Disease and ageing biomarker identification from multimodal magnetic resonance imaging

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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

Background

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

Neurodevelopmental Milestones

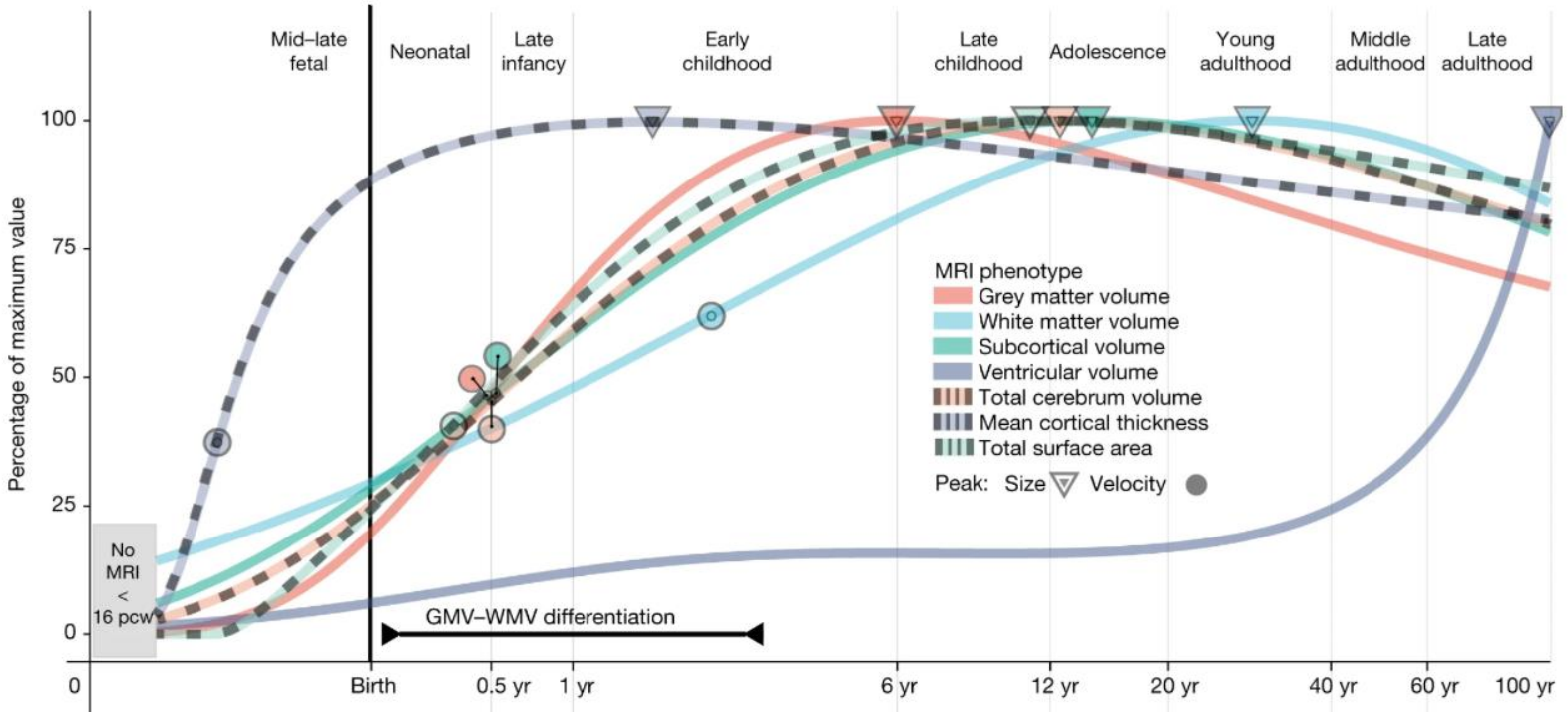
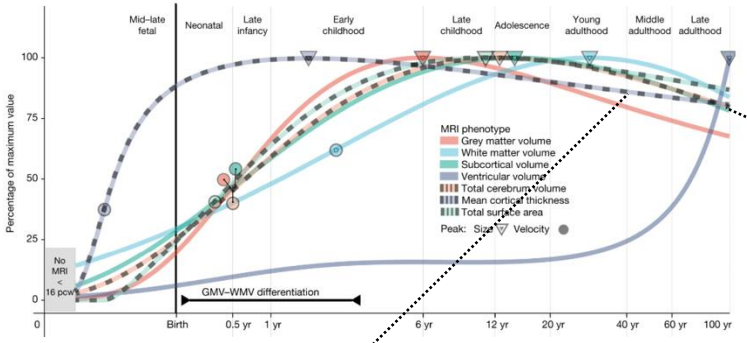


Fig: Betlehem et al., 2022, Nature

Background

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

- Deviations along this trajectory can signify pathology and disorders



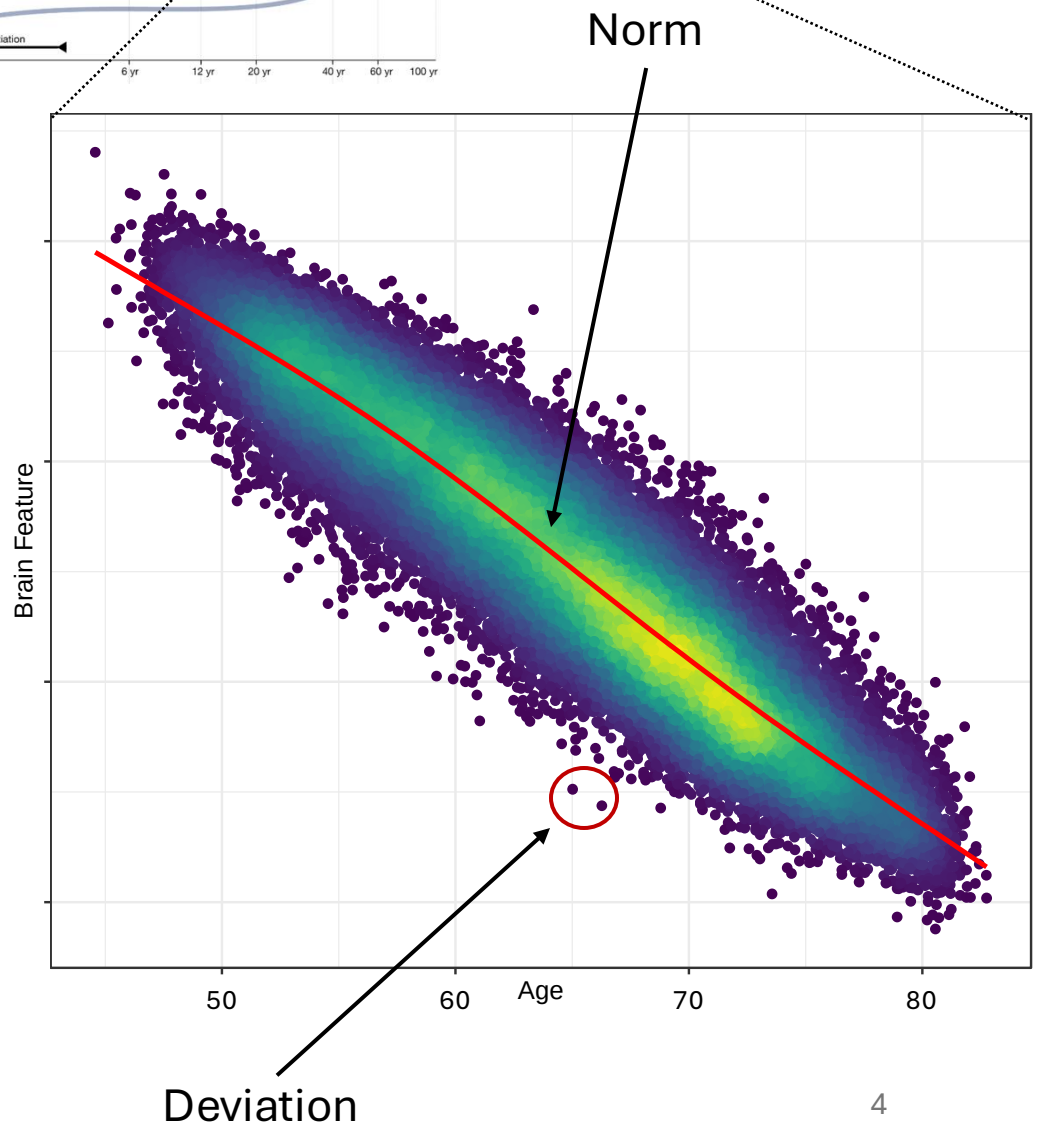


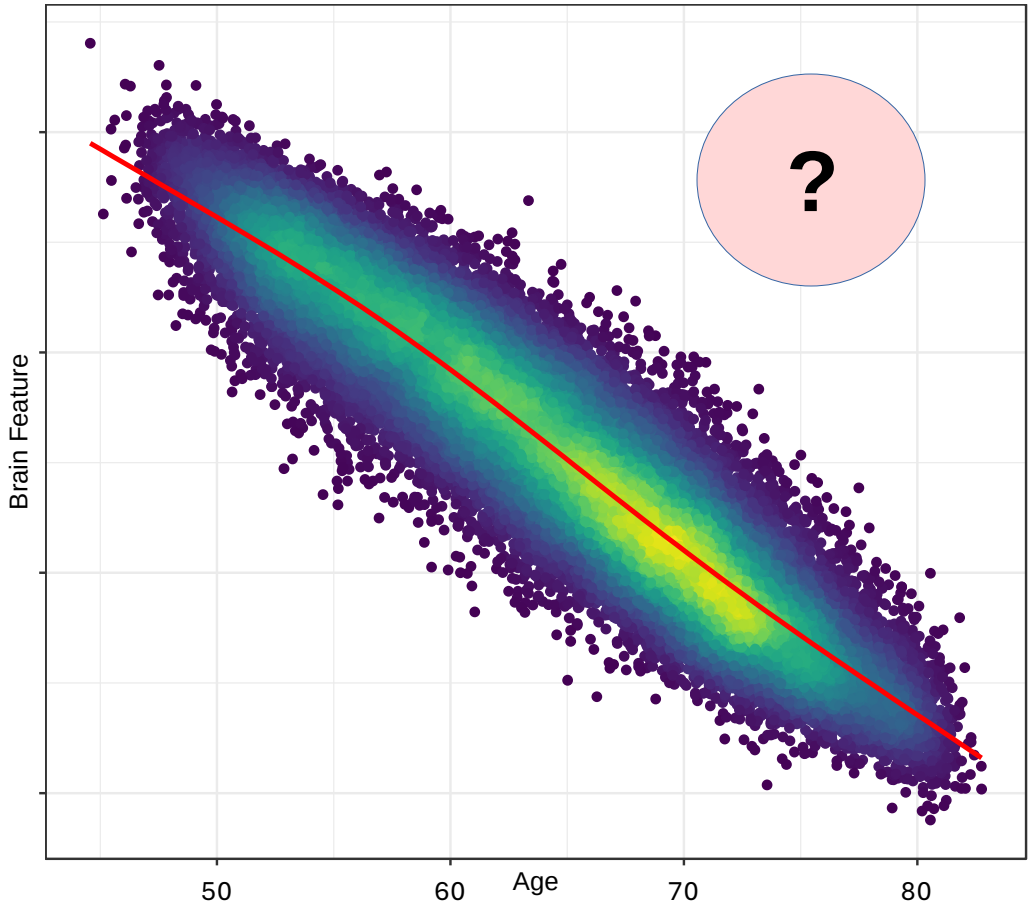
Fig: Korbmacher et al. (in prep)

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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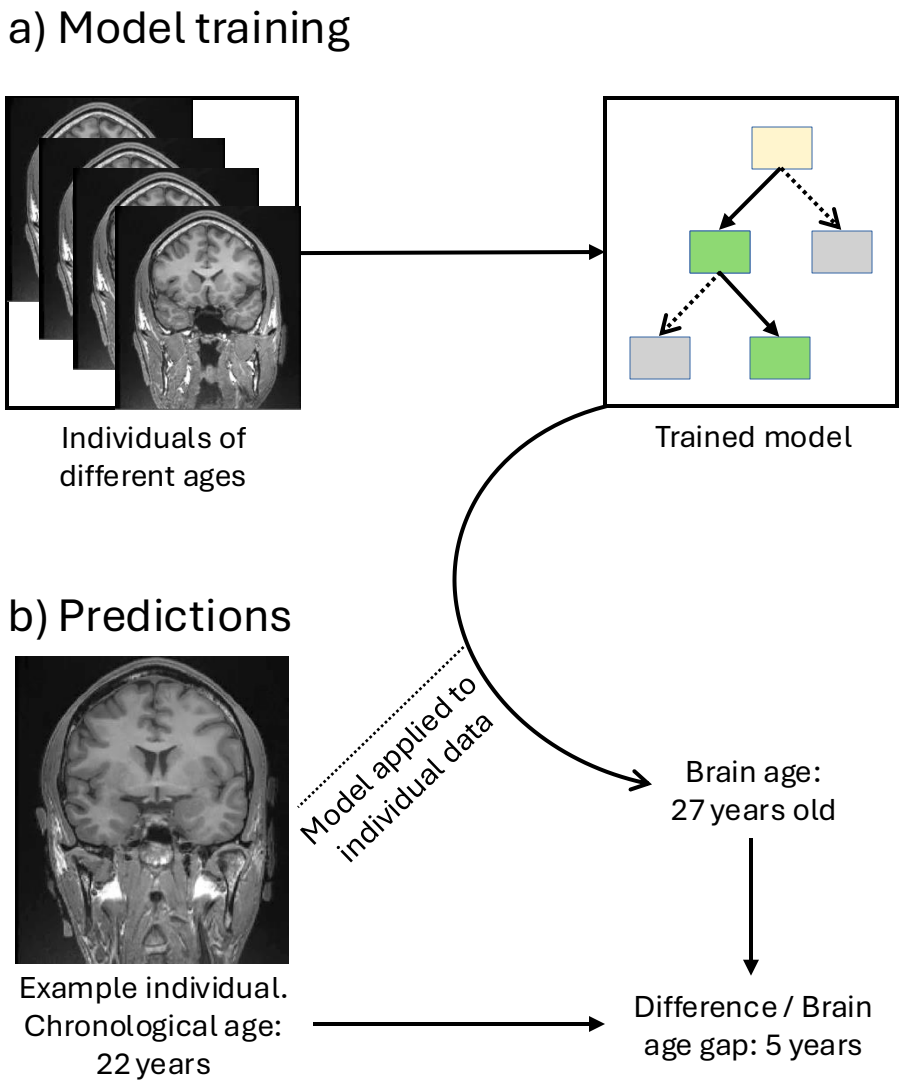
Background

