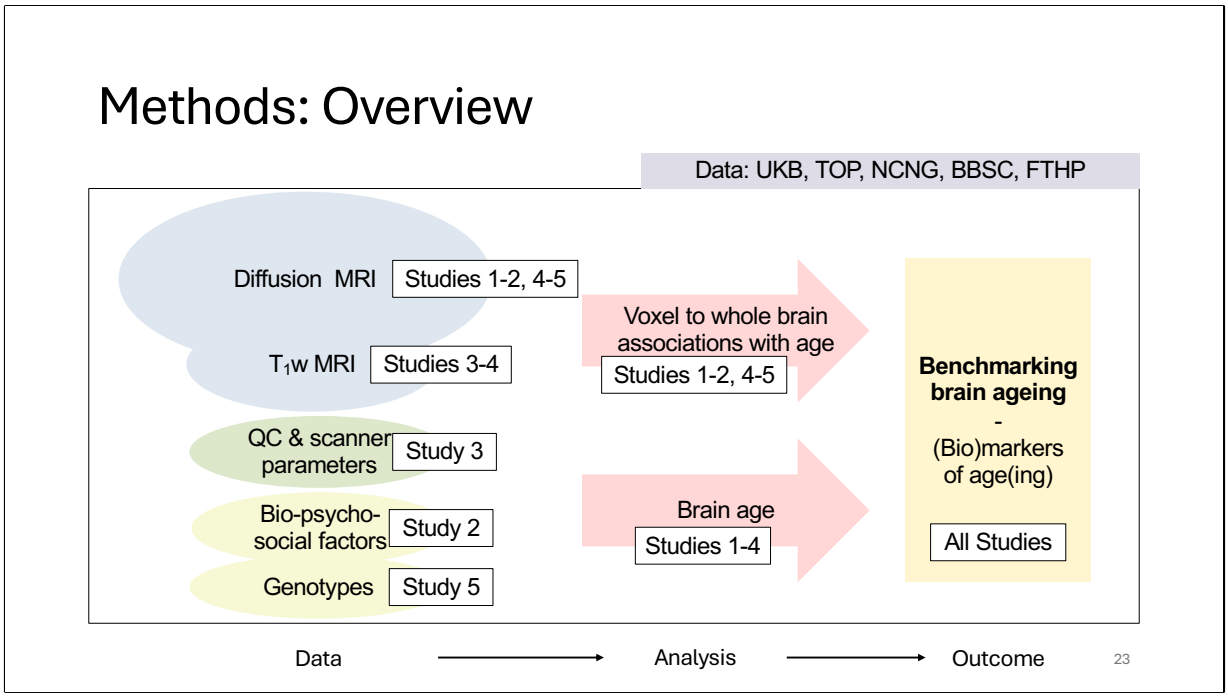


- To give an overview of Methods, including analyses and data …
- Used a breadth of data on **different spatial levels** generally …
    - associating brain features with age,
    - estimating brain age,
    - Both features and brain age with pheno and genotypes

- Benchmarking brain ageing was the goal, and more specifically, on the way there to identify some specific markers of ageing



- Different studies had some variations in methods, variables of interst and underlying data
- To provide an overview and allocation of the studies, see the figure
    - We started by studying cross-sectional brain age and white matter age associations (study 1)
        - Validation of approaches, largest white matter microstructure analysis
    - Then we looked at the bio-psycho-social associations of the estimated white matter brain age (study 2)
        - Further exploration of white matter brian age correlates
    - In the third study we looked at longitudinal brain age predictions in a few subjects (study 3)
        - Testing the concept of brain age

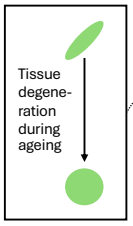


- To then introduce a new brain age concept estimating brain age per hemisphere (study 4)
    - Extension of the previous studies
- Finally, we looked at white matter ageing and genotype associations (study 5)
    - Validation of cross-sectional white matter findings + genotypes to provide context

- Note, not all studies used all modalities, and not all used the concept of brain age
- However, the idea was to look at brain ageing from a cross-sectional and then longitudinal perspective

Findings: White Matter Ageing (global)

- We confirm previous assumptions about white matter ageing
  - Tissue is more isotropic / more diffusion at higher ages



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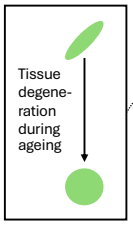
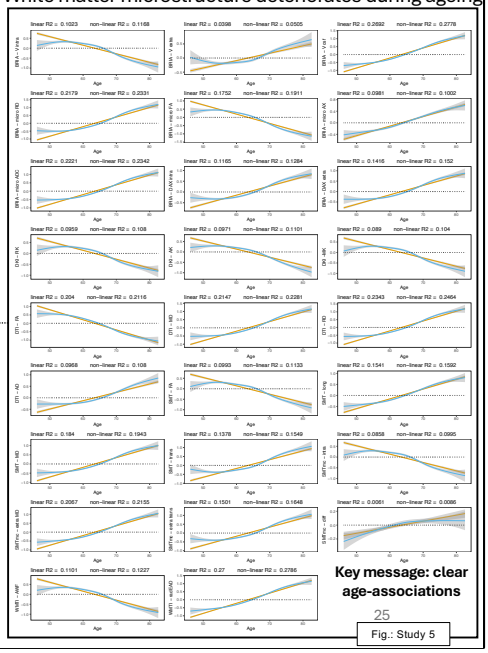
- We confirm previous assumptions about global / whole brain white matter ageing
  - Due to atrophy, tissue is more isotropic / more diffusion at higher ages

Findings: White Matter Ageing (global)

- We confirm previous assumptions about white matter ageing
  - Tissue is more isotropic / more diffusion at higher ages
  - This is reflected by different diffusion approaches clustering & showing similar age associations:
    - Diffusion coefficients & CSF
    - Anisotropy, kurtosis, intra axonal diffusion



White matter microstructure deteriorates during ageing



Key message: clear age-associations

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Fig.: Study 5

- This is reflected by the different diffusion approaches (remember the different possible approaches to estimate diffusivity)
- The figure presents whole brain white matter ageing assessed by different microstructure metrics
  - Diffusion coefficients & CSF cluster & are similarly age associated >> signify free water or extra axonal space?
  - Anisotropy, kurtosis, intra axonal diffusion cluster & similar ageing-trends >> signify intra-cellular structures?

Findings: White Matter Ageing (global)

- We confirm previous assumptions about white matter ageing
  - Tissue is more isotropic / more diffusion at higher ages
  - This is reflected by different diffusion approaches clustering & showing similar age associations:
    - Diffusion coefficients & CSF
    - Anisotropy, kurtosis, intra axonal diffusion
- Similar brain ages across diffusion approaches ≈ measuring the same construct

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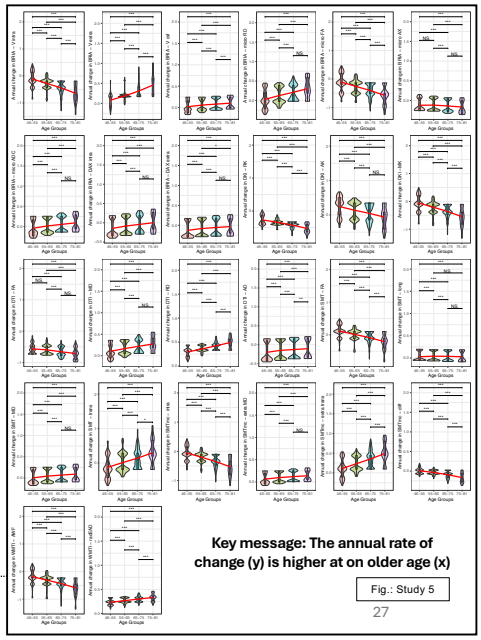
- This gives an **indication** of the **different approaches measuring** the **same construct**, which is white matter, and with it the age associations one can expect in white matter.
- **Multicompartment approaches** are **useful** here, as they **provide metrics separating intra and extra-axonal** space, and hence really **measuring microstructure**

Findings: White Matter Ageing (global)

- We confirm previous assumptions about white matter ageing
  - Tissue is more isotropic / more diffusion at higher ages
  - This is by different diffusion approaches clustering & showing similar age associations:
    - Diffusion coefficients & CSF
    - Anisotropy, kurtosis, intra axonal diffusion
- Similar brain ages across diffusion approaches ≈ measuring the same construct
- Brain ageing accelerates

White matter microstructure deterioration accelerates



Key message: The annual rate of change (y) is higher at on older age (x)

Fig.: Study 5

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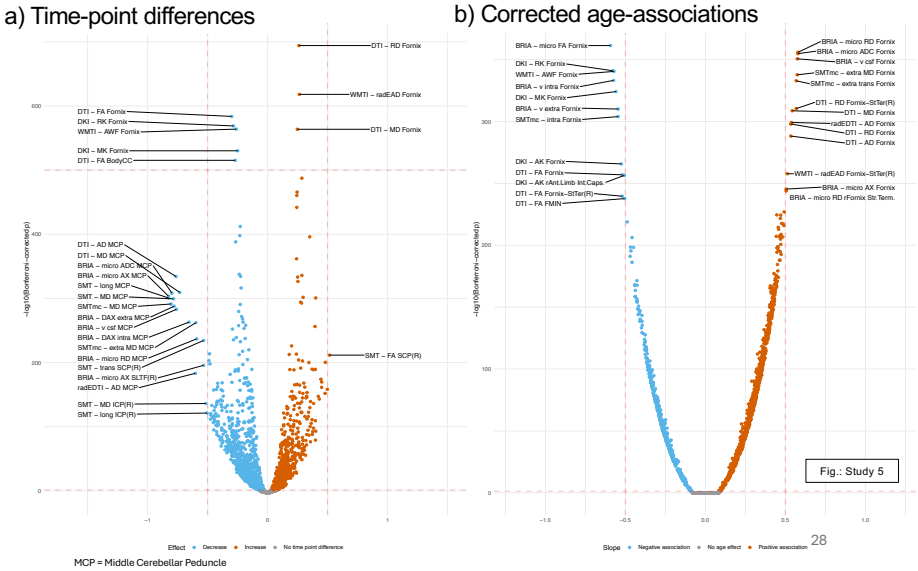
- We also show that the **rate of white matter ageing increases** at higher ages
- Any of the plots not showing a flat line indicates changes in the annual rate of white matter changes
- These values are not absolute & changes in both directions signify acceleration in deterioration effects

Findings: White Matter Ageing (regional)

- We identify particularly age-sensitive regions
  - Limbic: fornix
  - Corpus callosum
  - Brain stem: cerebellar peduncle

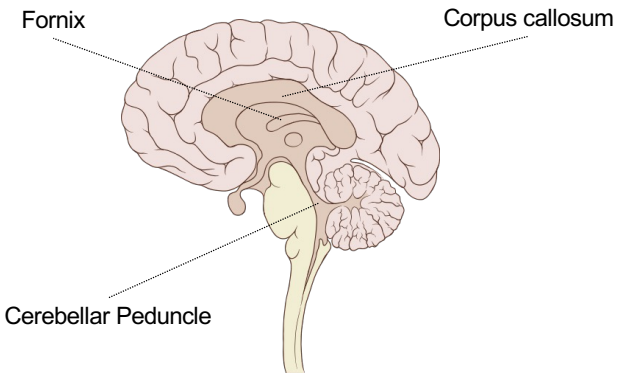


MCP = Middle Cerebellar Peduncle

- We also looked at the regional pattern of age-associations, e.g. in this volcano plot (usually used in genetics studies) indicating longitudinal changes raw (a) and corrected for age, sex, and scanner site (b)
  - x: effect magnitude; blue = negative, red = positive effect
  - y: log-transformed p-value > higher y = smaller p
  - Each dot represents effect of age on a diffusion metric in a brain region
- The labelled regions are those regions with largest effect sizes
- Across studies, we outline the **limbic region fornix, corpus callosum, and the brain-stem tract cerebral peduncle as age sensitive**

Findings: White Matter Ageing (regional)

- We identify particularly age-sensitive regions
  - Limbic: fornix
  - Corpus callosum
  - Brain stem: cerebellar peduncle