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



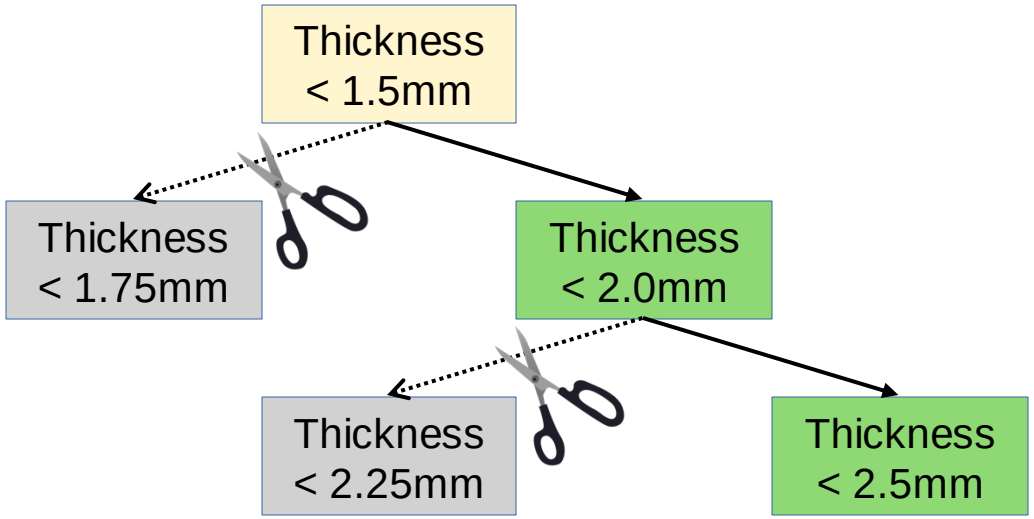
Methods: XGBoost

- 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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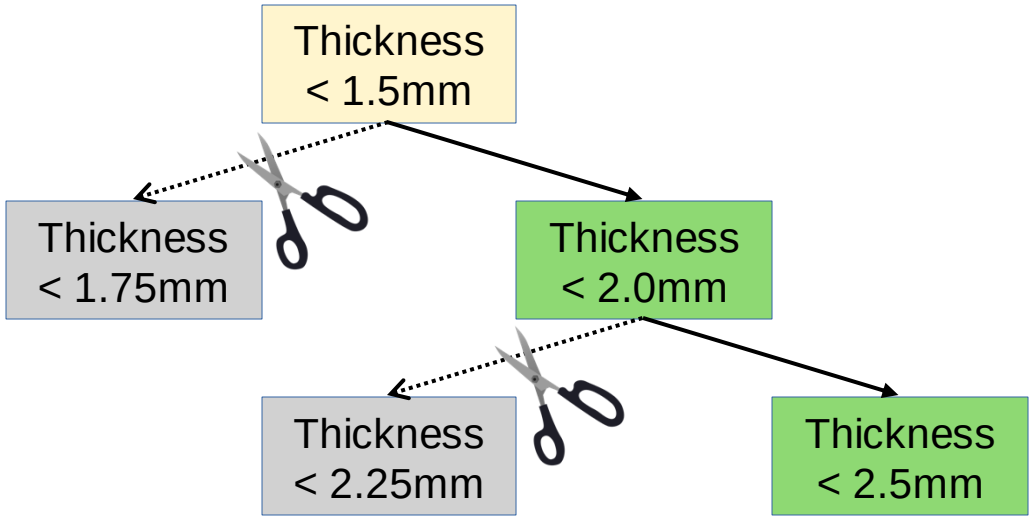

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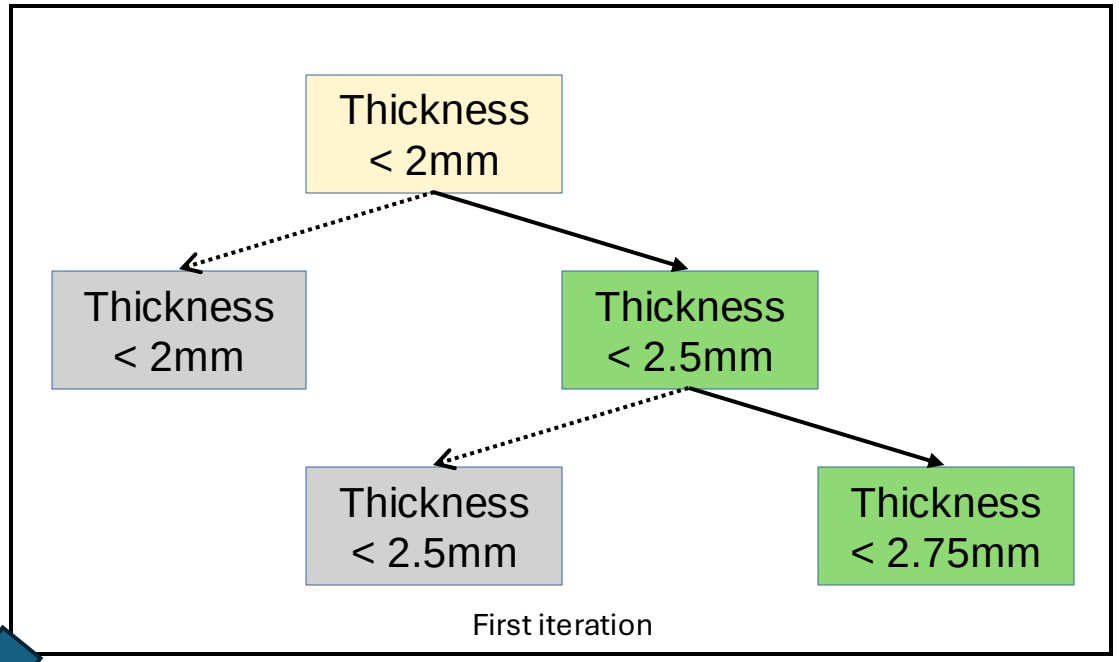
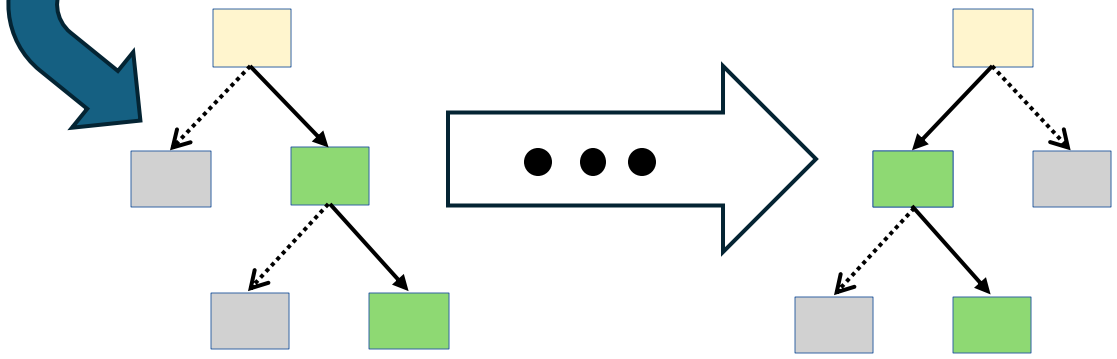
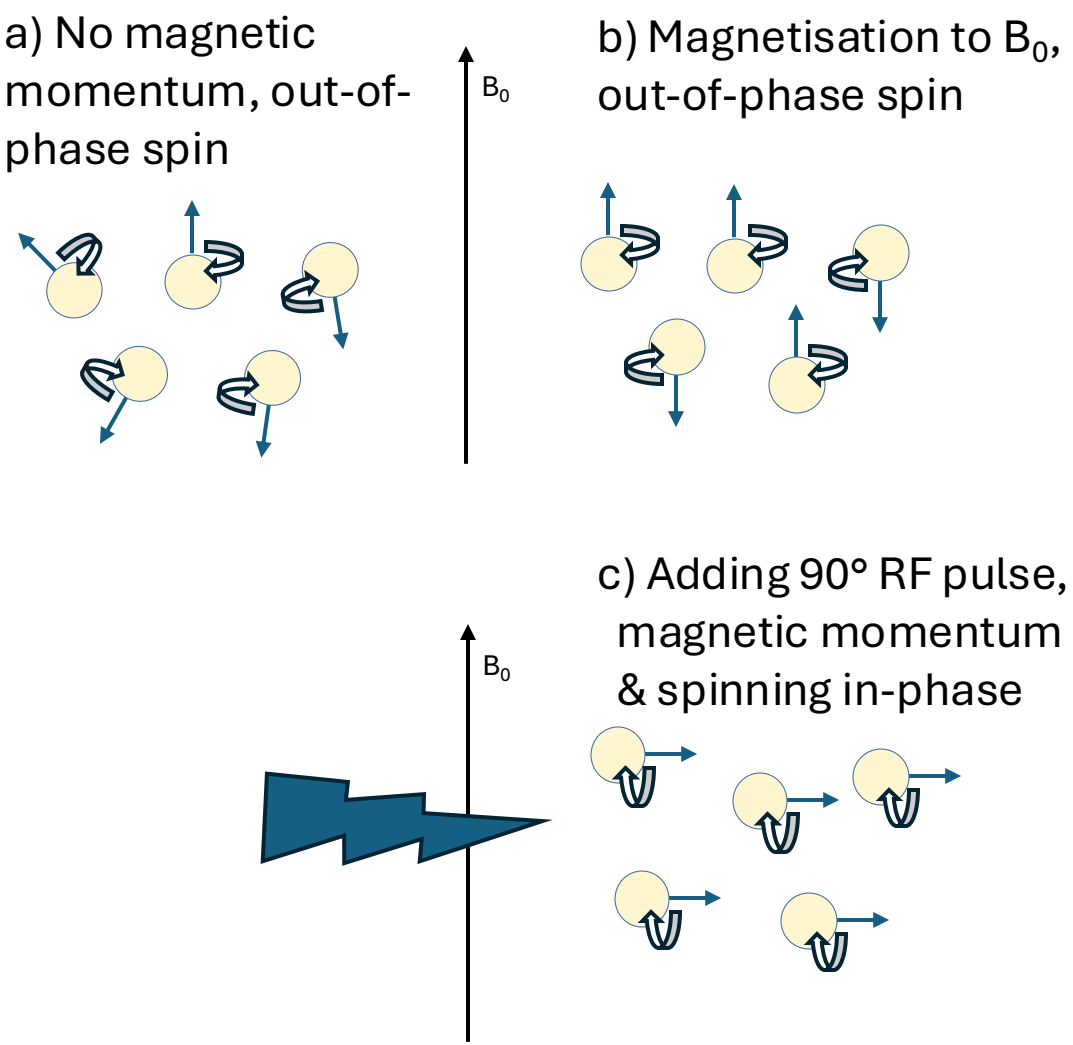


Optimisation process:



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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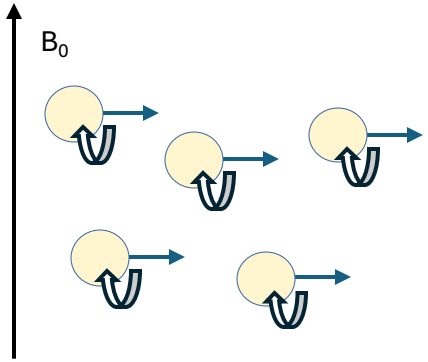
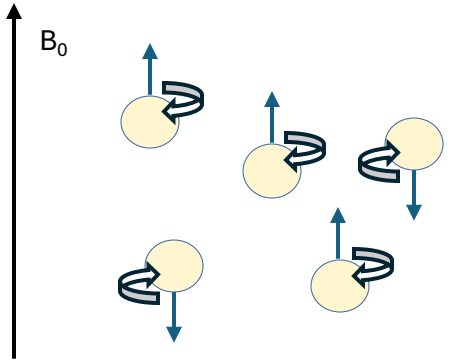
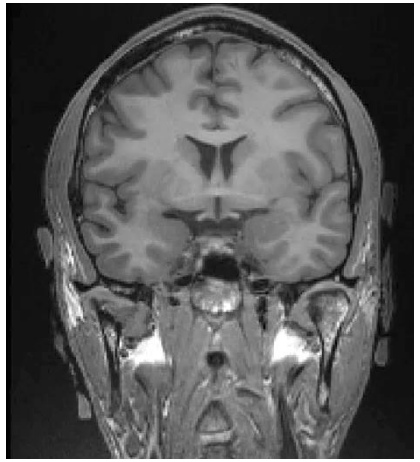


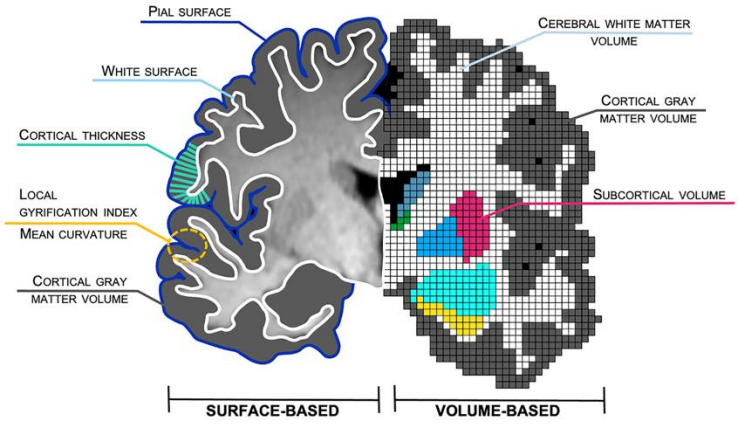
b) Equilibrium (in scanner)



c) Raw T1w image



d) Overview of T1w metrics



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

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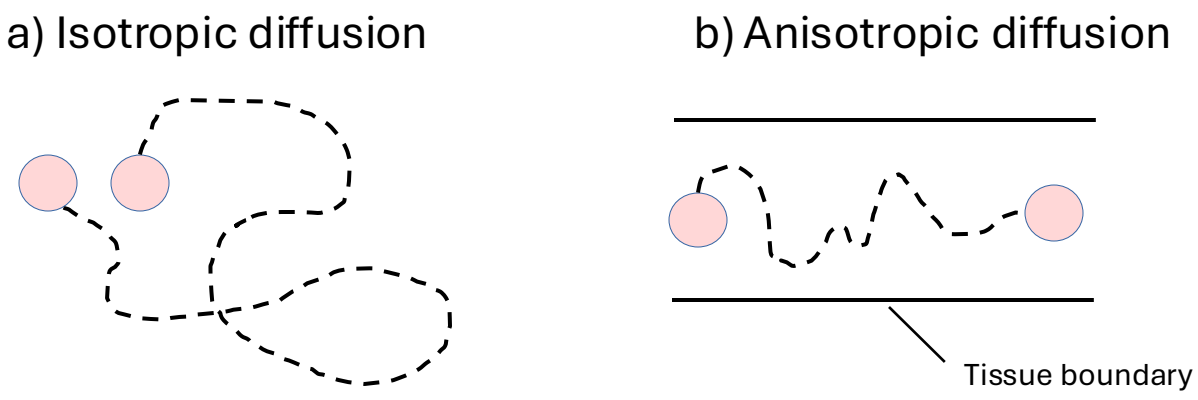

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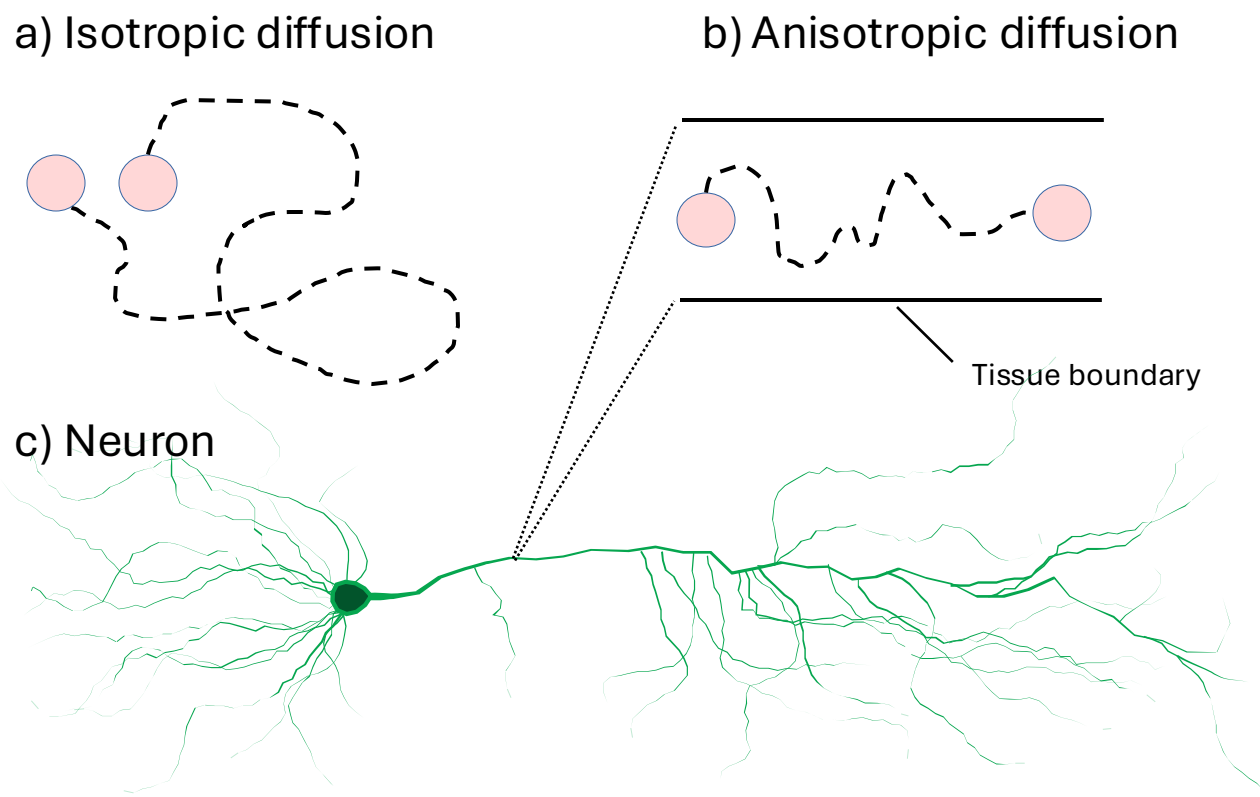

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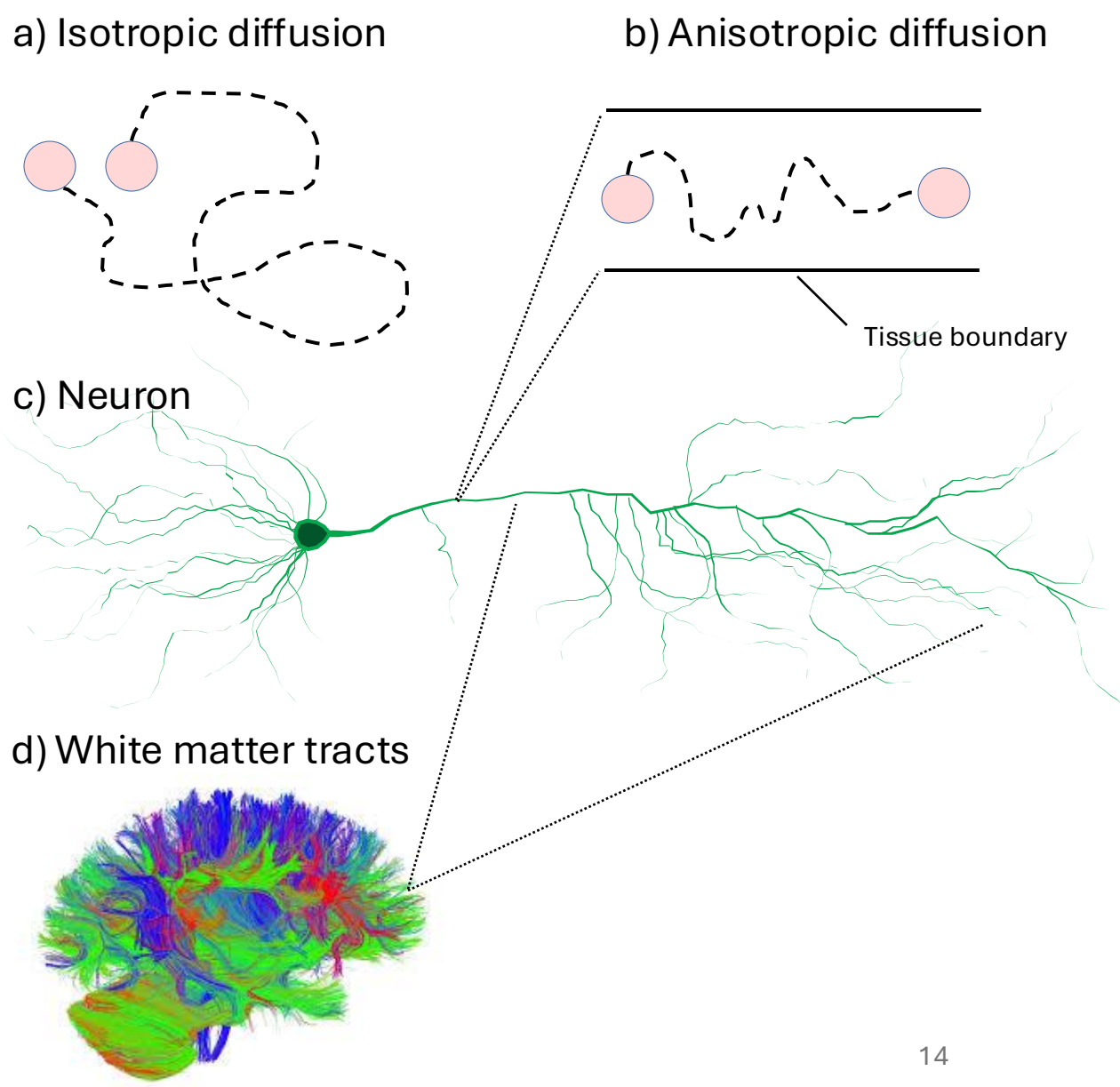

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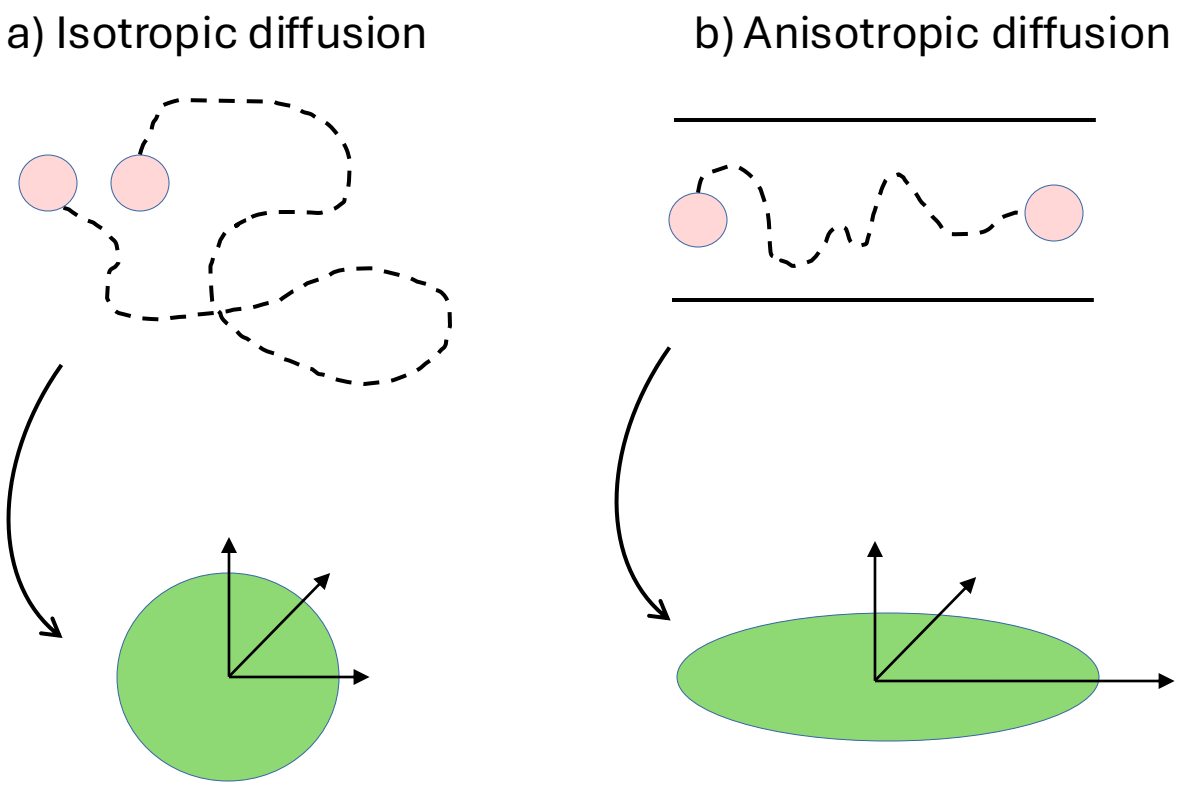
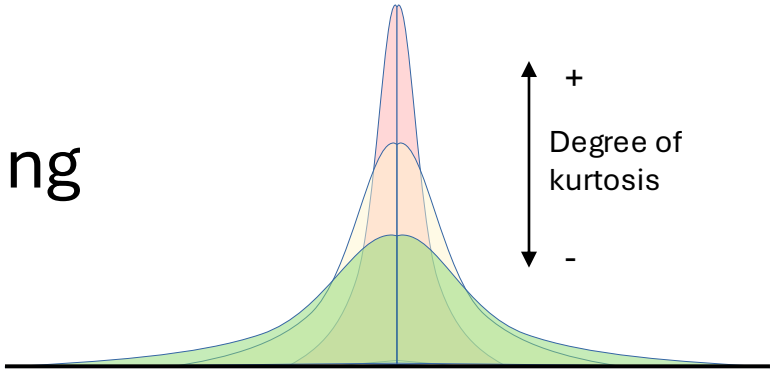


Most common approach: Diffusion Tensor Imaging (DTI)

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

Methods: Data

a) Diffusion Kurtosis Imaging



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

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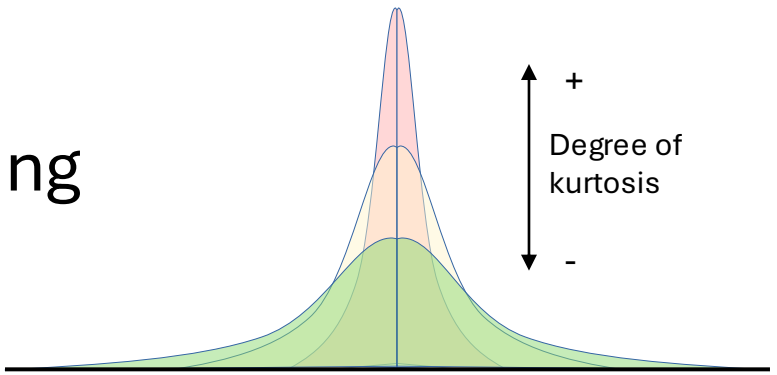
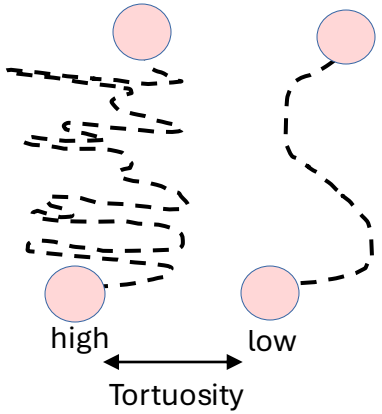


b) Spherical Mean Technique



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

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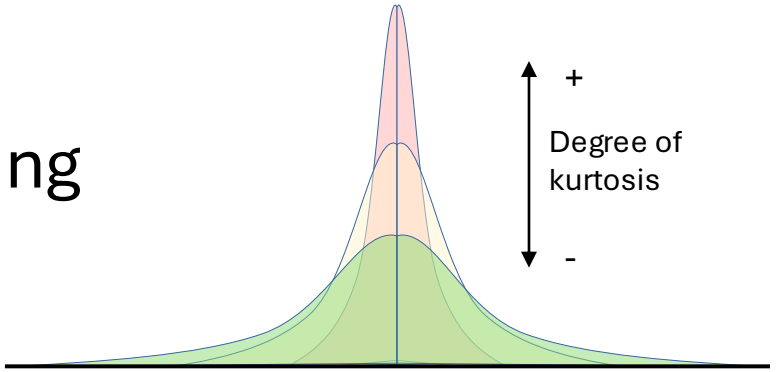