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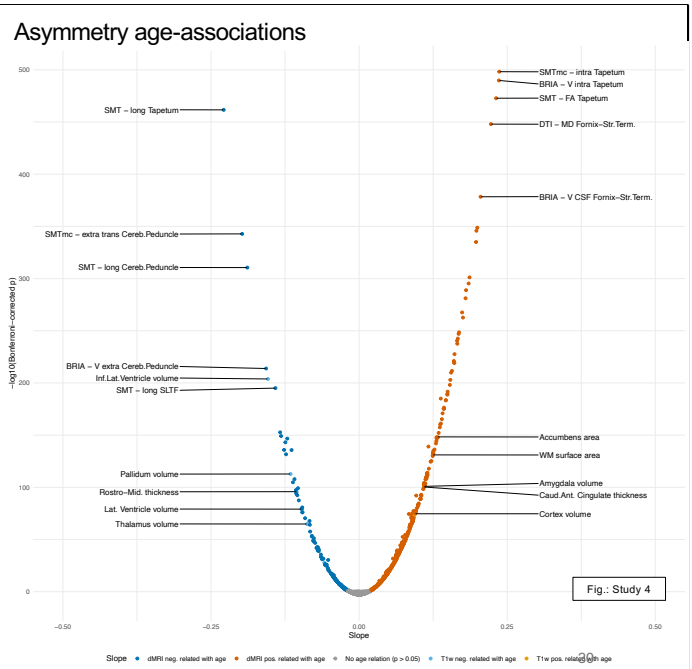
- Fornix is the hippocampal output tract
- Corpus callosum connects the two brain hemispheres
- Cerebellar peduncle

Findings: Brain Asymmetries

- Brain asymmetries' age-associations strongest in limbic & ventricle near and brain stem regions
- Coherent with other ageing findings



- **Asymmetry**
- Similar to the figure on recent slide: x = effect size, y = log-transformed p-value (associations were corrected for sex, age, scanner site)
- Each dot represents the association between regional white and grey matter asymmetry and age

- Brain asymmetries' age-associations **strongest in limbic & ventricle near and brain stem regions**
    - **Both white and grey matter**

Findings: Phenotype Associations of *Brain Age*

- White matter brain age relationships with bio-psycho-social factors

White matter brain age associations with health and lifestyle variables

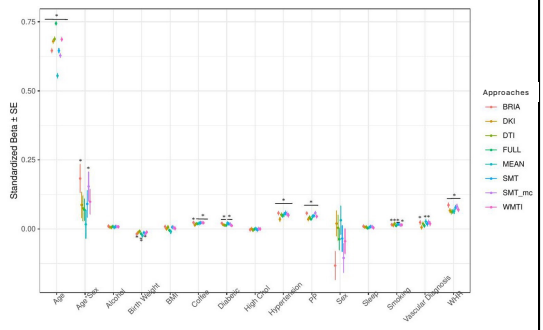


Fig.: Study 2

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- Phenotypes: Multiple multivariate regression to model different bio-psycho-social domains instead of only single variables
- SEE PANEL ON THE RIGHT
    - figure for illustration purposes of one of the three domains
    - The biological factors model presenting health and lifestyle predictors of brain age
    - Standardized beta coefficients (and standard errors) indicate the association strength between biological variables and brain age erstimated from white matter features of each utilised diffusion appraoch, such as DTI, DKI, etc.

Findings: Phenotype Associations of *Brain Age*

- White matter brain age relationships with bio-psycho-social factors
  - Significant predictors of brain age: waist-to-hip ratio, diabetes, hypertension, smoking, matrix puzzles solving, job- & health satisfaction and perception
  - WM brain age reflects overall health but is not well-predicted by any of the observed (BPS) domains

White matter brain age associations with health and lifestyle variables

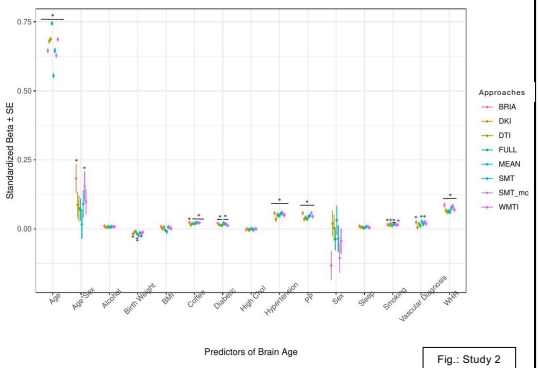

Fig.: Study 2

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- Overall, the results show that there are a **selection of variables** which are **consistently white matter brain age associated**
  - We can call these variables **bodily ageing indicators or indicators of health**
    - >>**white matter brain age reflective of health status**
- The **overall models** were however only **weakly reflecting brain age variability**
- Other modelling domains need to be explored (**SEM, Canonical Correlations**,etc.)

Findings: Genotype Associations of White Matter

- White matter microstructure ageing in the light of disease polygenicity
  - Potentially interesting: cerebellar peduncle
  - Yet…
    - These are small associations
    - No significance after correcting for multiple comparisons

Weak associations between white matter and the polygenic risk of psychiatric disorders and Alzheimer's disease

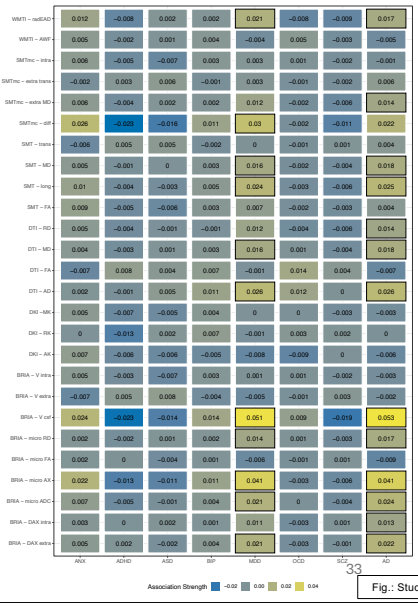


Fig.: Study 5

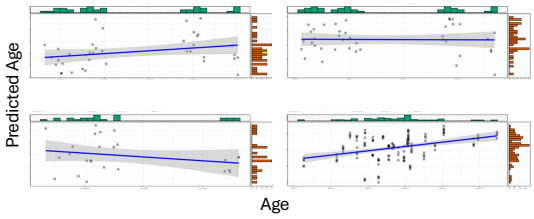
- **Genotypes**: polygenic risk of Alzheimer's disease and psychiatric disorders, here for the cerebellar peduncle
  - Y = peduncle white matter metrics
  - x = disorder polygenicity
  - Box colour & number indicates strength of association (standardized beta coefficients)
  - When framed by box $p < .05$
  - Note: none of the associations survived corrections for mulitple comparisons!

  - SMALL ASSOCIATIONS

Brain Age: Consideration and Extensions

- Brain age methodological investigations
  - Small within subject correlations
  - Effect of field strength

Within subject correlations between age and brain age (four individuals)



Single subject brain age predictions error is higher at 1.5T compared to 3T

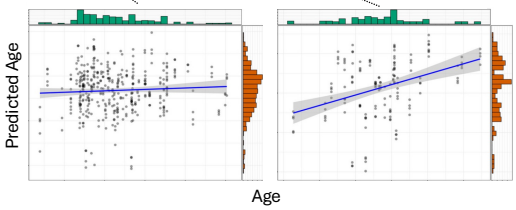


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Fig.: Study 3

- **Brain age often labelled** as an **indicator of ageing**
  - It is however unclear whether this statement is true
  - The only way to test this is using **longitudinal investigations** (which still need to be done)
- We tested an established pre-train convolutional neural network in our own (BBSC) and German (FTHP) data
  - Each panel in the plot represents one person, x = age, y = brain age over 1 year for first 3 panels and 3 years for bottom right panel
  - The associations were weak, and dependent on

Brain Age: Consideration and Extensions

- Brain age methodological investigations
  - Small within subject correlations
  - Effect of field strength

- A new (hemispheric) brain age prediction approach
  - Accurate hemisphere-specific predictions
  - Potential for unilaterally expressed (brain) disorders

Uni- and multimodal age predictions from single and both hemispheres are strongly correlated

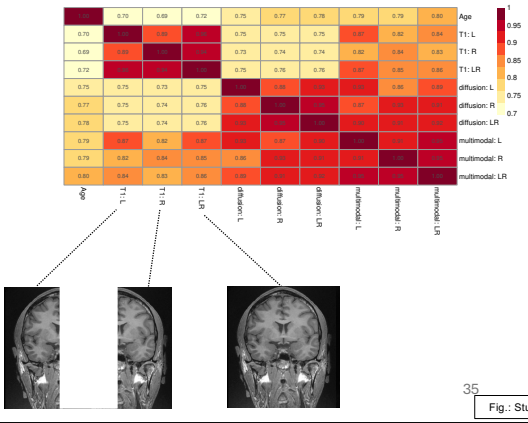

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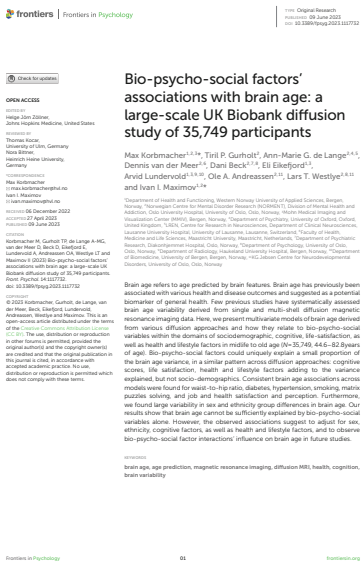
Fig.: Study 4

- The **findings call for new models**.
- Perhaps on more **diverse data**?
- Perhaps using a **different brain age approach**?
- Here, we tested age predictions from a single hemisphere compared to both hemispheres (or conventional brain age)
  - Hemispheric brain age performed similar to regular brain age
  - BUT it has potential use case for patients with unilaterally expressed brain disorders or damage, by combining the predictions from the hemispheres

Summary

- Brain age
  - general indicator of health



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Bio-psycho-social factors' associations with brain age: a large-scale UK Biobank diffusion study of 35,749 participants

Max Korbmacher[1,2,3*], Tiril P. Gurholt[2], Ann-Marie G. de Lange[2,4,5], Dennis van der Meer[2,6], Dani Beck[1,7,8], Eli Eikefjord[1,3], Arvid Lundervold[1,3,9,10], Ole A. Andreassen[2,6], Lars T. Westlye[2,6,11] and Ivan I. Maximov[1,2*]

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Brain age refers to age predicted by brain features. Brain age has previously been associated with various health and disease outcomes and suggested as a potential biomarker of general health. Few previous studies have systematically assessed brain age variability derived from single and multi-shell diffusion magnetic resonance imaging data. Here, we present multivariate models of brain age derived from various diffusion approaches and how they relate to bio-psycho-social variables within the domains of sociodemographic, cognitive, life-satisfaction, as well as health and lifestyle factors in middle to old age (N=35,749, 44.6–82.8years of age). Bio-psycho-social factors could uniquely explain a small proportion of the brain age variance, in a similar pattern across diffusion approaches: cognitive scores, life satisfaction, health and lifestyle factors adding to the variance explained, but not socio-demographics. Consistent brain age associations across models were found for waist-to-hip ratio, diabetes, hypertension, smoking, matrix puzzles solving, and job and health satisfaction and perception. Furthermore, we found large variability in sex and ethnicity group differences in brain age. Our results show that brain age cannot be sufficiently explained by bio-psycho-social variables alone. However, the observed associations suggest to adjust for sex, ethnicity, cognitive factors, as well as health and lifestyle factors, and to observe bio-psycho-social factor interactions' influence on brain age in future studies.

KEYWORDS
brain age, age prediction, magnetic resonance imaging, diffusion MRI, health, cognition, brain variability

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- Across paper, we showed that …

- Brain age is a general indicator of health

Summary

- Brain age
  - general indicator of health
  - can be conceptualised in different ways

nature communications

Article https://doi.org/10.1038/s41467-024-45282-3

Brain asymmetries from mid- to late life and hemispheric brain age

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Max Korbmacher[1,2,3], Dennis van der Meer[2,4], Dani Beck[2,5,6], Ann-Marie G. de Lange[2,7,8], Eli Eikefjord[1,3], Arvid Lundervold[2,9], Ole A. Andreassen[2,10], Lars T. Westlye[2,6,10] & Ivan I. Maximov[1,2]

The human brain demonstrates structural and functional asymmetries which have implications for ageing and mental and neurological disease development. We used a set of magnetic resonance imaging (MRI) metrics derived from structural and diffusion MRI data in N=48,040 UK Biobank participants to evaluate age-related differences in brain asymmetry. Most regional grey and white matter metrics presented asymmetry, which were higher later in life. Informed by these results, we conducted *hemispheric brain age* (HBA) predictions from left/right multimodal MRI metrics. HBA was concordant to conventional brain age predictions, using metrics from both hemispheres, but offers a supplemental general marker of brain asymmetry when setting left/right HBA into relationship with each other. In contrast to WM brain asymmetries, left/right discrepancies in HBA are lower at higher ages. Our findings outline various sex-specific differences, particularly important for brain age estimates, and the value of further investigating the role of brain asymmetries in brain ageing and disease development.