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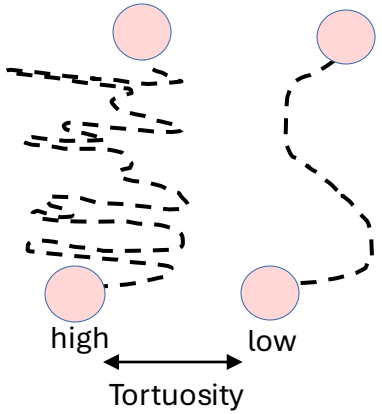
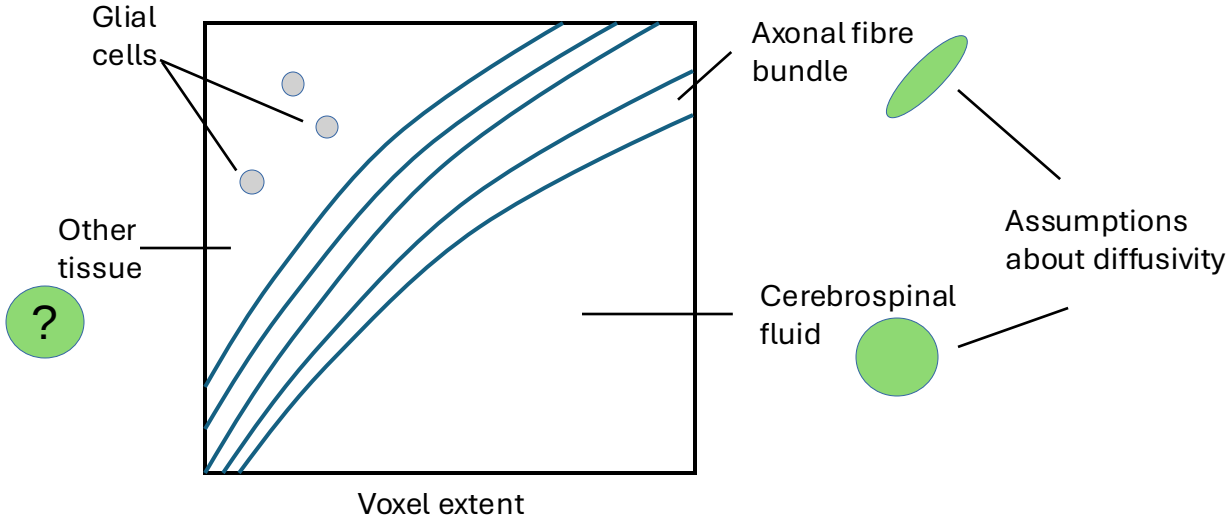


c) Multi compartment assumptions



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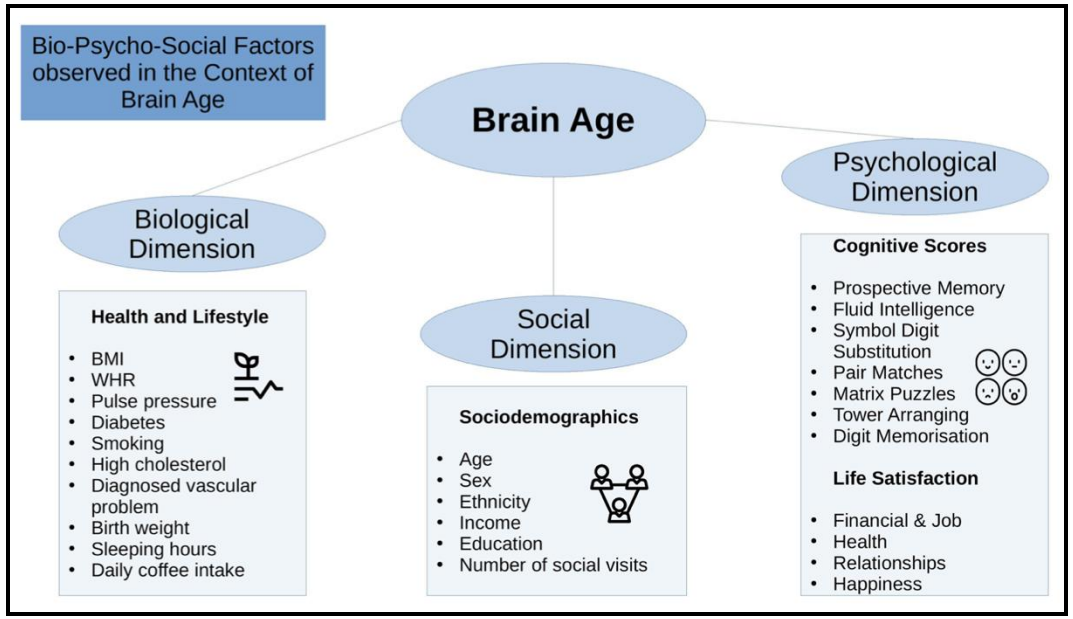
Phenotypes (bio-psycho-social factors)



Genotypes (polygenic risk)

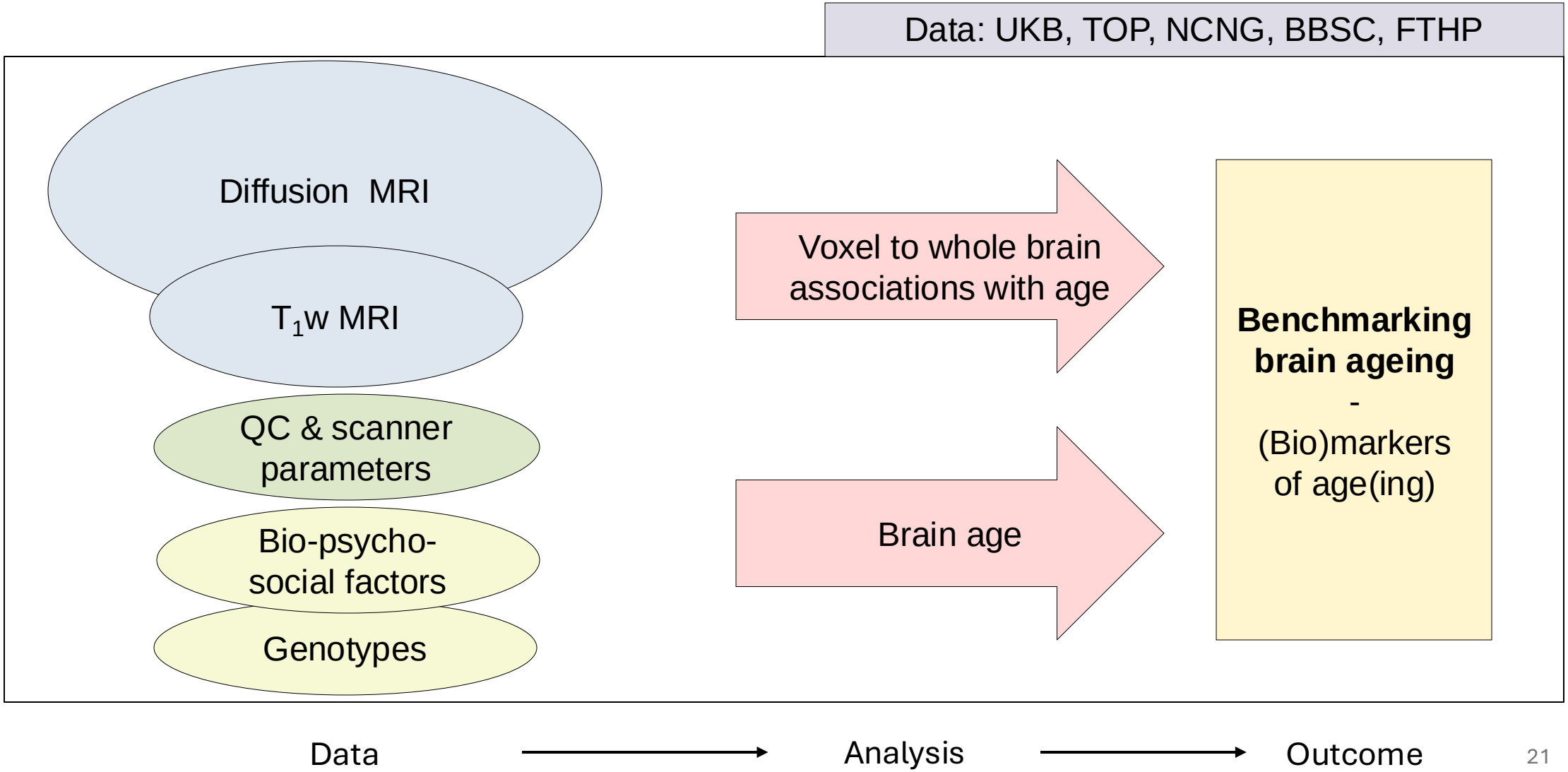
Alzheimer's Disease			Neuro-degenerative
Anxiety	Autism spectrum	Attention deficit hyperactivity	Psychiatric
Depression (uni-& bipolar)	Obsessive-compulsive	Schizophrenia	

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

Methods: Overview



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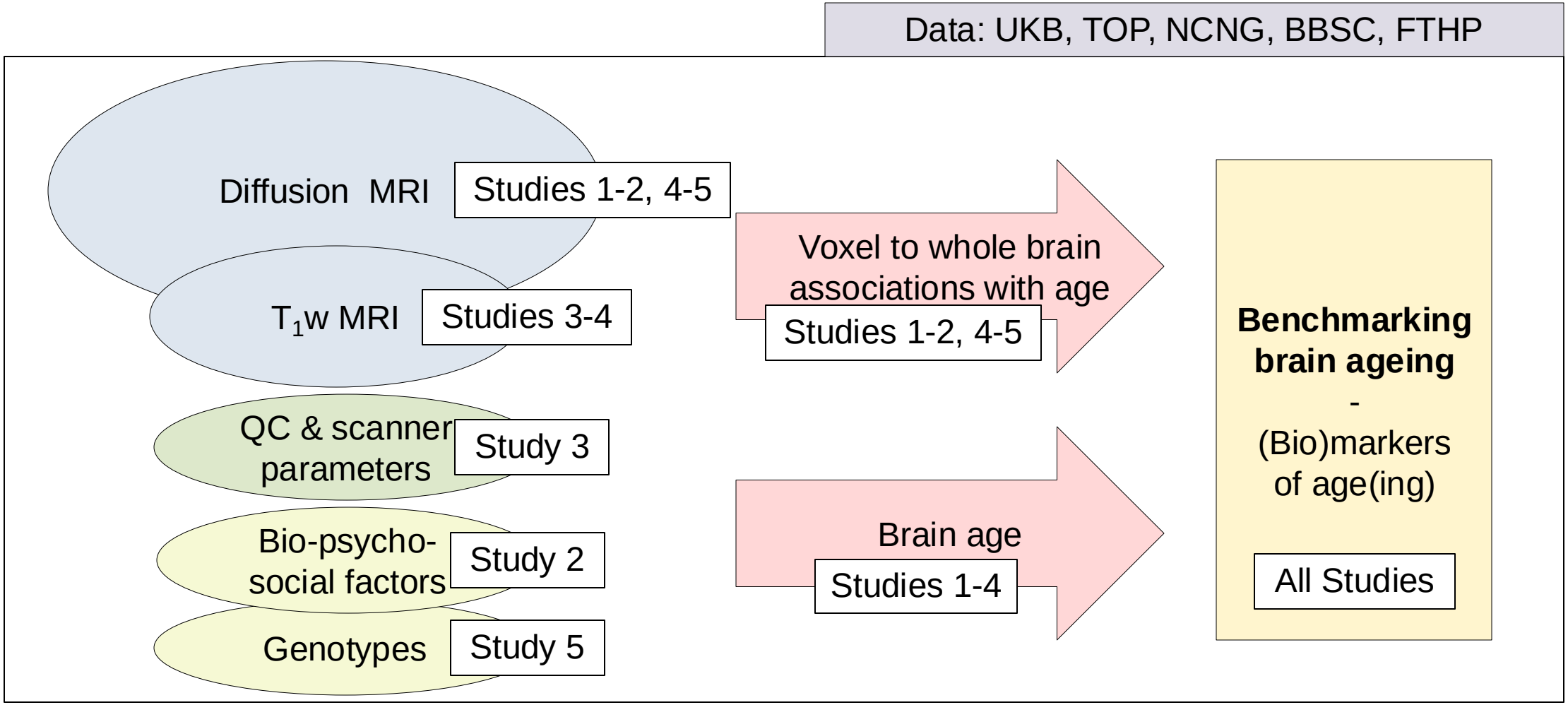

Data → Analysis → Outcome

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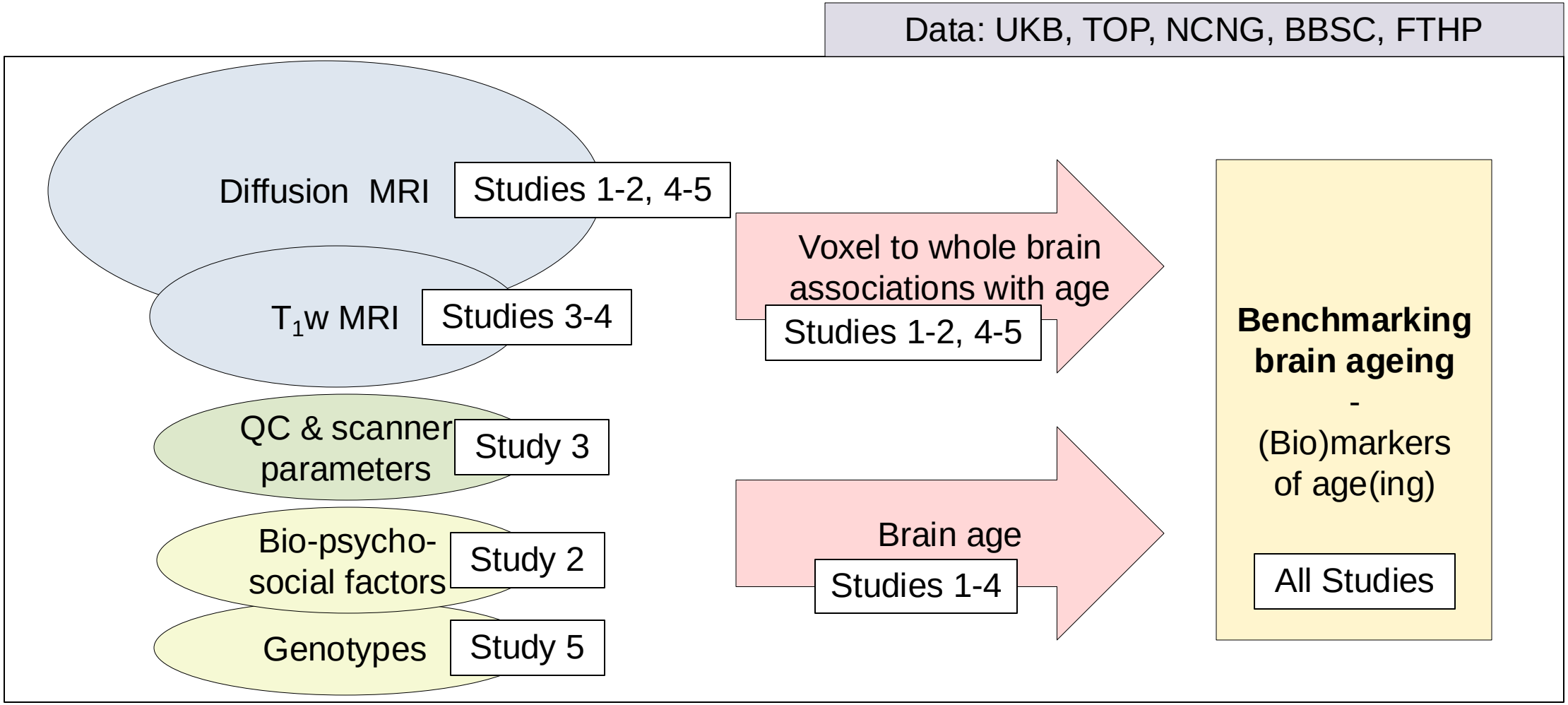
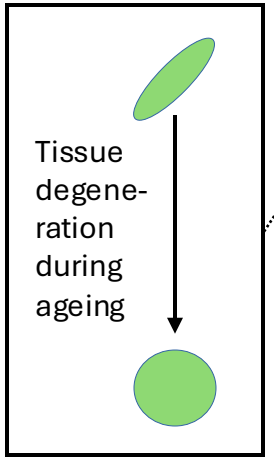


Data → Analysis → Outcome

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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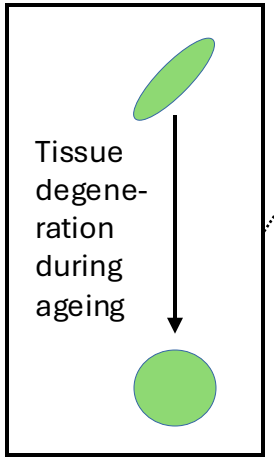
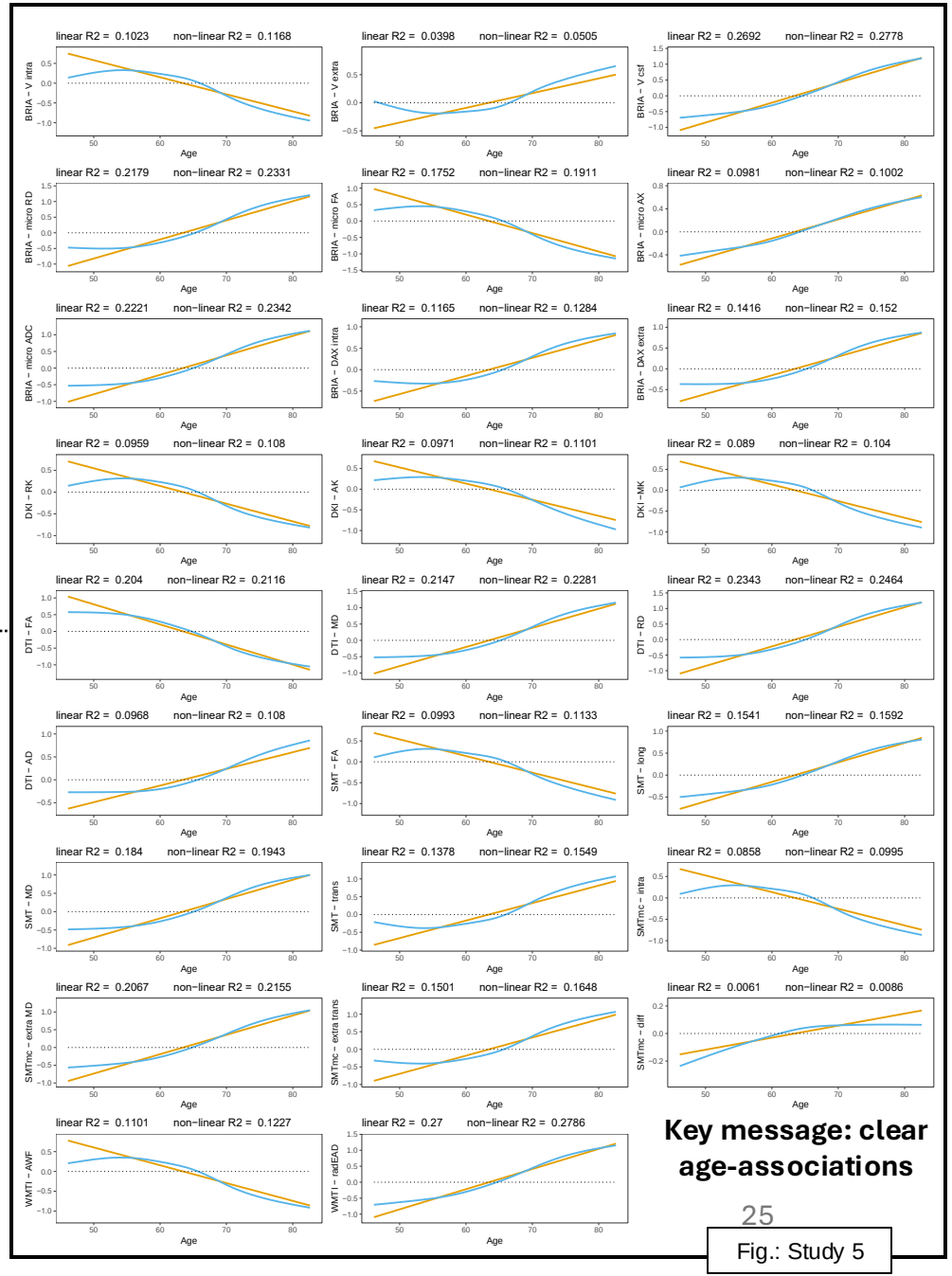
    - Anisotropy, kurtosis, intra axonal diffusion



White matter microstructure deteriorates during ageing



Key message: clear age-associations

Fig.: Study 5

Findings: White Matter Ageing (global)

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- Similar brain ages across diffusion approaches ≈ measuring the same construct

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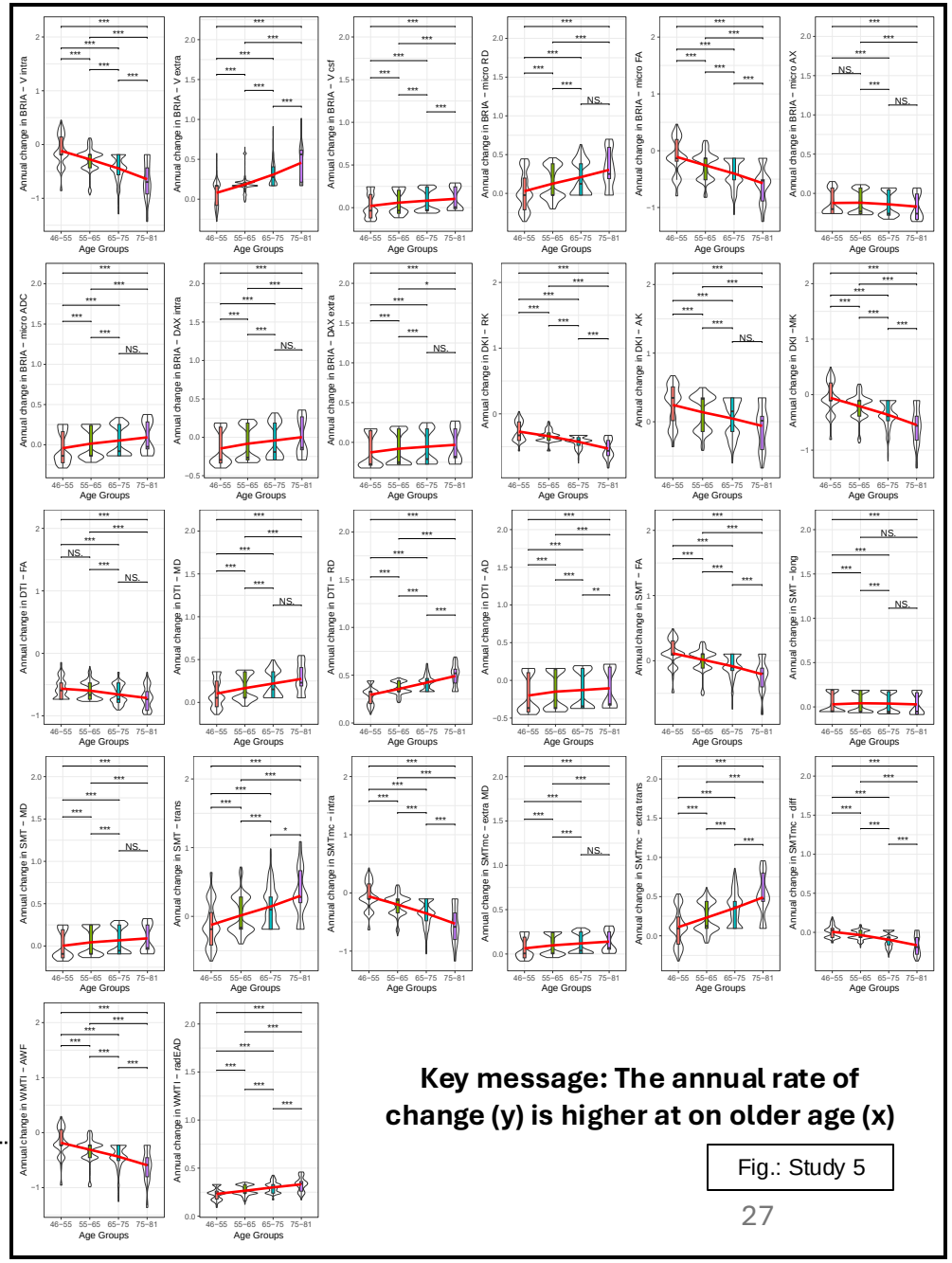
- Similar brain ages across diffusion approaches ≈ measuring the same construct
- Brain ageing accelerates

White matter microstructure deterioration accelerates



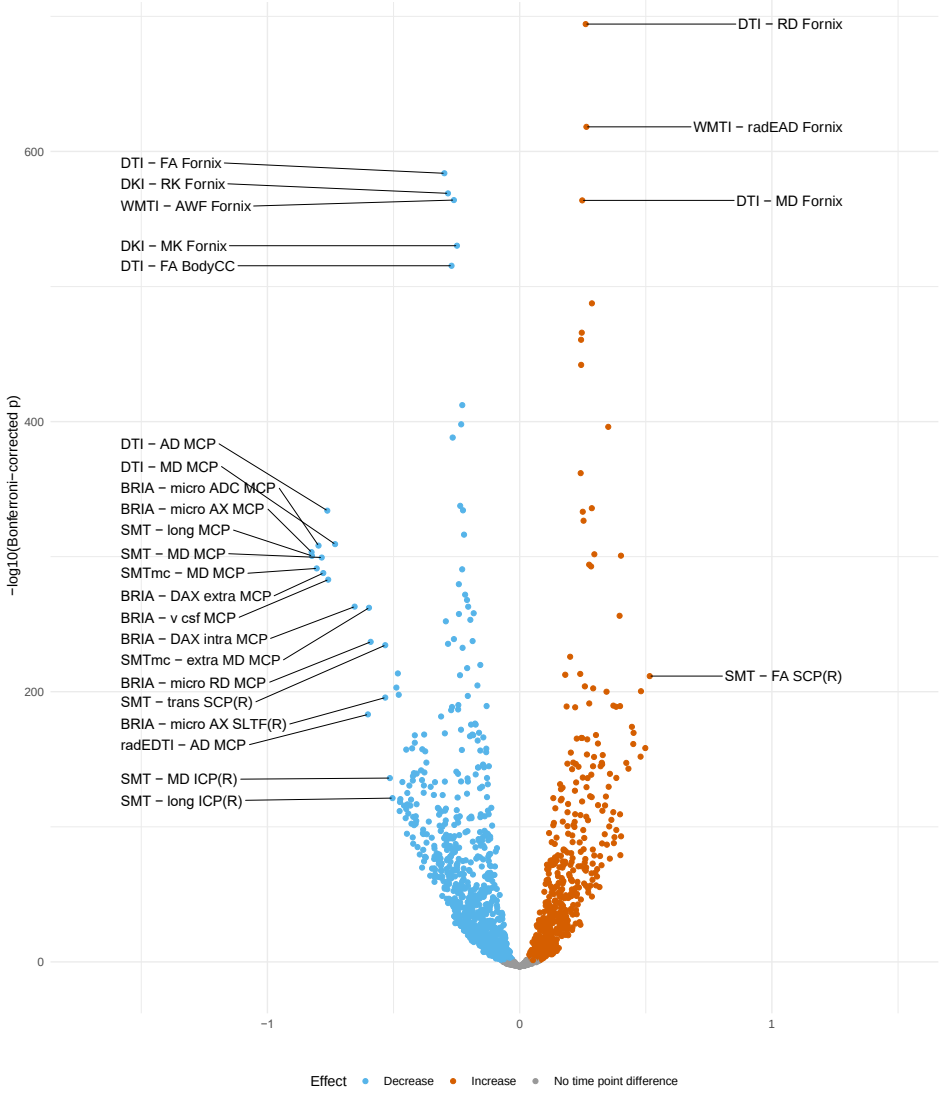
Key message: The annual rate of change (y) is higher at on older age (x)

Fig.: Study 5

Findings: White Matter Ageing (regional)

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

a) Time-point differences



b) Corrected age-associations

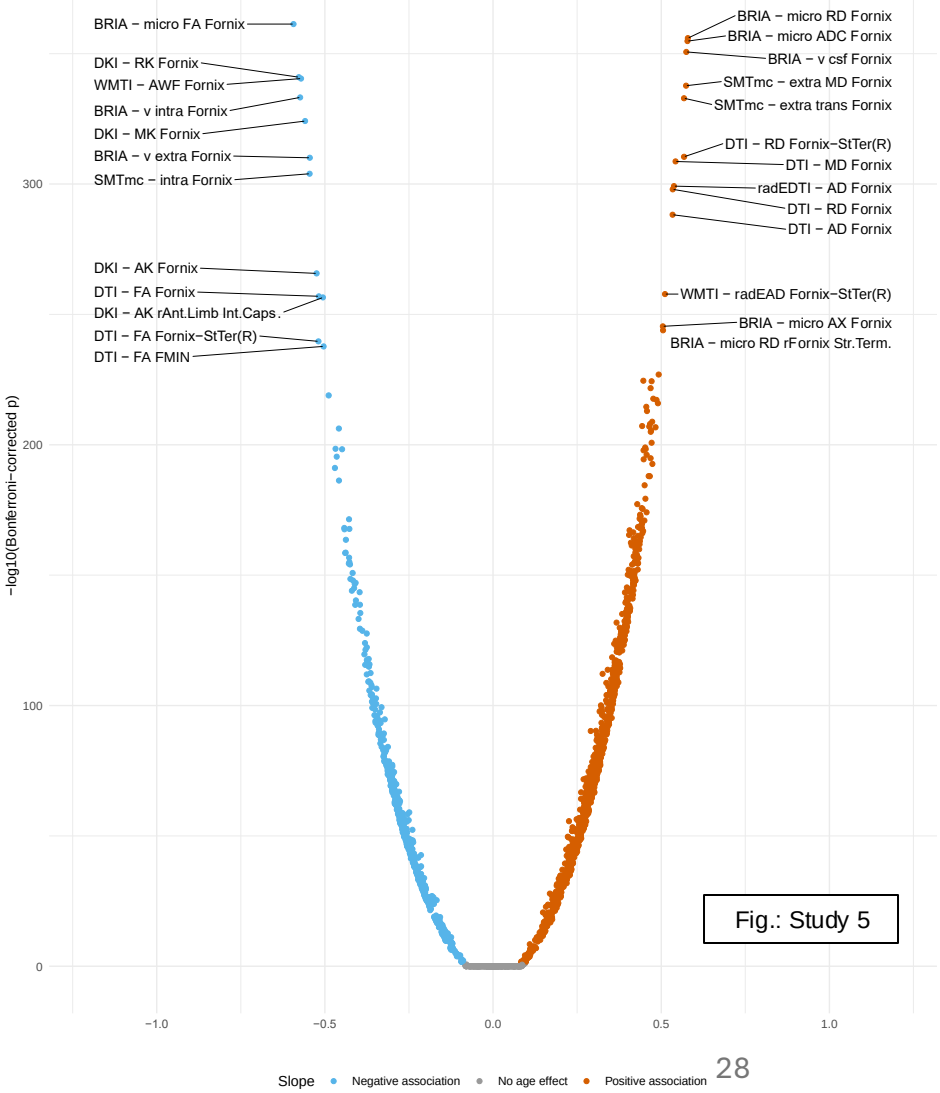


Fig.: Study 5

MCP = Middle Cerebellar Peduncle

Findings: White Matter Ageing (regional)