There are various structural and functional differences in brain architecture between the left and right hemispheres[1–4]. Microstructural brain characteristics, such as white matter (WM) pathways or intra- and extra-neurite water organisation, might underlie the brain's functional lateralisation[5]. Furthermore, handedness has been repeatedly assessed together with asymmetry in humans and animals, and relates to brain asymmetry[6]. Both structural and functional brain asymmetry exhibit clinical importance as there are differences in brain asymmetry between healthy controls and various disease groups, including neurodegenerative diseases such as Alzheimer's disease[7–9], Parkinson's disease[7], and psychiatric disease such as obsessive-compulsive disorder[10,11] and schizophrenia[12]. In that context and particularly relevant from a lifespan perspective, cortical thickness asymmetry decreases throughout ageing, with this alteration being potentially accelerated in the development of neurodegenerative disorders such as Alzheimer's Disease[7]. Similarly, some studies suggest lower WM microstructure asymmetry at higher ages, indicated by intra-axonal water fraction[13], fractional anisotropy, or the apparent diffusion coefficient[14]. Additional investigations into brain asymmetries' age-dependencies can provide a more comprehensive understanding of the influence of asymmetries on ageing and disease development.

Brain age is a developing integrative marker of brain health, particularly sensitive to neurodegenerative diseases[15–18]. Brain age refers to the predicted age in contrast to chronological age and is based on a set of scalar metrics derived from brain scans such as MR. To date, brain age has often been estimated using a global brain parametrisation such

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- Across paper, we showed that …

- Brain age can be conceptualised in different ways

Summary

- Brain age
  - general indicator of health
  - can be conceptualised in different ways
- However, transitioning brain age into the clinic requires further work

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ORIGINAL ARTICLE

Brain and Behavior Open Access WILEY

Considerations on brain age predictions from repeatedly sampled data across time

Max Korbmacher[1,2,3] | Meng-Yun Wang[3,4] | Rune Eikeland[3,4] | Ralph Buchert[5] | Ole A. Andreassen[2,6] | Thomas Espeseth[7,8] | Esten Leonardsen[2,7] | Lars T. Westlye[2,7] | Ivan I. Maximov[1,2] | Karsten Specht[3,4,9]

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Abstract

Introduction: Brain age, the estimation of a person's age from magnetic resonance imaging (MRI) parameters, has been used as a general indicator of health. The marker requires however further validation for application in clinical contexts. Here, we show how brain age predictions perform for the same individual at various time points and validate our findings with age-matched healthy controls.

Methods: We used densely sampled T1-weighted MRI data from four individuals (from two densely sampled datasets) to observe how brain age corresponds to age and is influenced by acquisition and quality parameters. For validation, we used two cross-sectional datasets. Brain age was predicted by a pretrained deep learning model.

Results: We found small within-subject correlations between age and brain age. We also found evidence for the influence of field strength on brain age which replicated in the cross-sectional validation data and inconclusive effects of scan quality.

Conclusion: The absence of maturation effects for the age range in the presented sample, brain age model bias (including training age distribution and field strength), and model error are potential reasons for small relationships between age and brain age in densely sampled longitudinal data. Clinical applications of brain age models should consider of the possibility of apparent biases caused by variation in the data acquisition process.

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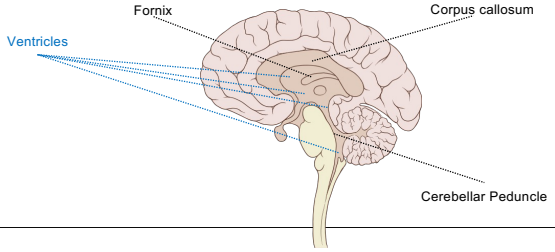
- However, clinical implication of brain age requires still further work
  - Brain age needs to be further validated, and generalisability, reliability, and interpretability need to be increased
    - Generalisability & reliability can be increased using diverse samples beyond white Europeans and North Americans
    - Reliability can be increased by firstly knowing the effects of analysis pipeline, sample characteristics, etc.
    - Interpretability can be increased by extending current study designs e.g., using correlates in longitudinal data, and more deeply/repeatedly sampled data (within subjects)
- This is also true for the rest of our findings

Summary

- Brain age
  - general indicator of health
  - can be conceptualised in different ways
- However, transitioning brain age into the clinic requires further work
- Age sensitive regions
  - Ventricle-near, brain stem



Distinct longitudinal brain white matter microstructure changes and associated polygenic risk of common psychiatric disorders and Alzheimer's disease in the UK Biobank

Running title: White matter aging and polygenic risk in the UK Biobank

Max Korbmacher[1,2,3*], Dennis van der Meer[2,4], Dani Beck[2,5,6], Daniel E. Askeland-Gjerde[2], Eli Eikefjord[1,3], Arvid Lundervold[3,7], Ole A. Andreassen[2,8], Lars T. Westlye[2,6,8], Ivan I. Maximov[1,2*]

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RESEARCH ARTICLE

WILEY

Brain-wide associations between white matter and age highlight the role of fornix microstructure in brain ageing

Max Korbmacher[1,2,3] | Ann Marie de Lange[2,4,5] | Dennis van der Meer[2,4] | Dani Beck[2,7,8] | Eli Eikefjord[1,3] | Arvid Lundervold[1,2,9,10] | Ole A. Andreassen[2,11] | Lars T. Westlye[2,8,11] | Ivan I. Maximov[1,2]

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Abstract
Unveiling the details of white matter (WM) maturation throughout ageing is a fundamental question for understanding the ageing brain. In an extensive comparison of brain age predictions and age-associations of WM features from different diffusion approaches, we analyzed UK Biobank diffusion magnetic resonance imaging (dMRI) data across midlife and older age (N = 35,749, 44.6–82.8 years of age). Conventional and advanced dMRI approaches were consistent in predicting brain age. WM-age associations indicate a steady microstructure degeneration with increasing age from midlife to older ages. Brain age was estimated best when combining diffusion approaches, showing different aspects of WM contributing to brain age. Fornix was found as the central region for brain age predictions across diffusion approaches in complement to forceps minor as another important region. Three regions exhibited a general pattern of positive associations with age for intra axonal water fractions, axial, radial diffusivities, and negative relationships with age for mean diffusivities, fractional anisotropy, kurtosis. We encourage the application of multiple dMRI approaches for detailed insights into WM, and the further investigation of fornix and forceps as potential biomarkers of brain age and ageing.

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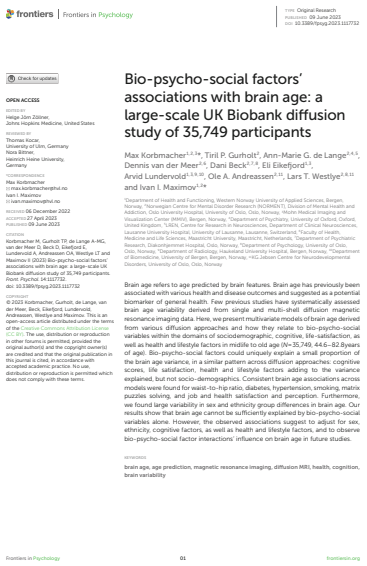
- We identify several highly age-sensitive regions, which might be useful as ageing markers
  - corpus callosum
  - brain stem
  - limbic system (+ ventricles)
- Multiple potential problems with these regions, not only in terms of directly obtaining signal, but also biological changes in ventricle near tissue

Summary

- Brain age
  - general indicator of health
  - can be conceptualised in different ways
- However, transitioning brain age into the clinic requires further work
- Age sensitive regions
  - Ventricle-near and brain stem
- Small associations between white matter brain age and bio-psycho-social factors



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Bio-psycho-social factors' associations with brain age: a large-scale UK Biobank diffusion study of 35,749 participants

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Brain age refers to age predicted by brain features. Brain age has previously been associated with various health and disease outcomes and suggested as a potential biomarker of general health. Few previous studies have systematically assessed brain age variability derived from single and multi-shell diffusion magnetic resonance imaging data. Here, we present multivariate models of brain age derived from various diffusion approaches and how they relate to bio-psycho-social variables within the domains of sociodemographic, cognitive, life-satisfaction, as well as health and lifestyle factors in middle to old age (N=35,740, 44.6–82.8years of age). Bio-psycho-social factors could uniquely explain a small proportion of the brain age variance, in a similar pattern across diffusion approaches: cognitive scores, life satisfaction, health and lifestyle factors adding to the variance explained, but not socio-demographics. Consistent brain age associations across models were found for waist-to-hip ratio, diabetes, hypertension, smoking, matrix puzzles solving, and job and health satisfaction and perception. Furthermore, we found large variability in sex and ethnicity group differences in brain age. Our results show that brain age cannot be sufficiently explained by bio-psycho-social variables alone. However, the observed associations suggest to adjust for sex, ethnicity, cognitive factors, as well as health and lifestyle factors, and to observe bio-psycho-social factor interactions' influence on brain age in future studies.

KEYWORDS
brain age, age prediction, magnetic resonance imaging, diffusion MRI, health, cognition, brain variability

- Associations between white matter brain age and bio-psycho-social factors were small
  - Single predictors reflecting ageing were significantly related to brain age

Summary

- Brain age
  - general indicator of health
  - can be conceptualised in different ways
- However, transitioning brain age into the clinic requires further work
- Age sensitive regions
  - Ventricle-near and brain stem
- Small associations between white matter brain age and bio-psycho-social factors
- Small associations between polygenic risk and white matter

Distinct longitudinal brain white matter microstructure changes and associated polygenic risk of common psychiatric disorders and Alzheimer's disease in the UK Biobank

Running title: White matter aging and polygenic risk in the UK Biobank

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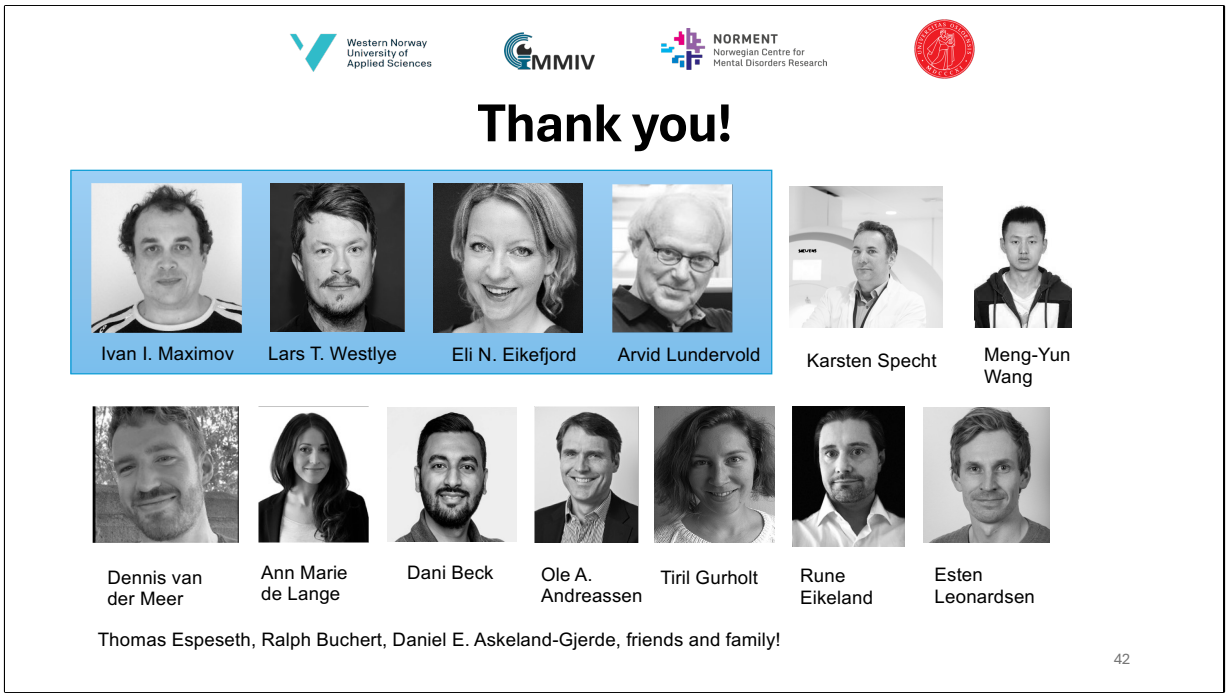
- Finally, we find a distributed spatial pattern of polygenic risk across WM
- Shows a pattern of small associations

- FINALLY:
- Our findings need to be validated in different, more diverse samples (we use mainly white Europeans) and tested on clinical data [logical next steps for me]



And with that, I would like to thank you for your attentions, as well as my collaborators, friends and family for supporting me during this project.

And a special thank you to my supervisors, and in particular my main supervisor Ivan Maximov for their guidance and insight.

Supplemental Information

Supplemental Information: Methods

Methods: Why using machine learning for brain age prediction?

- Brain age predictions are usually done using machine learning techniques due to the multidimentionality of the data
  - Classical statistics are here not providing meaningful results (due to underfitting & low explanatory value of coefficients when coefficients are in the hundreds)
  - Machine learning has the advantage to repeatedly predict, optimise modelling choices and thereby decrease prediction error = “LEARNING”
  - We chose XGBoost, as it is one of the best performing algorithms for tabular data
  - There are other algorithms, but here we focus on XGBoost

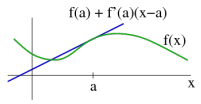
More details on XGBoost

- *l* is a function of CART learners, a sum of the current and previous additive trees
- We can start a predicted value = 0 and then add a new tree
- *t* refers to Taylor's Theorem, simple linear example
  - Helps to specify f(x) to the current iteration
- After Taylor expansion and defining the regularisation parameter

$$\hat{y}_i = \sum_{k=1}^{K} f_k(x_i), f_k \epsilon \mathcal{F}$$

$$obj(\theta) = \sum_i^n l(y_i, \hat{y}_i) + \sum_{k=1}^{K} \Omega(f_k)$$

$$\hat{y}_i^{(0)} = 0$$
$$\hat{y}_i^{(1)} = f_1(x_i) = \hat{y}_i^{(0)} + f_1(x_i)$$
$$\hat{y}_i^{(2)} = f_1(x_i) + f_2(x_i) = \hat{y}_i^{(1)} + f_2(x_i)$$
$$\ldots$$
$$\hat{y}_i^{(t)} = \sum_{k=1}^{t} f_k(x_i) = \hat{y}_i^{(t-1)} + f_t(x_i)$$



$$w_j^* = -\frac{G_j}{H_j + \lambda}$$
$$\text{obj}^* = -\frac{1}{2} \sum_{j=1}^{T} \frac{G_j^2}{H_j + \lambda} + \gamma T$$

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- Top row: how model,

- CART = classification and regression trees > own specific algorithm by Breiman et al, 1984
  - Defined by pruning, splitting
  - Tree-structure is modes and branches

The nodes represent different decision points, and the branches represent the possible outcomes of those decisions. The leaf nodes in the tree contain a predicted class label or value for the target variable.

Taylor's theorem allows to specify current iterations

Final equation in bottom line

G for groups

Gamma is pruning parameter

T the Tree (numbered)

H are the functions describing each branch

Last part is gamma, the pruning parameter and again the iteration/Tree

Collinearity and Feature Importance
Background

- Collinearity is an issue in all brain features, as none of them are statistically independent from each other.
- XGB claimed to be robust to multicollinearity due to pruning
  - Yet, all depends on loss function and regularisation
  - Restrictive hyperparameters, e.g. small learning rate, >> under- or overfitting >> misrepresentation of actually important feature(s)
    - But how to tune hyperparameters ”correctly”?
- Many ways to estimate feature importance
  - We used gain (contribution-based) and permutation-based feature importance (error-based)
  - SHAP as an alternative (magnitude-based; robust??)

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Collinearity

- Collinearity is an issue in all brain features, as none of them are statistically independent from each other.
- XGB claimed to be robust to multicollinearity due to pruning
  - Yet, all depends on loss function and regularisation
  - Restrictive hyperparameters, e.g. small learning rate, >> under- or overfitting >> misrepresentation of actually important feature(s)
    - But how to tune hyperparameters ”correctly”?
    - There is no straight forward answer to that, but randomly drawn training data over multiple iterations and then averaging across parameters might be an option (instead of using the best performing parameters)

Many ways to estimate feature importance
  - We used gain and permutation-based feature importance
  - SHAP as an alternative (robust?)

GAIN
- GAIN reflects the average contribution of a feature to the model's predictions across all trees

Permutation Feature Importance

- The concept is really straightforward: We measure the importance of a feature by calculating the increase in the model's prediction error after permuting the feature.
- A feature is "important" if shuffling its values increases the model error, because in this case the model relied on the feature for the prediction.
- A feature is "unimportant" if shuffling its values leaves the model error unchanged, because in this case the model ignored the feature for the prediction.

SHAP

- Features with large absolute Shapley values are important
- SHAP feature importance is an alternative to permutation feature importance.
- There is a big difference between both importance measures: Permutation feature importance is based on the decrease in model performance. S
- HAP is based on magnitude of feature attributions.

Collinearity and Feature Importance
Examples of Resulting Problems

- Examples for collinearity-induced problems with feature importance estimates (gain & permutation-based)
  - Collinearity means potentially unrealistic or even impossible feature combinations
    - E.g. artificially introducing the 2m tall and 30kg heavy person, or young brain at very old age
  - Adding a correlated feature can decrease the importance of the associated feature by splitting the importance between both features.
    - E.g., temperature as most important whether predicting feature
    - When included at different times, e.g. 8am, 9am, 10am only mediocre importance >> correlated features steal each other's importance

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- For permutation feature importance of a correlated feature, we consider how much the model performance decreases when we exchange the feature with values we would never observe in reality.
- **Adding a correlated feature**

can decrease the importance of the associated feature by splitting the importance between both features.

Collinearity and Feature Importance
Solutions? 1/3

- Are variance-based methods the solution to multicollinearity problems?
- Unclear.
  - SHAP is slow
  - SHAP ignores feature dependence (as permutation-based approaches do)
  - SHAP can be misinterpreted, needs new data (also true for other approaches)
  - One cannot be sure about the truthfulness of SHAP explanations

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- Also SHAP has multiple problems:
  - **KernelSHAP is slow**. This makes KernelSHAP impractical to use when you want to compute Shapley values for many instances. Also all global SHAP methods such as SHAP feature importance require computing Shapley values for a lot ofinstances.
  - **KernelSHAP ignores feature dependence**. Most other permutation based interpretation methods have this problem. By replacing feature values with values from random instances, it is usually easier to randomly sample from the marginal distribution. However, if features are dependent, e.g. correlated, this leads to putting too much weight on unlikely data points. TreeSHAP solves this problem by explicitly modeling the conditional expected prediction.
  - **TreeSHAP can produce unintuitive feature attributions**. While TreeSHAP solves the problem of extrapolating to unlikely data points, it does so by changing the value function and therefore slightly changes the game. TreeSHAP changes the value function by relying on the conditional expected prediction. With the change in the value function, features that have no influence on the prediction can get a TreeSHAP value different from zero.

- The disadvantages of Shapley values also apply to SHAP: Shapley values **can be misinterpreted** and access to data is needed to compute them for new data (except for TreeSHAP).
- It is **possible to create intentionally misleading interpretations** with SHAP, which can hide biases. If you are the data scientist creating the explanations, this is not an actual problem (it would even be an advantage if you are the evil data scientist who wants to create misleading explanations). For the receivers of a SHAP explanation, it is a disadvantage: they cannot be sure about the truthfulness of the explanation. (interpretation based)

Collinearity and Feature Importance
Solutions? 2/3

- Are variance-based methods the solution to multicollinearity problems?
- Generalized Functional ANOVA for Dependent Features
  - Perhaps the best option, but computationally expensive
- Another solution: use different algorithm than XGBoost, e.g. least absolute shrinkage and selection operator (Lasso)

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- If we integrate over the uniform distribution, when in reality features are dependent, we create a new dataset that deviates from the joint distribution and extrapolates to unlikely combinations of feature values.
- Hooker (2007) [40] proposed the generalized functional ANOVA, a decomposition that works for dependent features.
  - It is a generalization of the functional ANOVA we encountered earlier, which means that the functional ANOVA is a special case of the generalized functional ANOVA.
  - The components are defined as projections (of a function f) onto the space of additive functions
  - Instead of orthogonality, the components satisfy a hierarchical orthogonality condition
  - Hierarchical orthogonality is different from orthogonality.
  - For two feature sets S and U, neither of which is the subset of the other (e.g. $S=\{1,2\}$ and $U=\{2,3\}$), the components $\hat{f}_S$ and $\hat{f}_U$ need not be orthogonal for the decomposition to be hierarchically orthogonal.
  - But all components for all subsets of S must be orthogonal to $\hat{f}_S$. As a result, the interpretation differs in relevant ways: Similar to the M-Plot in the ALE chapter, generalized functional ANOVA components

can entangle the (marginal) effects of correlated features.

- Whether the components entangle the marginal effects also depends on the choice of weight function w(x). If we choose w to be the uniform measure on the unit cube, we obtain the functional ANOVA from the section above. A natural choice for w is the joint probability distribution function. However, the joint distribution is usually unknown, and difficult to estimate. A trick can be to start with the uniform measure on the unit cube, and cut out areas without data.
- The estimation is done on a grid of points in the feature space and is stated as a minimization problem that can be solved using regression techniques. However, the components cannot be computed individually, nor hierarchically, but a complex system of equations involving other components has to be solved. The computation is therefore quite complex and computationally intensive.

Collinearity and Feature Importance
Solutions? 3/3

```
==============
MODEL = Lasso
==============
validating train model
------------------------------
RMSE values:
Mean and STD for RMSE: -5.622 (0.241)
------------------------------
MAE values:
Mean and STD for MAE: -4.539 (0.191)
------------------------------
R2 values:
Mean and STD for R2: 0.405 (0.067)
running pearsons corr for predicted versus true age for train
r = 0.6416398401464694
r p-value = 4.3556432118041 28e-262
r CI = [0.6167068444488446,0.6652867426267055]
------------------------------
rh_inferiorparietal_volume 0.326918 +/- 0.014785
rh_inferiorparietal_area 0.296239 +/- 0.008964
lh_superiorfrontal_volume 0.209400 +/- 0.005854
lh_inferiortemporal_area 0.164863 +/- 0.009154
lh_lateralorbitofrontal_area 0.101468 +/- 0.004828
lh_inferiortemporal_volume 0.087494 +/- 0.003776
rh_superiortemporal_area 0.079522 +/- 0.005506
rh_superiortemporal_volume 0.078167 +/- 0.005365
rh_lateraloccipital_volume 0.069331 +/- 0.006520
lh_superiorfrontal_area 0.066431 +/- 0.005056
lh_superiorparietal_volume 0.063909 +/- 0.005826
lh_superiorparietal_area 0.063814 +/- 0.004386
rh_inferiortemporal_area 0.063764 +/- 0.003235
lh_superiortemporal_area 0.059980 +/- 0.003362
lh_inferiorparietal_area 0.058544 +/- 0.005459
lh_rostralmiddlefrontal_volume 0.051523 +/- 0.003879
lh_superiortemporal_volume 0.051497 +/- 0.002855
rh_lateralorbitofrontal_volume 0.046934 +/- 0.002976
rh_rostralanteriorcingulate_volume 0.045147 +/- 0.003525
lh_precentral_area 0.044108 +/- 0.003685
rh_caudalmiddlefrontal_volume 0.044098 +/- 0.003784
rh_superiorparietal_volume 0.044024 +/- 0.003518
lh_caudalmiddlefrontal_area 0.044008 +/- 0.003401
lh_precentral_volume 0.040874 +/- 0.002864
rh_lateraloccipital_area 0.040660 +/- 0.003651
```

```
==============
MODEL = XBGoost
==============
validating train model
------------------------------
RMSE values:
Mean and STD for RMSE: -6.059 (0.213)
------------------------------
MAE values:
Mean and STD for MAE: -4.844 (0.162)
------------------------------
R2 values:
Mean and STD for R2: 0.311 (0.053)
running pearsons corr for predicted versus true age for train
r = 0.5682351493163473
r p-value = 3.4499390953770 4e-193
r CI = [0.5396272262365295,0.5955323691675773]
------------------------------
lh_superiortemporal_thickness 0.101886 +/- 0.003640
lh_superiorfrontal_thickness 0.064666 +/- 0.001862
rh_inferiorparietal_thickness 0.063449 +/- 0.002296
rh_superiortemporal_thickness 0.042951 +/- 0.001683
rh_lateraloccipital_thickness 0.028974 +/- 0.001052
lh_parahippocampal_volume 0.028948 +/- 0.001289
lh_inferiortemporal_area 0.020683 +/- 0.000829
lh_temporalpole_volume 0.020561 +/- 0.000889
lh_lingual_thickness 0.017682 +/- 0.000784
rh_isthmuscingulate_thickness 0.017464 +/- 0.000802
lh_middletemporal_thickness 0.016810 +/- 0.000930
rh_temporalpole_volume 0.014493 +/- 0.000598
rh_entorhinal_volume 0.014457 +/- 0.000564
rh_rostralanteriorcingulate_thickness 0.013834 +/- 0.000776
lh_lateralorbitofrontal_area 0.013768 +/- 0.000617
lh_middletemporal_area 0.013675 +/- 0.000686
lh_caudalanteriorcingulate_thickness 0.011955 +/- 0.000602
rh_precuneus_thickness 0.011725 +/- 0.000453
lh_fusiform_area 0.009067 +/- 0.000411
rh_middletemporal_volume 0.008728 +/- 0.000558
rh_lingual_area 0.008703 +/- 0.000522
lh_rostralanteriorcingulate_thickness 0.007949 +/- 0.000520
lh_insula_thickness 0.007589 +/- 0.000462
lh_superiorparietal_thickness 0.007557 +/- 0.000313
lh_cuneus_thickness 0.007412 +/- 0.000375
```

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- We could also compare the two feature importance sets, here trained on 2.5k UKB participants (smaller sample than done in the presented studies)
- Feature importances differ to some extend, Lasso emerges as potentially better for brain age predictions (also shown by other investigations)
    - On the other hand, feature importances are still similar enough to being able to say that there is some order to it
- Advantage with Lasso is that variables which do not contribute are “nulled” and hence removed from function
- This does however also not prevent issues with severe multicollinearity
- Here also Lasso makes arbitrary choices on what to include.