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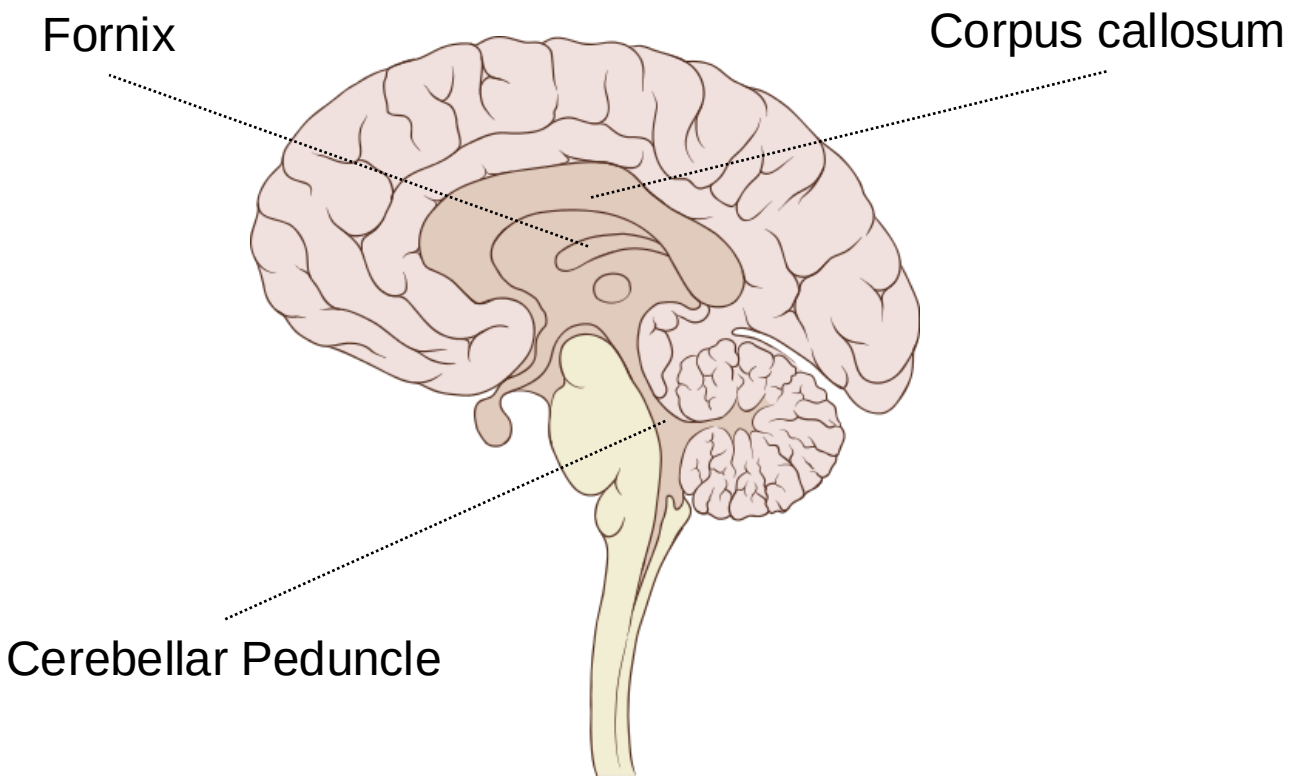
  - Brain stem: cerebellar peduncle



Findings: Brain Asymmetries

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

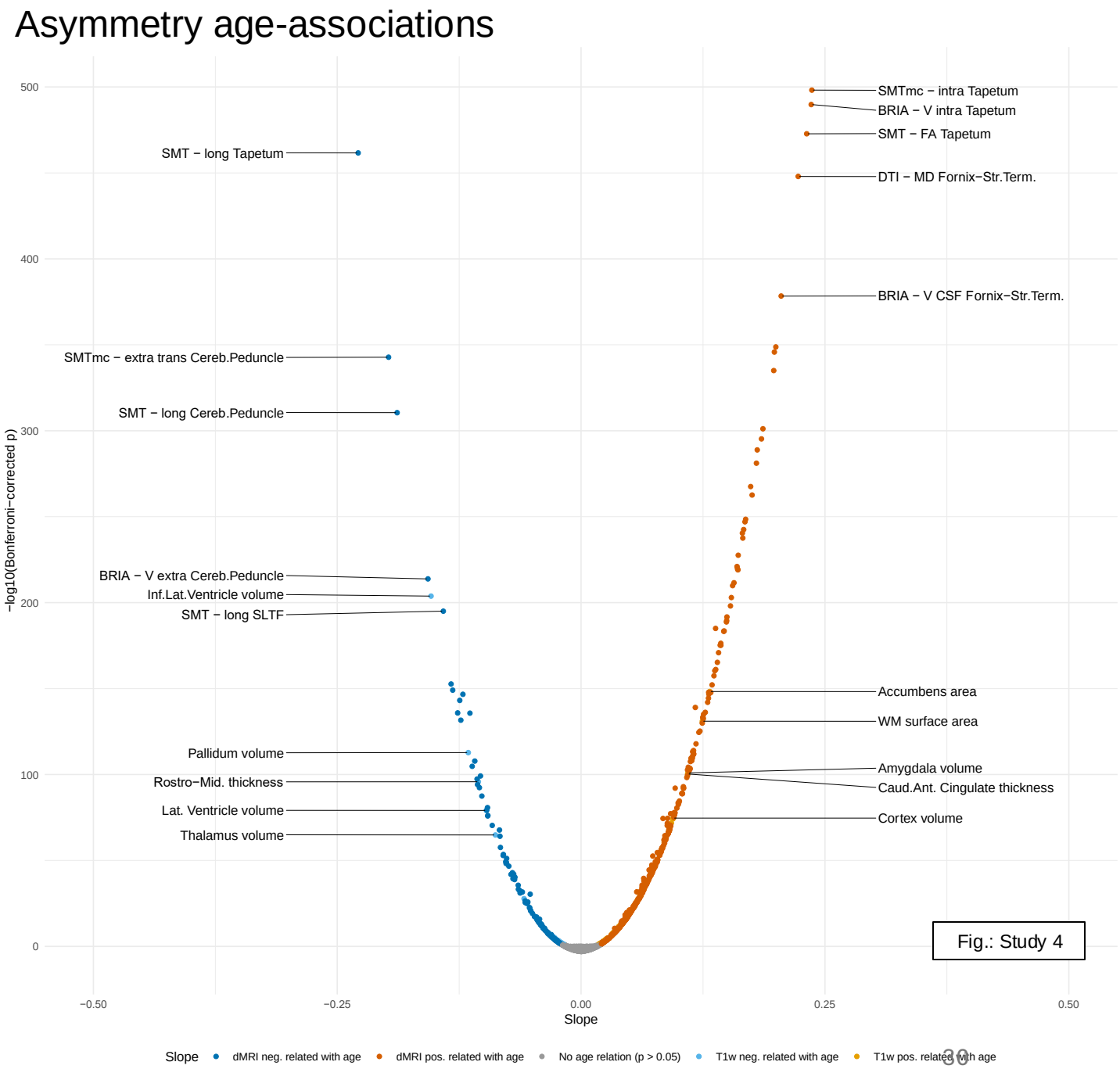


Fig.: Study 4

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

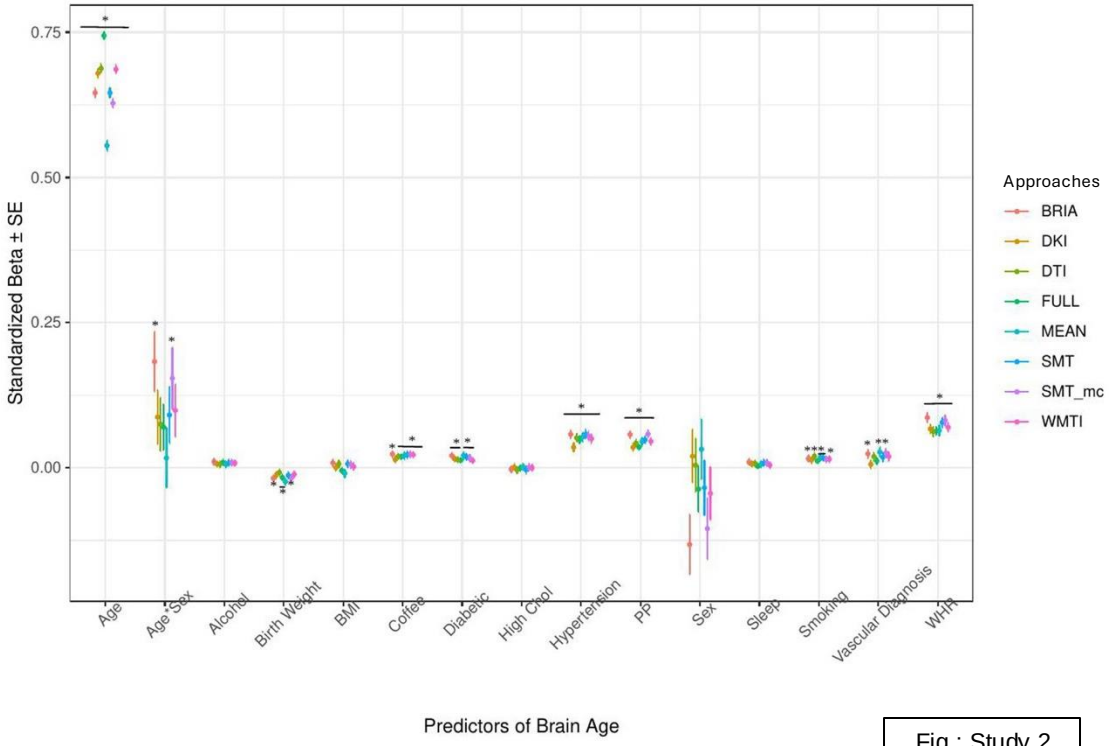


Fig.: Study 2

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

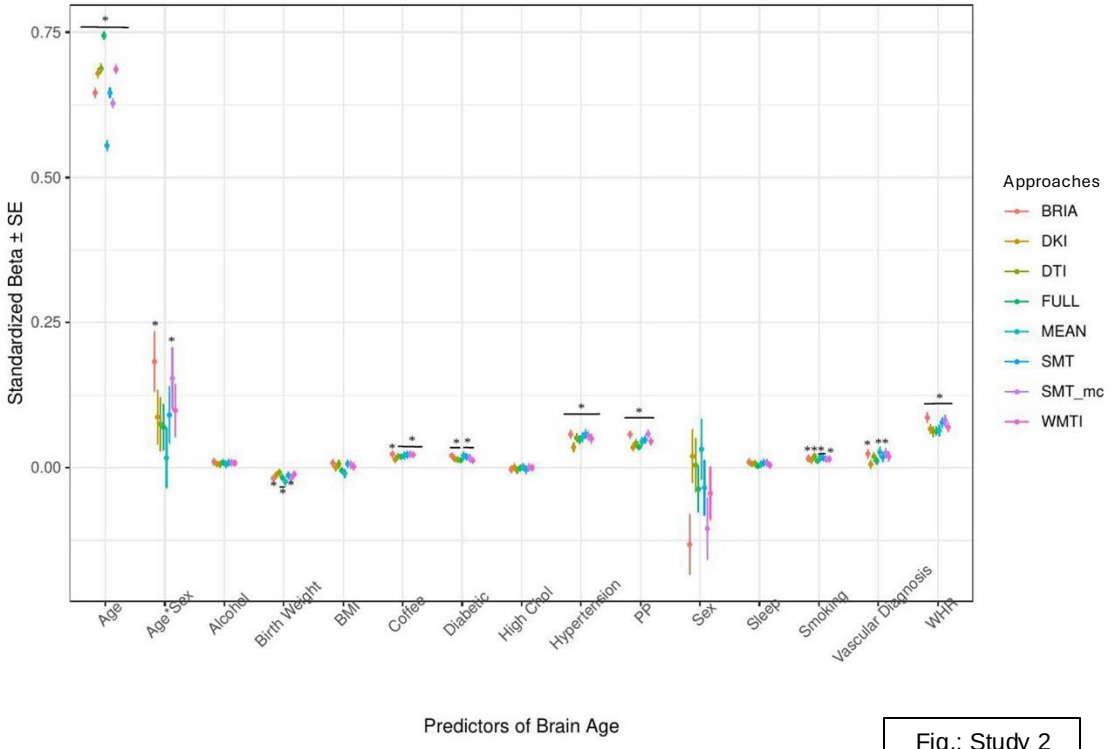


Fig.: Study 2

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

	ANX	ADHD	ASD	BIP	MDD	OCD	SCZ	AD
WMTI – radEAD	0.012	–0.008	0.002	0.002	0.021	–0.008	–0.009	0.017
WMTI – AWF	0.005	–0.002	0.001	0.004	–0.004	0.005	–0.003	–0.005
SMTmc – intra	0.006	–0.005	–0.007	0.003	0.003	0.001	–0.002	–0.001
SMTmc – extra trans	–0.002	0.003	0.006	–0.001	0.003	–0.001	–0.002	0.006
SMTmc – extra MD	0.006	–0.004	0.002	0.002	0.012	–0.002	–0.006	0.014
SMTmc – diff	0.026	–0.023	–0.016	0.011	0.03	–0.002	–0.011	0.022
SMT – trans	–0.006	0.005	0.005	–0.002	0	–0.001	0.001	0.004
SMT – MD	0.005	–0.001	0	0.003	0.016	–0.002	–0.004	0.018
SMT – long	0.01	–0.004	–0.003	0.005	0.024	–0.003	–0.006	0.025
SMT – FA	0.009	–0.005	–0.006	0.003	0.007	–0.002	–0.003	0.004
DTI – RD	0.005	–0.004	–0.001	–0.001	0.012	–0.004	–0.006	0.014
DTI – MD	0.004	–0.003	0.001	0.003	0.016	0.001	–0.004	0.018
DTI – FA	–0.007	0.008	0.004	0.007	–0.001	0.014	0.004	–0.007
DTI – AD	0.002	–0.001	0.005	0.011	0.026	0.012	0	0.026
DKI –MK	0.005	–0.007	–0.005	0.004	0	0	–0.003	–0.003
DKI – RK	0	–0.013	0.002	0.007	–0.001	0.003	0.002	0
DKI – AK	0.007	–0.006	–0.006	–0.005	–0.008	–0.009	0	–0.006
BRIA – V intra	0.005	–0.003	–0.007	0.003	0.001	0.001	–0.002	–0.003
BRIA – V extra	–0.007	0.005	0.008	–0.004	–0.005	–0.001	0.003	–0.002
BRIA – V csf	0.024	–0.023	–0.014	0.014	0.051	0.009	–0.019	0.053
BRIA – micro RD	0.002	–0.002	0.001	0.002	0.014	0.001	–0.003	0.017
BRIA – micro FA	0.002	0	–0.004	0.001	–0.006	–0.001	0.001	–0.009
BRIA – micro AX	0.022	–0.013	–0.011	0.011	0.041	–0.003	–0.006	0.041
BRIA – micro ADC	0.007	–0.005	–0.001	0.004	0.021	0	–0.004	0.024
BRIA – DAX intra	0.003	0	0.002	0.001	0.011	–0.003	0.001	0.013
BRIA – DAX extra	0.005	0.002	–0.002	0.004	0.021	–0.003	–0.001	0.022