- Overall, it might however be arbitrary which exact features are selected (also in XGBoost feature importances), but the regions might be of interest?

Model Training Choices

- Splitting procedure, cross-validation
  - With large samples best to do split when the goal is to obtain a predictive model *and* do inference on predictions (best with independent data)
  - In the first paper, I experimented with splitting choices
- Used nested cross-validation, in the future rather random sampling/CV with several iterations or bootstrapping for small N

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Brain-wide associations paper: Splitting procedure

- The splitting procedure was chosen to learn more about sample size requirements for hyperparameter tuning on the data at hand. This would allow to leverage the largest possible data set while assuring that the hyperparameter tuning set wasn't too small.
- Again, in hindsight there are many choices which could have been done better, such as the ones described in the paper you suggested:
  - Using standard/default hyperparameter settings instead of tuning at all (Varoquaux et al., 2017, NeuroImage: non-sparse models'

performance does not seem to increase from hyperparameter tuning CV procedures for logistic regression & SVM)
  - Averaging across hyperparameters for different folds instead of choosing the best performing iteration
  - Splitting for proper train, validation, test sets, instead of just using 2 independent CV procedures.
- The improvement of prediction accuracy based on the selected hyperparameters plateaued at 10%. So, this portion was used for tuning. The hyperparameters were then used in the test, where we used 10-fold CV. Language could have been clearer in this paragraph.

Cross validation

Nested CV was the procedures at our lab at the time. A few reasons are:

- Increased computational costs for each repeat
- Loss of statistical power when splitting up the sample
- Missingness at random in the predictors of brain age making the selection of a test set difficult

However, I am aware that better procedures are available and will in the future rather work with train-test splits and randomly repeated CVs when the sample size is large enough.

In future work, I will use (or have already used) randomized CV / several iterations (or bootstrapping in case of small N or P>N, which otherwise does not outperform k-fold CV). The runtime is quite high for the procedures I used, being around 1-2 days. So, there must be a feasible approach with not too many iterations to allow training which does not take too many resources. A reasonable approach is to avoid hyperparameter tuning (using standard hyperparameters) and to use a number of k folds that is not too high - Varoquaux et al. (2017, NeuroImage) show that increasing the number of folds does not necessarily reflect strong prediction performance increases.

Also, Steyerberg et al (2001, J of Clinical Epidemiology) show that bootstrapping is the preferrable approach (over CV) for logistic regression, and stated to be optimal at ca 200 repetitions (whereas there simulations indicated 50 to 100 reps), but such approach can be computationally even more costly.

Tissue relaxation

- T1: fluids long, fat-based short
- T2: fluids short, fat-based shorter
- Examples:
  - CSF, T1=1.9 seconds and T2=0.25 seconds
  - brain white matter, T1=0.5 seconds and T2=0.07 seconds (70 msec)

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- T1: fluids long, fat-based short
- T2: fluids short, fat-based shorter
- Examples:
  - CSF, T1=1.9 seconds and T2=0.25 seconds
  - brain white matter, T1=0.5 seconds and T2=0.07 seconds (70 msec)

Repetition of what the different weightings represent:

- T1-w indicating orientation/direction (63% of longitudinal magnetization recovered)
- T2 spin of protons (63% of transverse magnetization lost)
- T2* T2 relaxation and magnetic field inhomogeneities

→ T1w signal becomes stronger over time, T2w signal

weaker (opposing to what I said in the dissertation)!

RF pulses add energy to the protons and change their orientation (longitudinal magnetization) and phase synchronize (transverse magnetization).

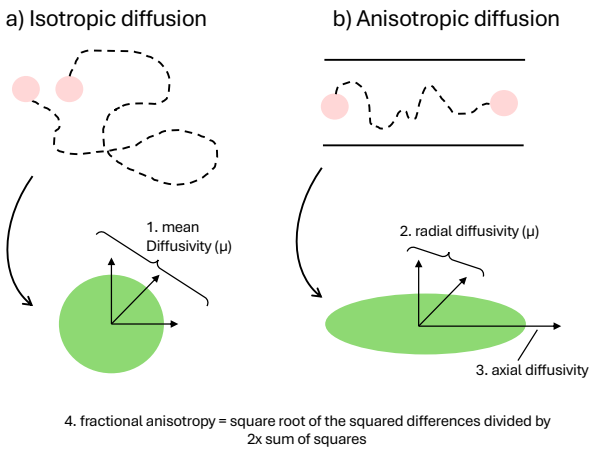
Protons returning collectively into their natural state spirals the magnetization vector from transverse back to longitudinal inducing energy (via free induction decay). This is the emitted energy which can be measured as signal.

TOP Data Acquisition

- Scanner
  - TOP data were acquired at 3T on a GE 3T Signa HDxT (TR = 7.8ms, TE = 2.956ms, FA = 12°; one subset with HNS coil, one subset with 8HRBRAIN coil), and a GE 3T Discovery GE750 (TR = 8.16ms, TE = 3.18ms, FA = 12°).
- Sequence
  - Magnetization prepared rapid acquisition gradient echo (MPRAGE) sequence with the following parameters: repetition time (TR) = 2730 ms, echo time (TR) = 3.93 ms, inversion time (TI) = 1000 ms, field of view (FOV) = 240 mm, flip angle (FA) = 7 °, matrix = 192 × 256, voxel size = 1.33 × 0.94 × 1 mm, 160 sagittal slices.

Methods: Data (DTI Metrics)

- Magnetic resonance imaging (MRI)
  - T1-weighted MRI
    - Clear contrasts between grey and white matter
  - Diffusion MRI
    - Diffusion restricted by tissue, hence useful for white matter mapping
- Pheno- & genotypes



Most commonly approach: Diffusion Tensor Imaging (DTI)

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Sequence (most common)

Pulsed Gradient Spin Echo (PGSE): first 90 degree RF, gradient pulse 1, 180 degree RF, gradient pulse 2. Gradient pulses manipulates the magnetic field linearly in one direction (i.e., along the x, y, or z-axis), RF pulse to flip magnetization vector. Gradient pulses can encode spins for their position, whilst still having the advantage of a uniform field during signal acquisition. PGSE is used to control phase shifts and signal decay, considering random proton displacement.

Metrics

- Diffusion can be represented by tensors (see a-b)

- Anisotropic diffusion has a dominant diffusion direction b)
- Using Gaussian tensors to model the diffusion direction is called diffusion tensor imaging
- Here, we can use some general metrics
    - 1. All vectors' average = mean diffusivity
    - 2. Short vectors' average = radial diffusivity
    - 3. Longest vector describes axial diffusivity
    - 4. square root (Squared difference / 2 x sum of squares) = Fractional Anisotropy

- Problem: in most voxels, the organisation of tissue is complex, including crossing fibres and different tissue types
- In these cases, we might need other diffusion approaches providing similar or different metrics

Methods: diffusion MRI – probabilistic approach

- Probabilistic approach
  - Diffusion equation can be solved into Gaussian function or kernel
  - Discretizing space and time, one obtains random walk, the Gaussian distribution
- Different distributions for different tissues necessary, hence kurtosis

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The probabilistic approach considers differential probabilities for a molecule traveling a distance given random motion within a limited diffusion time. The probability is lower for longer travels in a given time. But the distribution becomes flatter / more spread at longer times, as the distance travelled is time dependent. Mathematically, the diffusion equation / Green's function can be solved into a Gaussian function, here, kernel (sets of spread = distance travelled in a time interval), when assuming a discrete value for space. When discretizing space and time, one obtains a random walk (single Gaussian

distribution).

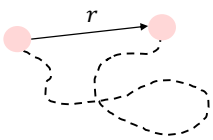
Different tissues (different from water) require different distributions to approximate random motion, for example indicated by varying degrees of kurtosis. (Particles are also moving at different speeds.).

Diffusion: background

$$MSD(t) = 1/N*(r_1^2(t) + r_2^2(t) + \cdots + r_n^2(t)$$

Mean square displacement

Number of particles



Isotropic diffusion

Time dependent

Brown (1827) Edinburgh New Philosophical Journal;
Einstein (1905). Annalen der Physik

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- We can estimate mean displacement from the direct path travelled within a given time, assuming isotropic diffusion

Diffusion: background

$$MSD(t) = 1/N*(r_1{}^2(t) + r_2{}^2(t) + \cdots + r_n{}^2(t)$$

$$MSD(t) = 6Dt$$

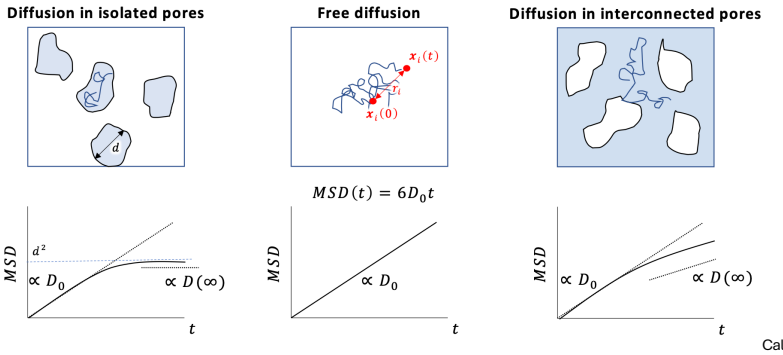
Constant depending on the dimensions, here 3
$D_{iso} = 3\mu m^2/ms$

Example: Diffusion length: L(t) = sqrt(6Dt)
For t = 20ms: L = sqrt(6*3*20) = 19μm

Brown (1827) Edinburgh New Philosophical Journal;
Einstein (1905). Annalen der Physik

Diffusion: background

$$MSD(t) = 1/N*(r_1^2(t) + r_2^2(t) + \cdots + r_n^2(t)$$



Callaghan (2011) Diffusion MRI

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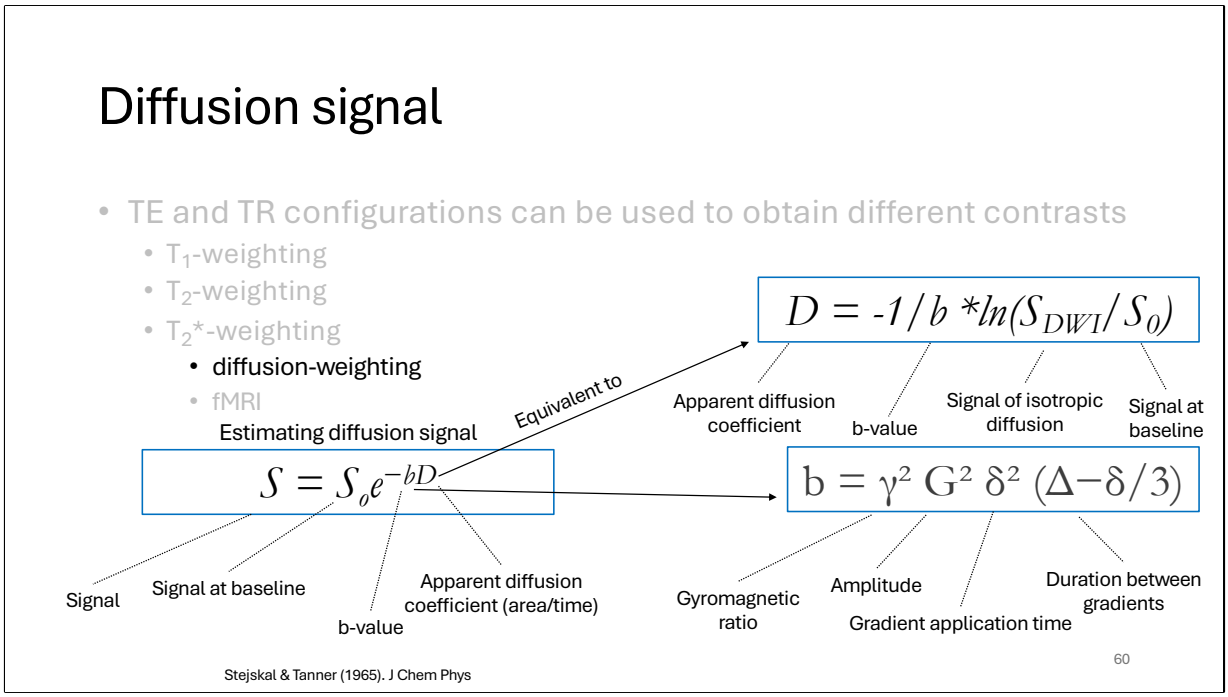
- What that translates to are differing diffusion times or displacement in different tissue types
- logarith



- **Diffusion signal** depends on b-value and diffusion coefficient, as well as signal at baseline
- Baseline signal is established using b=0, reflecting no diffusion weighting
    - captures the inherent signal intensity of tissues without directional sensitivity to water diffusion
- **Diffusion coefficient**
    - Can also be estimated from the standard
- **B-value**
    - indicates the diffusion weighting
    - Consists of amplitude (G), time of applied gradients (δ) and duration between the paired gradients (Δ)
    - If wanting to detect slow moving molecules, higher b-values are necessary

Diffusion signal

- TE and TR configurations can be used to obtain different contrasts
  - T_1-weighting
  - T_2-weighting
  - T_2*-weighting
    - diffusion-weighting
    - fMRI

Estimating diffusion signal

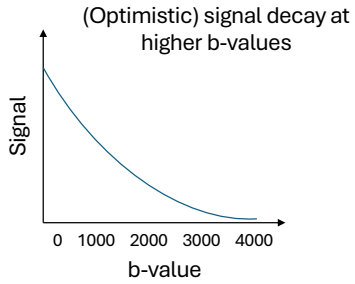
$$S = S_0 e^{-bD}$$

Signal

Signal at baseline

b-value

Apparent diffusion coefficient (area/time)



Stejskal & Tanner (1965). J Chem Phys

- Dependence of the diffusion signal on the b-value
- B-values > 1000 introduce parameters sensitivities when using DTI. We want insensitive paramters >> avoid b > 1000 for DTI

Diffusion signal

- TE and TR configurations can be used to obtain different contrasts
  - T_1-weighting
  - T_2-weighting
  - T_2*-weighting
    - diffusion-weighting
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Estimating diffusion signal

$$S = S_0 e^{-bD}$$

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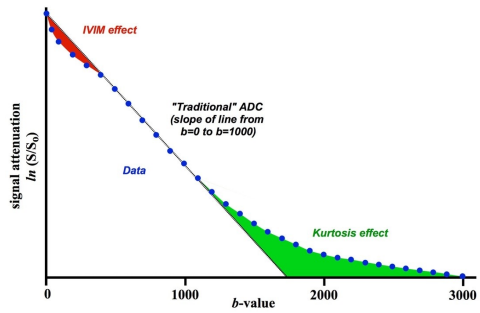
Diffusion coefficient (area/time)

Stejskal & Tanner (1965). J Chem Phys



https://mriquestions.com/diffusion-kurtosis.html

- Dependence of the diffusion signal on the b-value
- B-values > 1000 introduce parameters sensitivities when using DTI. We want insensitive paramters >> avoid b > 1000 for DTI

b-value parametrisation

- TE and TR configurations can be used to obtain different contrasts
  - T_1-weighting
  - T_2-weighting
  - T_2*-weighting
    - diffusion-weighting
    - fMRI

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

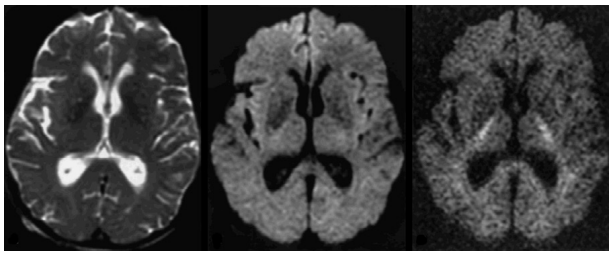
Gyromagnetic ratio

Amplitude

Gradient application time

Duration between gradients

b = 0, b = 1,000, b = 2,000



https://mriquestions.com/what-is-the-b-value.html

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- The b value indicates the diffusion weighting in time by area (inverse of the signal)
- Consists of amplitude (G), time of applied gradients (δ) and duration between the paired gradients (Δ)
- If wanting to detect slow moving molecules, higher b-values are necessary
- B = 0 serves as a reference value

b-value parametrisation: *more practical*

- Imaging techniques
  - T_1-weighting
  - T_2-weighting
  - T_2*-weighting
    - diffusion-weighting
    - fMRI

0) Basic formula

$$b = \gamma^2 G^2 \delta^2 (\Delta - \delta/3)$$

Gyromagnetic ratio

Amplitude

Gradient application time

Duration between gradients

1) For sinusoidal pulses

$$b = 4\gamma^2 G^2 \delta^2 (\Delta - \delta/4)/\pi^2$$

2) For trapezoidal pulses (ξ is the rise time)

$$b = \gamma^2 G^2 [\delta^2(\Delta - \delta/3) + \xi^3/30 - \delta\xi^2/6]$$

3) For single long gradient G

$$\gamma^2 G^2 TE^3/12$$

4) Fast spin echo with n echoes

$$b = \gamma^2 G^2 TE^3/12n^2$$

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- this particular implementation is seldom used in modern clinical or experimental systems. Rather than pure rectangular pulses, either sinusoidal or trapezoidal pulses are more frequently employed. (1-2)

- Diffusion schemes other than the pulsed gradient method have also been studied, with the calculation of the b-value depending on the details of the gradient scheme used. (3-4)

b-value parametrisation: *more practical*

- Imaging techniques
  - T_1-weighting
  - T_2-weighting
  - T_2*-weighting
    - diffusion-weighting
    - fMRI

Introducing kurtosis into the diffusion equation

$$\ln S(b) = \ln S_o - bD + 1/6 b^2 D^2 K + \ldots$$

Diffusion approaches

Diffusion Approach	Metrics
Bayesian Rotationally Invariant Approach (BRIA) [254]	intra-axonal axial diffusivity (DAX intra)
	extra-axonal radial diffusivity (DRAD extra)
	microscopic fractional anisotropy (micro FA)
	extra-axonal axial diffusivity (DAX extra)
	intra-axonal water fraction (V intra)
	extra-axonal water fraction (V extra)
	cerebrospinal fluid fraction (vCSF)
	microscopical axial diffusivity (micro AX)
	microscopic radial diffusivity (micro RD)
	microscopical apparent diffusion coefficient (micro ADC)
Diffusion Kurtosis Imaging (DKI) [143]	mean kurtosis (MK)
	radial kurtosis (RK)
	axial kurtosis (AK)
Diffusion Tensor Imaging (DTI) [27]	fractional anisotropy (FA)
	axial diffusivity (AD)
	mean diffusivity (MD)
	radial diffusivity (RD)
Spherical Mean Technique (SMT) [150]	fractional anisotropy (SMT FA)
	mean diffusivity (SMT md)
	transverse diffusion coefficient (SMT trans)
	longitudinal diffusion coefficient (SMT long)
Multi-compartment Spherical Mean Technique (SMTmc) [149]	extra-neurite microscopic mean diffusivity (SMTmc extra md)
	extra-neurite transverse microscopic diffusivity (SMTmc extra trans)
	mc SMTdiffusion coefficient (SMT mcd)
	intra-neurite volume fraction (SMTmc intra)
White Matter Tract Integrity (WMTI) [97]	axonal water fraction (AWF)
	radial extra-axonal diffusivity (radEAD)
	axial extra-axonal diffusivity (axEAD)

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BRIA – machine learning approach [mutli compartment]
DTI – commonly used Gaussian tensor based
DKI – kurtosis extension of DTI, assuming that water diffusion is different in different tissue types (hence different diffusion distribution shapes)
SMT - spherical mean technice introduces turtuosity (travelled distance)
SMTmc - mutli compartment extension of SMT
WMTI – multi compartment

- Or we use concrete assumptions about diffusivity, such as similar radial but dissimilar axial diffusivity (mcSMT)
- Or independent axially diffusing compartments (WMTI)

Diffusion approaches

BRIA	• Bayesian prior informed training data used to predict tissue properties. • Machine learning approach is used to parameterize the orientation distribution function (ODF), i.e. the tensor expressions in different microstructure compartments **[multi compartment]** • Estimation problems of extra axonal radial diffusivity in whole brain (paper 1).
DKI	• Kurtosis allowed (both higher & lower peaks in diffusion density function possible, being the reality for different tissue types) • Similar estimates as for DTI: AK, RK, MK, which are however inversely age-related
DTI	• Tensor model of diffusion along 3 planes. • Eigenvalues' relationships lead to metrics (AD, RD, MD, FA). FA decreases, rest increases with ageing.
SMT	• DTI model extended by tortuosity (distance travelled corrected by tortuosity). • Coefficients correspond generally with DTI in their age-relationships.
mcSMT	• SMT model extended by multi-compartment assumptions (intra and extra axonal space, both with equal axial diff, and intra-ax radial diff=0) **[multi compartment]**
WMTI	• Two water compartments (intra-&extra-axonal space as bundles of impermeable cylinders) **[multi compartment]** • faster axial diffusivity assumed in the intra axonal space (due to anisotropic diffusion) • Hence, estimation problems of such extra axonal axial diffusivity (axEAD).

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Terminology

- Apparent Diffusion Coefficient (ADC) allows to estimate the true diffusion coefficient in a homogenous medium from two b-factors.
  - for example, used in WMTI
- Tortuosity = molecules not diffusion in a straight line and potentially longer paths due to obstacles. Usually a property of the medium, yet, relationship to geometry remains unclear.

Multi compartment vs single compartment

- BRIA: machine learning; mcSMT and WMTI

restricting assumptions about diffusivity
- These assumptions contrast single-compartment approaches such as DTI or DKI which do not make assumptions about different tissue compartments.