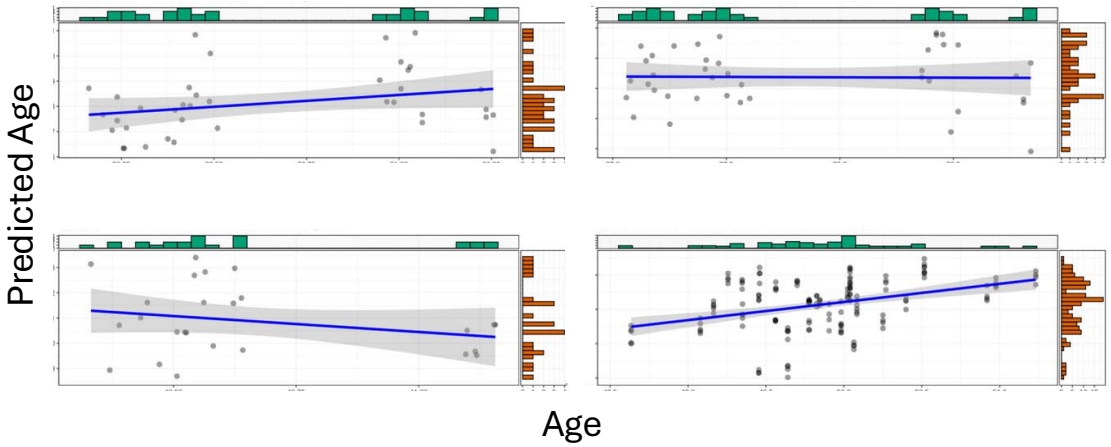
Association Strength –0.02 0.00 0.02 0.04

Fig.: Study 5

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

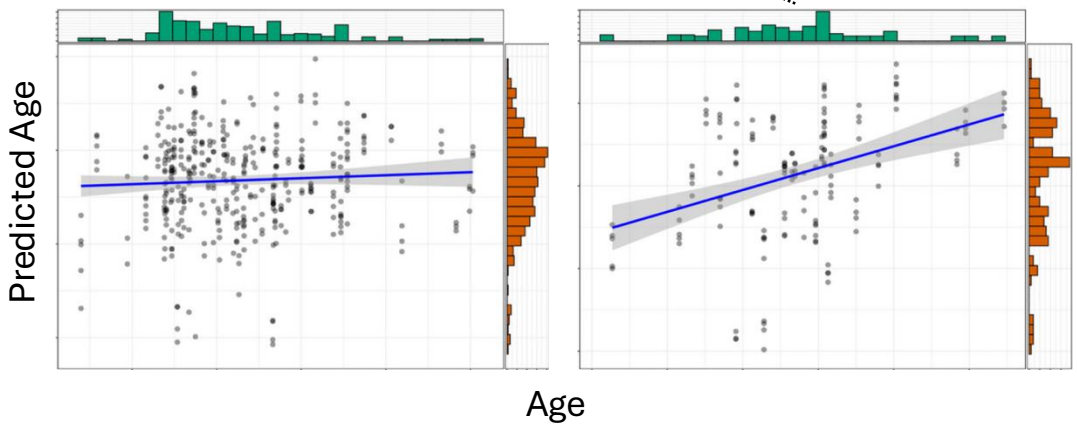


Fig.: Study 3

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

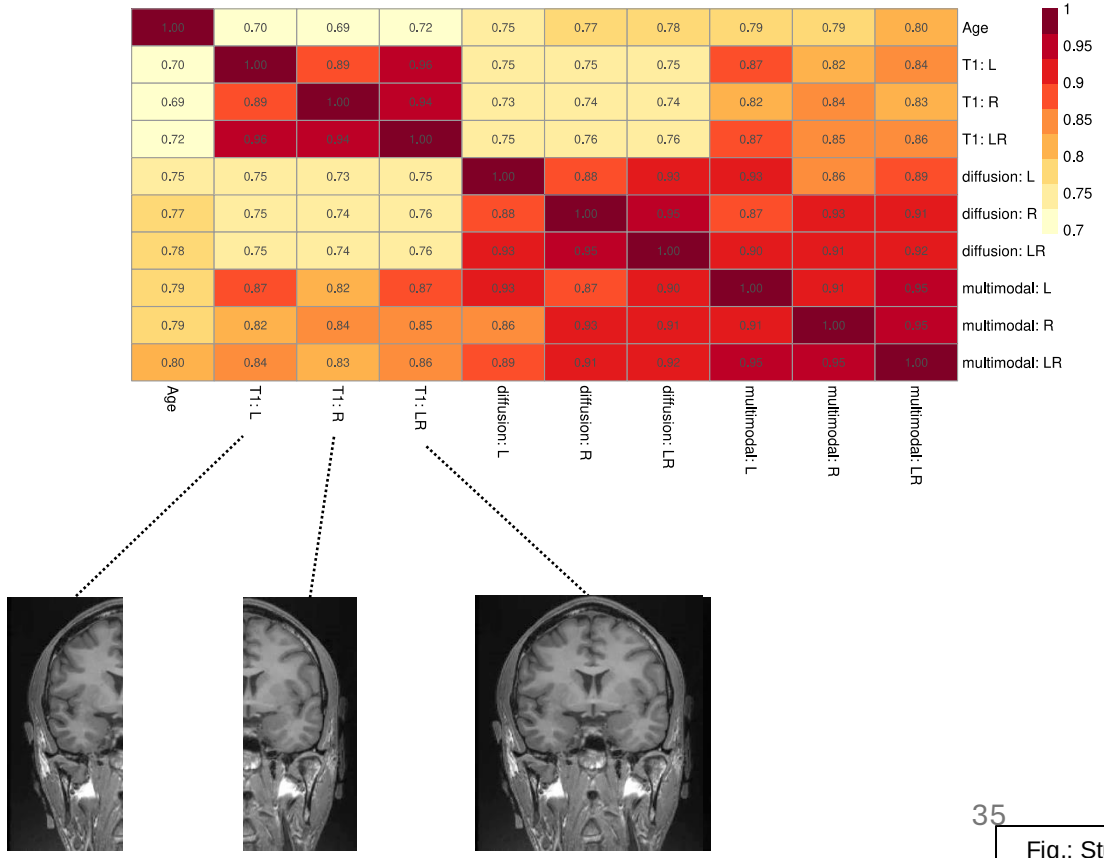


Fig.: Study 4

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[2,7,8], Eli Eikefjord[1,3], Arvid Lundervold[1,3,9,10], Ole A. Andreassen[2,11], Lars T. Westlye[2,8,11] 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 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

Summary

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

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Article

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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[1–6]. Microstructural brain characteristics, such as white matter (WM) pathways or intra- and extra-neurite water organisation, might underlie the brain's functional lateralisation[7]. Furthermore, handedness has been repeatedly assessed together with asymmetry in humans and animals, and relates to brain asymmetry[8]. 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[9,10], Parkinson's disease[11], and psychiatric disease such as obsessive-compulsive disorder[12,13] and schizophrenia[14]. 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[9]. Similarly, some studies suggest lower WM microstructure asymmetry at higher ages, indicated by intra-axonal water fraction[15], fractional anisotropy, or the apparent diffusion coefficient[16]. 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[17,18]. 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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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

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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Summary

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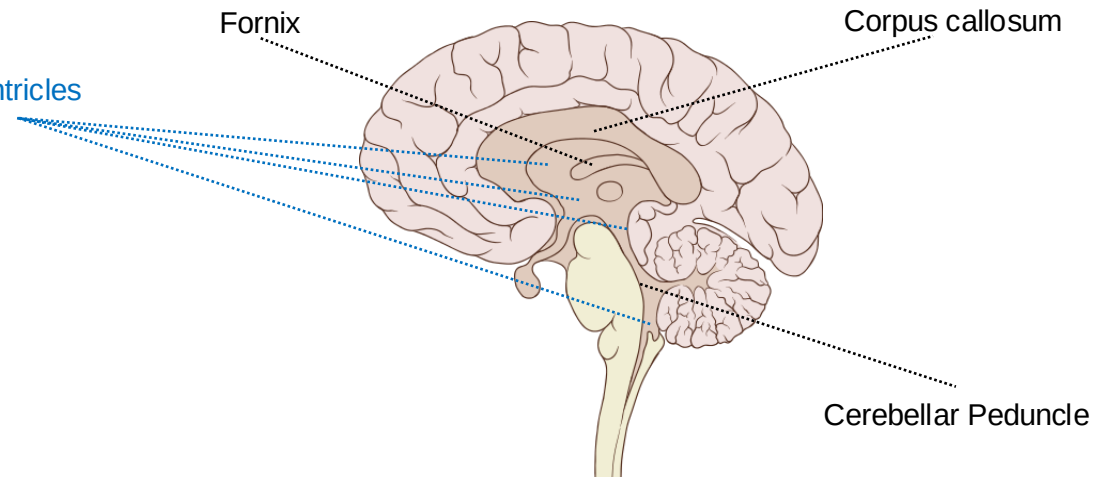
- However, transitioning brain age into the clinic requires further work
- Age sensitive regions
  - Ventricle-near, brain stem



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[2,6] | Dani Beck[2,7,8] | Eli Eikefjord[1,3] | Arvid Lundervold[1,3,9,10] | 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. 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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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

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[2,7,8], Eli Eikefjord[1,3], Arvid Lundervold[1,3,9,10], Ole A. Andreassen[2,11], Lars T. Westlye[2,8,11] and Ivan I. Maximov[1,2]*

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

Summary

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- 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

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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Thank you!

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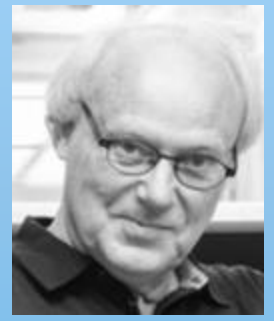

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Rune Eikeland

Esten Leonardsen

Thomas Espeseth, Ralph Buchert, Daniel E. Askeland-Gjerde, friends and family!

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

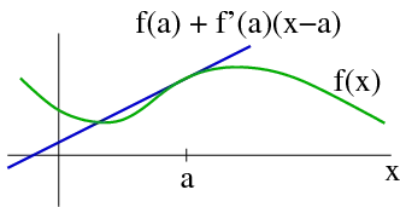
More details on XGBoost

- *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

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

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

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



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

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??)

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

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

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)