Estimation problems

- Neurite orientation dispersion and density imaging (NODDI) assumes fixed diffusion parameters such as D, which should not be fixed / is not a constant (in NODDI based on corpos callosum) , which is not the case
    - Leads to high CSF compartment estimations which in HCP which is not the case (Reisert et all., 2017: comparision with BRIA)
- restriction spectrum imaging (RSI) has as a strength to identify different water fractions, but shows promises for prostate imaging

BRIA & SMT(mc)

- Meso-macro structure entanglement expressed as spherical convolution of microstructural and mesostructural properties
- SMT: long and transverse compartments
- BRIA: Usage of signal directly, establishing tissue compartment models which are invariant of each other

Spherical Mean Technique (SMT)

$$h_b(\mathbf{g},\boldsymbol{\omega}) = \underbrace{\exp\left(-b\langle \mathbf{g},\boldsymbol{\omega}\rangle^2\lambda_{\parallel}\right)}_{\text{longitudinal}} \underbrace{\exp\left(-b(1-\langle \mathbf{g},\boldsymbol{\omega}\rangle^2)\lambda_{\perp}\right)}_{\text{transverse}}.$$

Multi compartment Spherical Mean Technique (mcSMT)

$$h_b(g,\omega \mid v_{\text{int}},\lambda) = \underbrace{v_{\text{int}} h_b^{\text{int}}(g,\omega)}_{\text{intra-neurite}} + \underbrace{(1-v_{\text{int}}) h_b^{\text{ext}}(g,\omega)}_{\text{extra-neurite}}$$

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- Idea from the spherical mean technique or powder averaging
- Simply said: use of spheres to estimate diffusion within the sphere
- The mean diffusion signal of the sphere is *independent* of the fiber orientation distribution
    - Instead, the mean diffusion signal is *only* a function of the microscoping diffusion signal
- Different sphere sizes mean different tissue types in the multi compartment approach
- And the we can model different compartments

- For BRIA, however, the features used are not invariant against mesostructure
- As well not the first machine learning approach, but potentially more sensitive to low quality data

BRIA: three compartments

Three compartments

$$M(b, c) = v_i e^{-bD_{\parallel}^{i} c^2} + v_e e^{-b(D_{\parallel}^{e} c^2 - D_{\perp}(1-c^2))} + v_f e^{-D_f b}$$

D and v diffusivity and describe volume fractions, respectively.
Subscripts: i = intra axonal, e = extra axonal, f = water fraction
$D_{\parallel}$ diffusion in parallel direction
$D_{\perp}$ diffusion in transverse direction
D_f = 3 μm^2/ms (free water diffusion)

Meso- microstructure entanglement

$$S(b, \mathbf{n}) = S_0 \int_{S_2} M(b, \mathbf{n} \cdot \mathbf{n}_f) p(\mathbf{n}_f) \, d\mathbf{n}_f$$

Acquired dMRI signal at certain *b*-value and gradient direction

b = 0

Microstructural tissue model

Mesostructural tissue model

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- Intra & extra axonal AND free water fractions

WMTI

- Assumption of
  - Two impermeable tissue compartments: Intra-axonal & extra-axonal
  - Tensors which can be fitted to each compartment
  - Slower diffusion in extra-axonal space

$$S(b)/S(0) = f\exp\left(-b\mathbf{n}^T\mathbf{D}_{\mathrm{a}}\mathbf{n}\right) + (1-f)\exp\left(-b\mathbf{n}^T\mathbf{D}_{\mathrm{e}}\mathbf{n}\right)$$

Signal intensity | Axonal water fraction | Axonal tensor | Diffusion weighting | Extra-axonal tensor | Direction

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- Assumption of
  - Two impermeable tissue compartments: Intra-axonal & extra-axonal
    - Impermeability might be a wrong assumption (even when axons are highly myelinated
  - Tensors which can be fitted to each compartment

  - Slower diffusion in extra-axonal space
    - This might be a wrong assumption

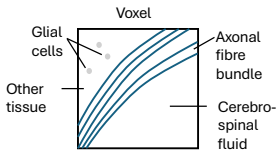
Future direction for dMRI

- Double diffusion encoding
- Stronger gradients, e.g., Connectome scanner

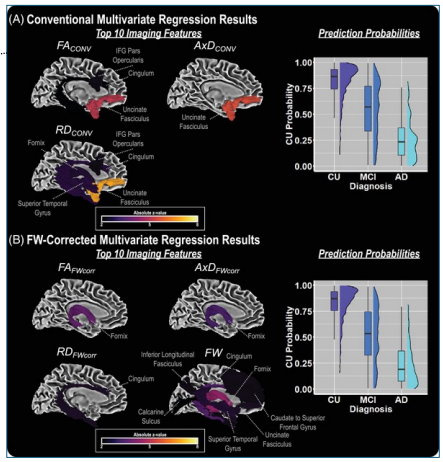
Supplemental Information: Findings

Findings: Fornix as ageing marker?

- The same (limbic) structures age differently in Alzheimer's disease (see Fig., N = 1,607)
- Partial volume effects



White matter ageing in Alzheimer's Disease



Yang et al., 2023, Alz. Dem. 15(2)

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Other evidence

- Larger literature outlining limbic structures as age-dependent and also clinically relevant (especially hippocampus, which fornix connects to)
- The same (limbic) structures age differently in Alzheimer's disease (see Fig., N = 1,607)

Discussion of evidence in our study

- However, fornix is susceptible to partial volume effects, affecting single compartment approaches such as DTI
- Multi-compartment approaches might be more robust against these effects
- Overall, fornix was highly age-associated across approaches

- Hence, associations are not approach dependent
- Feature importance seems hence to reflect the actual correlation, not some inflated metric
- Also, fornix features from different approaches correspond to each other in meaningful clusters, indicating that the fornix-age associations are not just noise based

Finally, recent efforts, for example by Andreas Horn and collaborators, indicates neuromodulation of the fornix as a potential treatment option for Alzheimer's (and recently potentially also for Parkinson's).

(NEXT SLIDE)s

Findings: Fornix as ageing marker?

- The same (limbic) structures age differently in Alzheimer's disease (see Fig., N = 1,607)
- Also used as treatment target in deep brain stimulation

Journal of Alzheimer's Disease 54 (2016) 777–787
DOI 10.3233/JAD-160817
IOS Press

A Phase II Study of Fornix Deep Brain Stimulation in Mild Alzheimer's Disease

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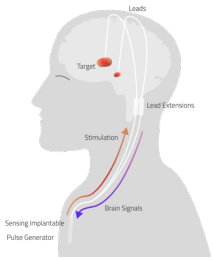
Review

Deep brain stimulation of fornix for memory improvement in Alzheimer's disease: A critical review

Ruofan Li[a b], Chencheng Zhang[b c], Yunxia Rao[a c], Ti-Fei Yuan[a d e]



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Article
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Optimal deep brain stimulation sites and networks for stimulation of the fornix in Alzheimer's disease

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- Also used as treatment target in deep brain stimulation
- However, treatments are experimental and still require further data collection for validation

Interpreting effect sizes

- What is a small effect?
  - It depends on the context.
  - Small effect ≠ small practical effect
  - Bio-psycho-social factors might have accumulative effects which were not represented by our models.
  - These small effects might hence still be highly influential for (brain) health outcomes
  - The same is true for the effect of polygenic risk scores on white matter microstructre (change)

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Bio-psycho-social factors

- I would say that explaining a small proportion of the variance is not the same as a small practical effect.
- And what I called a small proportion here (around 2%) might have large health outcomes.
- Here, we looked at overall healthy individuals.
- The observed effects might be bigger in disordered samples, and accumulative effects are yet unclear. Modelling choices (e.g., non-linearity) might also play a role.
- In other words, it is unclear what the findings might

mean in other contexts.

- But for the quite healthy UK Biobank imaging sample, which is entails a positive health bias and is not representative of the UK population, there seem to be only small associations between the examined predictors and BAG.

Polygenic risk scores

- The coefficients beta are rather small. This raises the question if the values are compatible with zero?
- And this is an important point to underline. Gene-brain associations are small, especially when not examining disease groups. That raises the question whether PGRS-brain associations are of interest. The answer might be no, considering that there are other correlates which are easier to obtain than genotyping (although also this has become easy nowadays).

Surprising Findings in the Bio-Psycho-Social Associations

- Cognitive factors did have a rather small influence
- Adding them to baseline model decreased model performance
- Potential explantion: biassed sample
  - Good health bias in the selected sample
  - Older people with better health, potentially also higher intelligence and cognitive reserves tend to convolute cognitive test results.
  - The variability induced by these individuals might explain why the cognitive abilities contributed negatively to the variance explained.

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- What was surprising was that the cognitive factors did not have a bigger influence.
- Strong between sexes and ethnicities variability was expected, but useful to be lined out.
- What was unclear was that to which degree the brain ages from different diffusion approaches would align in terms of bio-psycho-social factor associations.
- Here, we expected some subtle differences, which we found, to some degree.
- This was for example interesting considering that the different approaches explain WMM in different

detail, and provide differing numbers of predictors when estimating brain age.

- There was no clear association between prediction accuracy or number of features used to train models and the resulting associations between brain age and phenotypes.

- Finally, sampling bias

Considerations on Brain Age Paper

- Different Models
  - Age binning
    - Might be biologically informed
    - Might add information to predictions which is otherwise "averaged over"
    - Lack of statistical power might then be a problem
- Follow-ups or improvements
  - More (diverse) participants: females, different origins than Norway, Germany, China
  - Different QC parameters might have been a better choice

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In general, what limitations does this paper highlight for the usage of brain age models in crosssectional datasets? A potential approach for future brain age modelling is proposed that would employ multiple, more specific models which are better tuned to individual differences, developmental trajectories, and scan quality. Is this reasonable and feasible to do? How should groupings be defined? Are there issues of intersectionality?

The paper highlights the known problem of any group-level statistic, which do usually transfer to the level of

the individual to a limited extend. It also shows that models which work well based on commonly used model-assessment metrics such as root mean squared or mean absolute error do not necessarily work for individual level predictions. This is an ongoing problem to be solved to establish person-centered models, for example, for clinical applications.

Currently, most available larger neuroimaging data has been obtained from white people, with an origin from North America or Europe. The rest of the world is hence not represented appropriately either by brain age models or in general by neuroscientific research. So, we should start at the basic level of comparative studies. There seem to be subtle differences in anatomy and its changes throughout ageing, which will also be expressed in brain age models. E.g.: Brickman, A. M., Schupf, N., Manly, J. J., Luchsinger, J. A., Andrews, H., Tang, M. X., ... & Brown, T. R. (2008). Brain morphology in older African Americans, Caribbean Hispanics, and whites from northern Manhattan. *Archives of neurology*, *65*(8), 1053-1061.

When it comes to splitting up samples into age bins, in the onset, the splitting choices are arbitrary. However, there might be biologically relevant explanations for splitting. For example, degeneration processes in the brain accellerate at higher ages.

Perhaps these phenomenons are heavily influencing predictions for individuals at younger ages which do not present norm deviations large enough to be then picked up by a model. Yet, these sub-threshold changes might exactly be what is a main characteristic of transition processes towards neurodegenerative disorders. Bethlehem and others have shown pretty clearly that the strongest age dependencies in the brain appear very early and very late in life. Changes in between might hence be better captured by these age range specific models.
For now, we are probably lacking sample sizes to do all at once, but it would be interesting to check whether age-range models could lead to some sort of prediction advantages. Then, one could add ethnicity, sex, etc., or train these models, just to outline the effects of such modelling choices. However, the ground truths must also be available which represents potentially an even bigger challenge. So, if we want to use brain age as a marker of neurodegenerative disease, then we would probably like to have longitudinal data sampled before disease onset, across groups in a regular interval. So, in the end, it all becomes a data availability problem.

Detailed comments:
The QC metrics are all based on the qMRIC package, but they don't relate well to more ISMRM based

metrics such as tested and related to radiological reports in e.g. as shown in ISMRM 2022 https://archive.ismrm.org/2022/2061.html for a clinical dataset.
The authors also mention that "QC metrics might be sensitive to individual differences, and vary across scanner sites." If that is the case then maybe other QC metrics should have been utilized?

We can certainly not exclude the possibility that other QC measures might have been a better choice. The selection was done based on the fact that MRIQC delivers several metrics and has been validated. At that time, I had no knowledge of other software packages that could do something like that or even metrics beyond the ones presented in MRIQC. However, there are of course many useful alternatives.
Simple estimates like the Euler number might have been helpful, just as similarity indices or peak-signal-to-noise-ratio (as outlined by senior author Melanie Ganz's ISMRM 2022 Abstract).

Or estimates such as
- Structural similarity index (SSIM)
- Peak signal to noise ratio (PNSR)

These metrics' associations with brain age would

require further testing.

Power / false negatives (example: paper 5)

- Estimation-based power analysis
  - For the largest PGRS-WM associations of beta = 0.05, we had around 82.2%, assuming a constant variance explained by the linear model of R2 = 0.3.
  - This decreased to near 0 towards the smaller associations until beta = 0.01:
    - beta = 0.04, power = .635
    - beta = 0.03, power = .409
    - beta = 0.02, power = .211
    - beta = 0.01, power = .089

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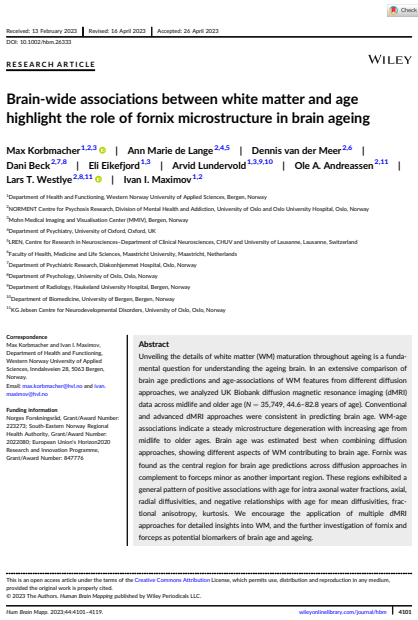
```
library(pwrss)
pwrss.t.reg(beta1 = 0.01, k = 5, r2 = .3,
        power = NULL, alpha = 0.05, alternative = "not equal", n = 2329)
```

Supplemental Information: Quick Overview of Papers

Paper A

- Validation of multiple diffusion approaches against each other
  - Cluster 1: Diff. coefficients & CSF
  - Cluster 2: anisotropy, kurtosis, intra axonal diffusion
  - Age associations reflect clusters
- Fornix (limbic) and forceps minor (corp. colassum) presented strongest age-associations



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RESEARCH ARTICLE

WILEY

Brain-wide associations between white matter and age highlight the role of fornix microstructure in brain ageing

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Abstract
Unveiling the details of white matter (WM) maturation throughout ageing is a fundamental question for understanding the ageing brain. In an extensive comparison of brain age predictions and age-associations of WM features from different diffusion approaches, we analyzed UK Biobank diffusion magnetic resonance imaging (dMRI) data across midlife and older age ($N = 35{,}749$, 44.6–82.8 years of age). Conventional and advanced dMRI approaches were consistent in predicting brain age. WM-age associations indicate a steady microstructure degeneration with increasing age from midlife to older ages. Brain age was estimated best when combining diffusion approaches, showing different aspects of WM contributing to brain age. Fornix was found as the central region for brain age predictions across diffusion approaches in complement to forceps minor as another important region. These regions exhibited a general pattern of positive associations with age for intra axonal water fractions, axial, radial diffusivities, and negative relationships with age for mean diffusivities, fractional anisotropy, kurtosis. We encourage the application of multiple dMRI approaches for detailed insights into WM, and the further investigation of fornix and forceps as potential biomarkers of brain age and ageing.

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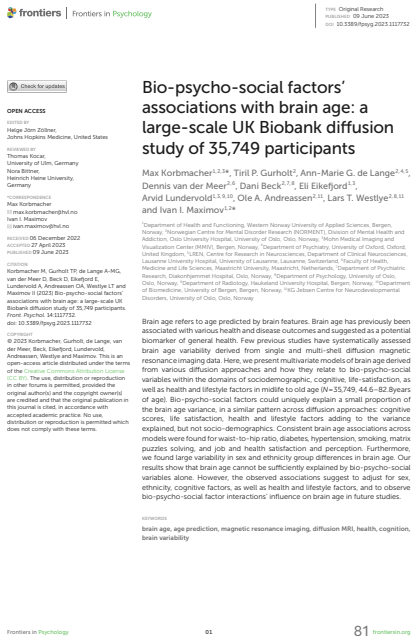
- UK Biobank cross sectional N = 35,749, dMRI
- Diffusion approaches
  - Produce similar brain age scores
  - Associate in clusters and similarly with age
  - Interpretation is diffucult, as there is variability between spatial locations
  - In fornix and foceps there seem to be two clusters
    - Cluster 1: Diff. coefficients & CSF = “Free water cluster”?
    - Cluster 2: anisotropy, kurtosis, intra axonal diffusion = “Tissue cluster”?

- Partial volume effect is present in the fornix. This was even reflected, to some degree by the BRIA CSF metric (higher in Fornix than other regions/global)
- So, yes, we need new and different methods to examine fornix closer to confirm out consistent findings (acros diffusion approaches)
- At the same time there is plenty of evidence for the value of fornix as a treatment target

Paper B

- Building upon paper A, usage of brain age models to associate these with bio-psycho-social (BPS) factors
- Significant predictors
  - Waist-to-hip ratio, diabetes, hypertension, smoking, matrix puzzles solving, job- & health satisfaction and perception
- WM brain age reflects overall health but is not well-predicted by any of the observed (BPS) domains



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Bio-psycho-social factors' associations with brain age: a large-scale UK Biobank diffusion study of 35,749 participants

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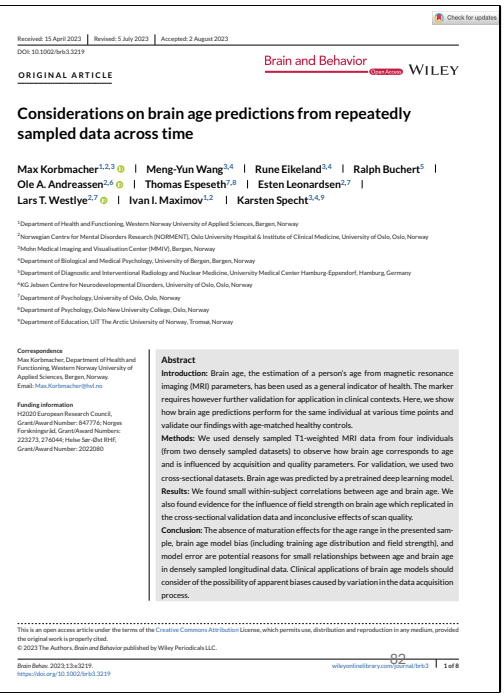
Brain age refers to age predicted by brain features. Brain age has previously been associated with various health and disease outcomes and suggested as a potential biomarker of general health. Few previous studies have systematically assessed brain age variability derived from single and multi-shell diffusion magnetic resonance imaging data. Here, we present multivariate models of brain age derived from various diffusion approaches and how they relate to bio-psycho-social variables within the domains of sociodemographic, cognitive, life-satisfaction, as well as health and lifestyle factors in midlife to old age (N=35,749, 44.6–82.8years of age). Bio-psycho-social factors could uniquely explain a small proportion of the brain age variance, in a similar pattern across diffusion approaches: cognitive scores, life satisfaction, health and lifestyle factors adding to the variance explained, but not socio-demographics. Consistent brain age associations across models were found for waist-to-hip ratio, diabetes, hypertension, smoking, matrix puzzles solving, and job and health satisfaction and perception. Furthermore, we found large variability in sex and ethnicity group differences in brain age. Our results show that brain age cannot be sufficiently explained by bio-psycho-social variables alone. However, the observed associations suggest to adjust for sex, ethnicity, cognitive factors, as well as health and lifestyle factors, and to observe bio-psycho-social factor interactions' influence on brain age in future studies.

KEYWORDS
brain age, age prediction, magnetic resonance imaging, diffusion MRI, health, cognition, brain variability

- Same sample as in paper A
- Multiple multivariate regression to model different bio-psycho-social domains instead of only single variables
- Results show that there are a selection of variables which are brain age associated
- The overall models were however only weakly reflecting brain age
- Other modelling domains need to be explored (SEM, Canonical Correlations,etc.)

Paper C

- Brain age was weakly associated with age (Δ = 1-3 years)
- Large prediction error, potentially absence of maturation effects
- Brain age is still limited in accounting for individual differences



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ORIGINAL ARTICLE

Brain and Behavior Open Access WILEY

Considerations on brain age predictions from repeatedly sampled data across time

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Abstract
Introduction: Brain age, the estimation of a person's age from magnetic resonance imaging (MRI) parameters, has been used as a general indicator of health. The marker requires however further validation for application in clinical contexts. Here, we show how brain age predictions perform for the same individual at various time points and validate our findings with age-matched healthy controls.
Methods: We used densely sampled T1-weighted MRI data from four individuals (from two densely sampled datasets) to observe how brain age corresponds to age and is influenced by acquisition and quality parameters. For validation, we used two cross-sectional datasets. Brain age was predicted by a pretrained deep learning model.
Results: We found small within-subject correlations between age and brain age. We also found evidence for the influence of field strength on brain age which replicated in the cross-sectional validation data and inconclusive effects of scan quality.
Conclusion: The absence of maturation effects for the age range in the presented sample, brain age model bias (including training age distribution and field strength), and model error are potential reasons for small relationships between age and brain age in densely sampled longitudinal data. Clinical applications of brain age models should consider of the possibility of apparent biases caused by variation in the data acquisition process.

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- Multiple samples, both deeply/repeatdly sampled (longitudinal) from Bergen and across Germany, as well as cross-sectional data from UiO, T1w
- Brain age predictions in these data sets using a pretrained model "pyment"
- Model performance was relatively poor and dependent on field strength (better at higher field strength)
- The model is still the best performing model there is based on common model evaluation metrics, yet limited by individual differences.
- Refinement necessary before clinical usage is possible

Paper D

- Brain age can be used to make acurate hemisphere-specific predictions
  - Potential for unilaterally expressed (brain) disorders
- Asymmetries are lower at higher age
  - Fundamental insight into brain physiology

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Brain asymmetries from mid- to late life and hemispheric brain age

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The human brain demonstrates structural and functional asymmetries which have implications for ageing and mental and neurological disease development. We used a set of magnetic resonance imaging (MRI) metrics derived from structural and diffusion MRI data in N=48,040 UK Biobank participants to evaluate age-related differences in brain asymmetry. Most regional grey and white matter metrics presented asymmetry, which were higher later in life. Informed by these results, we conducted *hemispheric brain age* (HBA) predictions from left/right multimodal MRI metrics. HBA was concordant to conventional brain age predictions, using metrics from both hemispheres, but offers a supplemental general marker of brain asymmetry when setting left/right HBA into relationship with each other. In contrast to WM brain asymmetries, left/right discrepancies in HBA are lower at higher ages. Our findings outline various sex-specific differences, particularly important for brain age estimates, and the value of further investigating the role of brain asymmetries in brain ageing and disease development.

There are various structural and functional differences in brain architecture between the left and right hemispheres[1–4]. Microstructural brain characteristics, such as white matter (WM) pathways or intra- and extra-neurite water organisation, might underlie the brain's functional lateralisation[5]. Furthermore, handedness has been repeatedly assessed together with asymmetry in humans and animals, and relates to brain asymmetry[6]. Both structural and functional brain asymmetry exhibit clinical importance as there are differences in brain asymmetry between healthy controls and various disease groups, including neurodegenerative diseases such as Alzheimer's disease[7,8], Parkinson's disease[9], and psychiatric disease such as obsessive-compulsive disorder[10,11] and schizophrenia[12]. In that context and particularly relevant from a lifespan-perspective, cortical thickness asymmetry decreases throughout ageing, with this alteration being potentially accelerated in the development of neurodegenerative disorders such as Alzheimer's Disease[7]. Similarly, some studies suggest lower WM microstructure asymmetry at higher ages, indicated by intra-axonal water fraction[13], fractional antisotropy, or the apparent diffusion coefficient[14]. Additional investigations into brain asymmetries' age-dependencies can provide a more comprehensive understanding of the influence of asymmetries on ageing and disease development.

Brain age is a developing integrative marker of brain health, particularly sensitive to neurodegenerative diseases[15,16]. Brain age refers to the predicted age in contrast to chronological age and is based on a set of scalar metrics derived from brain scans such as MR. To date, brain age has often been estimated using a global brain parametrisation such

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- UK Biobank, new data release N = 48,040, T1w & dMRI (cross-sectional)
- Systematic mapping of brain asymmetries
- New conceptualisation of brian age
- Brain age predictions from a single hemisphere similar to both hemispheres
  - Meaning that we can apply these predicitons without larger information loss
  - This makes them useful for applications where hemispheric data differs, e.g. stroke or head trauma
- The strong presence & age dependencies of asymmetries underline their value for further investigations
- The findings also support the brain dedifferentiation hypothesis (usually in functional MRI), stating that functions become less specific to single brain networks and more distributed. Our findings might supply some anatomical detail.
- Finally, the regions with strongest age-impact on asymmetries were again ventricle near
  - Potential evidence for a reversed last-in-first-out hypothesis (see also Yeatman et al. 2014, Nat.Comms.)

Paper E

- White matter ageing ageing trajectories reflect previously outlined age dependencies
- Accelerated ageing at higher ages
- Associations between annual brain changes and polygenic risk of different disorder was small

Distinct longitudinal brain white matter microstructure changes and associated polygenic risk of common psychiatric disorders and Alzheimer's disease in the UK Biobank

Running title: White matter aging and polygenic risk in the UK Biobank

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- Final paper: Longitudinal data (UK Biobank: N = 2,329)
- Confirm general trends from cross-sectional data of decreasing anisotropy, increasing diffusivity
- Confirm strongest ageing in fornix & forceps minor[1]
- Additionally cerebral peduncle (for which the annual rate of change presented also the strongest polygenic risk correlated)
- Accelerated ageing at higher ages (quicker degeneration)
- Brain-genetics correlates were small, both in cross sectional and longitudinal data
    - This is often not clearly reported and important to be outlined: polygenic risk scores might be more suitable when disorders are expressed, not sub-threshold individuals and closer to, not necessarily prognostic when looking at the brian