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 = 4.355643211804128e-262
r CI = [0.616706844488446,0.6652867426267055]
------------------------------
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 = 3.44993090537704e-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
```

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

Tissue relaxation

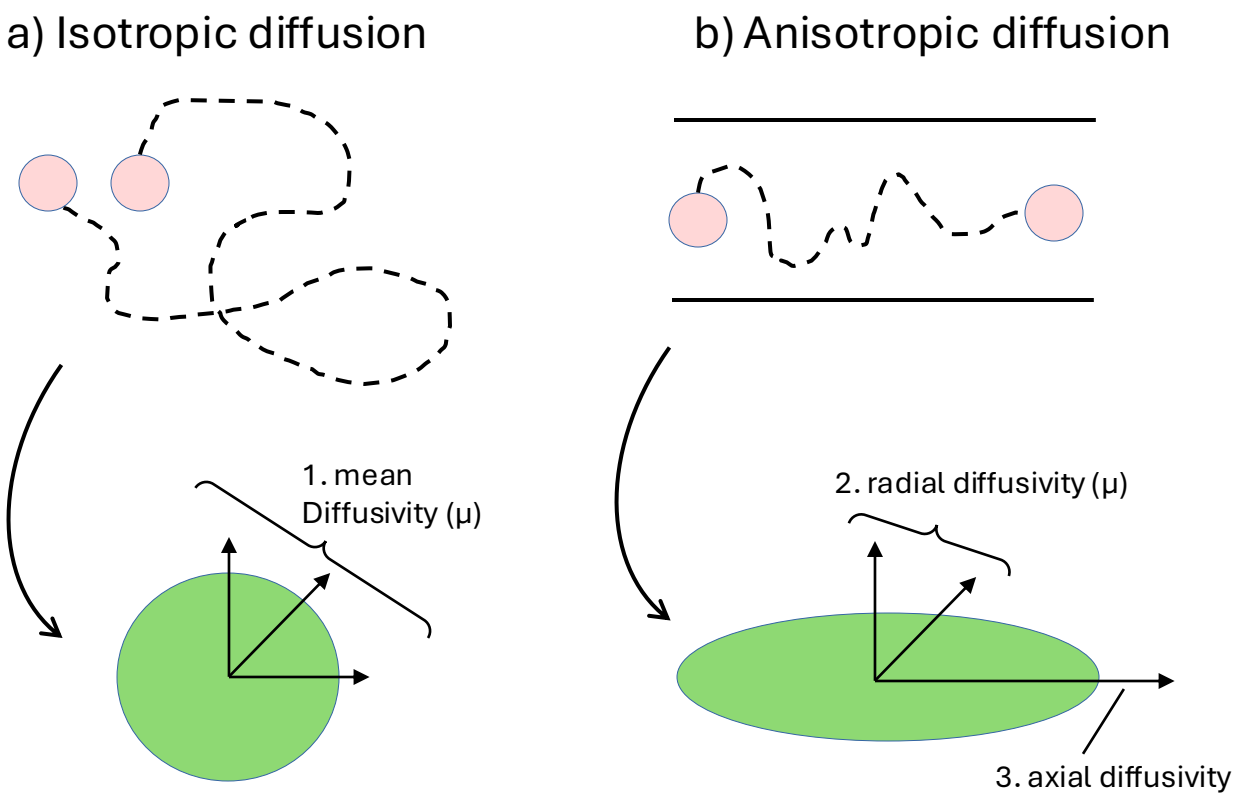
- T1: fluids long, fat-based short
- T2: fluids short, fat-based shorter
- Examples:
  - CSF, T1=1.9 seconds and T2=0.25 seconds
  - brain white matter, T1=0.5 seconds and T2=0.07 seconds (70 msec)

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



4. fractional anisotropy = square root of the squared differences divided by 2x sum of squares

Most commonly approach: Diffusion Tensor Imaging (DTI)

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

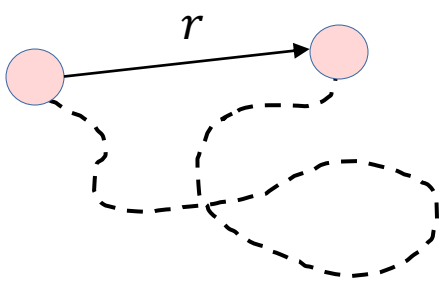
Diffusion: background

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

Mean square displacement

Number of particles

Time dependent



Isotropic diffusion

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

Diffusion: background

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

$$MSD(t) = 6\mathrm{Dt}$$

Constant depending on the dimensions, here 3

$D_{iso} = 3\mu m^2/ms$

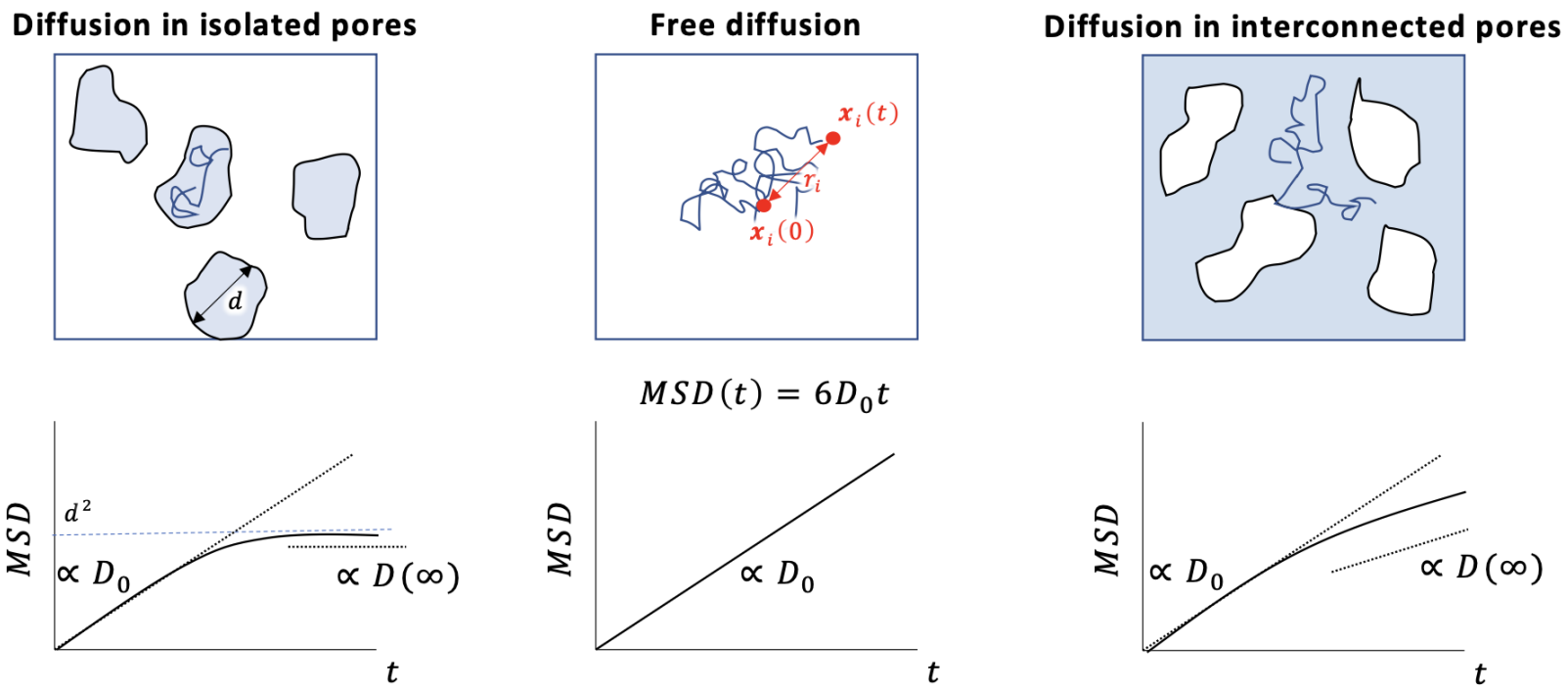
Example: Diffusion length: L(t) = sqrt(6Dt)

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

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)

Equivalent to

$$D = -1/b * ln(S_{DWI}/S_0)$$

Apparent diffusion coefficient

b-value

Signal of isotropic diffusion

Signal at baseline

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

Gyromagnetic ratio

Amplitude

Gradient application time

Duration between gradients

Stejskal & Tanner (1965). J Chem Phys

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

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

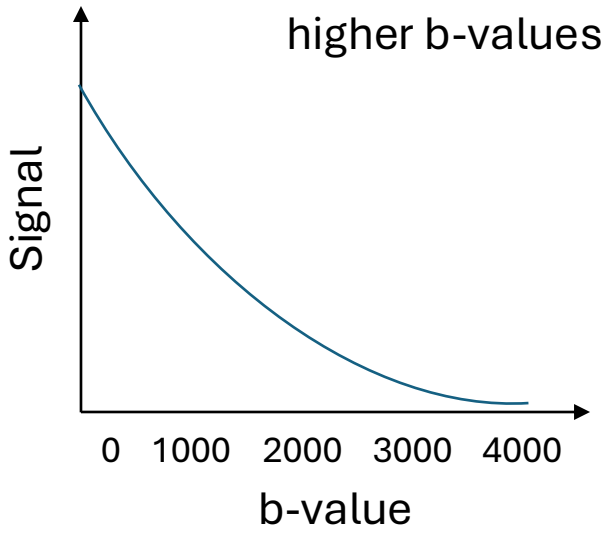
Signal

Signal at baseline

b-value

Apparent diffusion coefficient (area/time)

(Optimistic) signal decay at higher b-values



Stejskal & Tanner (1965). J Chem Phys

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

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

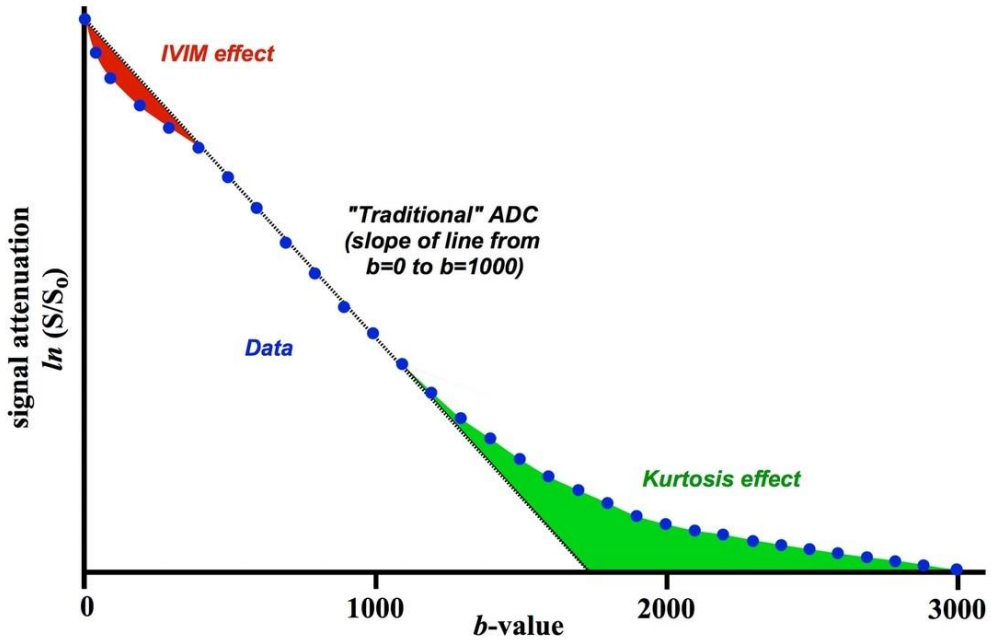
Signal

Signal at baseline

b-value

Diffusion coefficient (area/time)

Stejskal & Tanner (1965). J Chem Phys



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

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

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

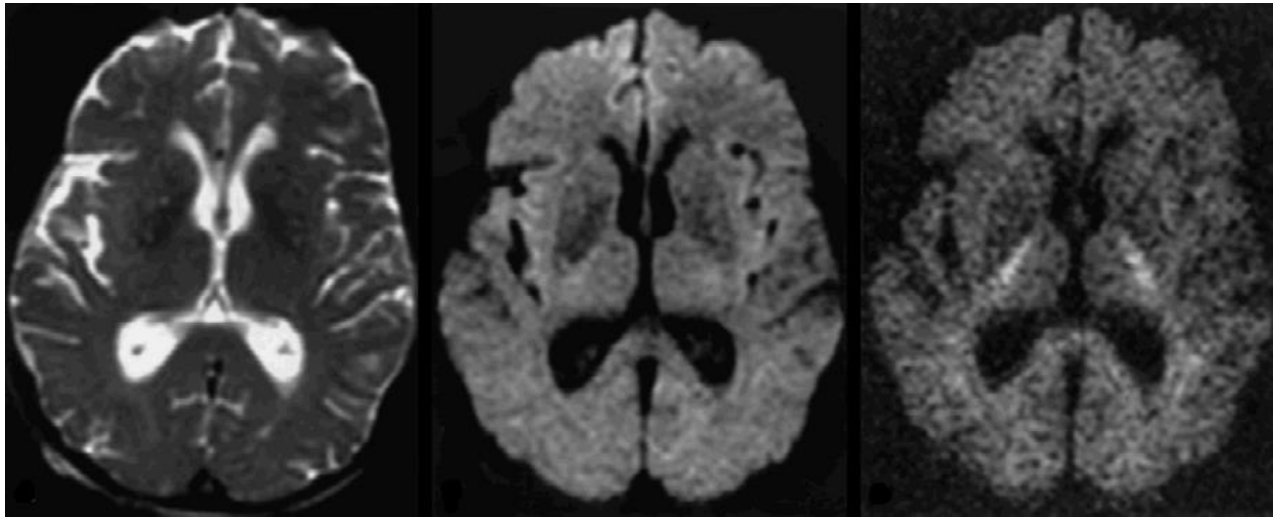
Gyromagnetic ratio

Amplitude

Gradient application time

Duration between gradients

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



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

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

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

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)

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).

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)

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

Multi compartment Spherical Mean Technique (mcSMT)

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

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

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

b = 0

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

Microstructural tissue model

Mesostructural tissue model

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

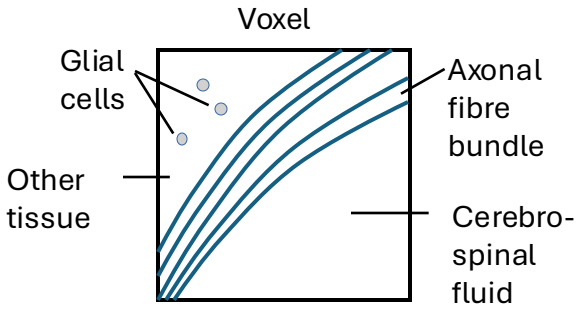
Future direction for dMRI

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

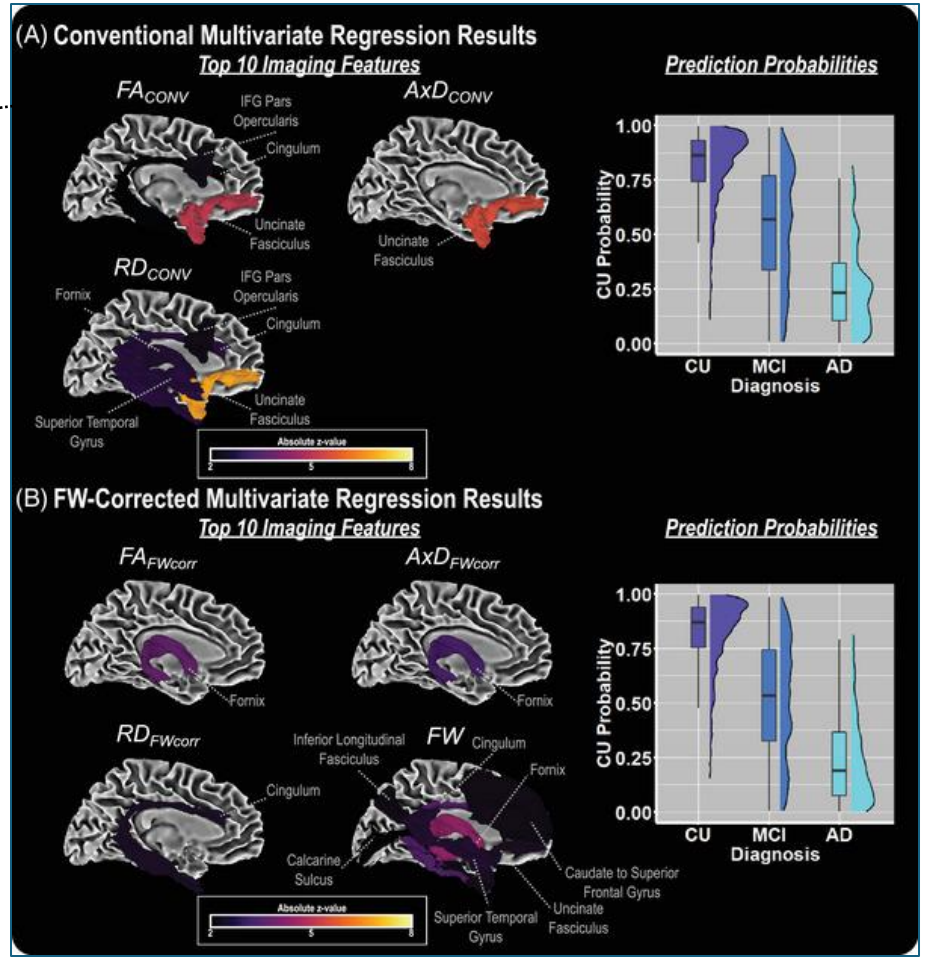
Supplemental Information: Findings

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)

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-160017
IOS Press

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

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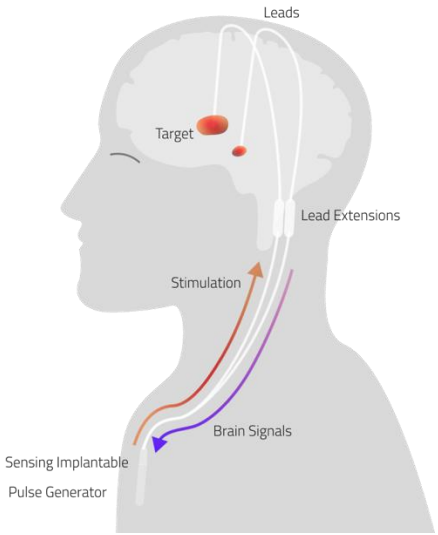
Review

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

Ruofan Li [a 1], Chencheng Zhang [b 1], Yanxia Rao [a c], Ti-Fei Yuan [a d e]



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

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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)

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.

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

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

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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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

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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Brain and Behavior Open Access WILEY

ORIGINAL ARTICLE

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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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

nature communications

Article

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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[1–6]. Microstructural brain characteristics, such as white matter (WM) pathways or intra- and extra-neurite water organisation, might underlie the brain's functional lateralisation[7]. Furthermore, handedness has been repeatedly assessed together with asymmetry in humans and animals, and relates to brain asymmetry[8]. 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[9,10], Parkinson's disease[11], and psychiatric disease such as obsessive-compulsive disorder[12,13] and schizophrenia[14]. 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[9]. Similarly, some studies suggest lower WM microstructure asymmetry at higher ages, indicated by intra-axonal water fraction[15], fractional anisotropy, or the apparent diffusion coefficient[16]. 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[17,18]. 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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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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