Distinguishing Lifelong Individual Differences from Divergent Aging Trajectories of Adult Brain Volumes

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Abstract: Differences in the volumes of brain structures between individuals are often linked to various conditions, including Alzheimer's disease, schizophrenia, and overall brain health. However, it remains unclear to what extent these differences reflect individual levels present at young adulthood or diverging aging trajectories at later ages. In this study, we analyze the aging dynamics of the volume of six brain structures based on MRI scans from a large cross-cohort longitudinal sample of cognitively healthy adults (n = 8,311 with 18,520 MRIs, ages from 18 to 97 years). From general assumptions about structural brain dynamics and measurement noise, a stochastic dynamical model was fit to the data to estimate both the variability and persistence of structural changes across adulthood. Using this model, we calculated how much of the variance in individual volumetric differences can be attributed to stable levels from young adulthood versus systematic changes at older ages, as well as the theoretical sensitivity of longitudinal studies to detect individual differences in changes. The findings were as follows: 1) Before age 60 years, inter-individual differences in neuroanatomical volumes almost exclusively reflect stable differences between individuals, while the influence from systematic differences in rate-of-change increases thereafter; up to 40 % of the variation being due to differences in change at 80 years. In contrast, ventricular volume reflects differences in change from early adulthood. 2) Current brain-age models are unlikely to be sensitive to detect differences in aging trajectories. 3) Imaging studies have a low reliability to detect inter-individual brain change before age 60. After 60 years , the study reliability increases sharply with longer intervals between scans and more modestly with additional intermediate observations. In conclusion, it is critical to distinguish between stable levels from early adulthood and systematic differences in change when studying adult brain aging.

1 Introduction

Adult humans show enormous variation in the size of brain structures within the normal, healthy population. For example, a study found that young healthy adults vary in cortical gray matter volume by 52%, white matter volume by 49% and hippocampal volume by 43% compared to the mean (4 SD / mean) (Walhovd et al., 2011). These differences are very large compared to the modest amount of change over time in the same structures when measured longitudinally, which even in old age is less than 1% annually for most regions (Driscoll et al., 2009; Fjell et al., 2009; Sele et al., 2021). Thus, it is likely that a major part of volumetric differences in adulthood reflects stable, individual differences originating earlier in life (Walhovd et al., 2023). However, the continuous morphological changes throughout life also implies a

balance between early adulthood levels and systematic differences in change (aging) contributions with effects of change accumulating over time potentially being more important later in life. Here, we aim to study the degree to which single observations capture early adulthood level vs. change effects in adulthood and how the relative contribution of each change throughout the lifespan.

Due to the greater availability and logistical feasibility of acquiring cross-sectional MRIs (i.e., a single measurement per person), there is considerable interest in estimating individualized aging trends based on cross-sectional observations. Although it is unclear whether these measures can capture the ongoing decline of individual brains (Raz & Lindenberger, 2011; Rohrer, 2025), such inferences are frequently drawn with respect to brain aging (Franke & Gaser, 2019), schizophrenia (Blake et al., 2023), brain health (Bashyam et al., 2020), a variety of genetic and lifestyle-related risk factors for Alzheimer's disease (AD)(Habes et al., 2016), and even mortality (Cole et al., 2018).

The assumption that cross-sectional data can be used to index individual differences in change is problematic, because research has demonstrated that cross-sectional differences often do not translate into differences in change (Nyberg et al., 2010, 2021; Raz et al., 2005) with formal analyses further confirming this weak correspondence (e.g., Lindenberger et al., 2011). This issue has resurfaced with the increasing popularity of Brain Age Gap (BAG), often interpreted as a marker of accelerated brain aging and ongoing brain change. However, this interpretation has been repeatedly challenged. Studies show that baseline effects are likely to dominate the BAG signal (Smith et al., 2019, 2025) and other studies find that there is a modest-to-null correlations between cross-sectional BAG and longitudinal brain change (Dörfel et al., 2025; Korbmacher et al., 2024). For example, we previously showed that having a higher BAG was not associated with a faster rate of brain aging, but rather reflected stable differences originating from very early in life (Vidal-Pineiro et al., 2021).

It is therefore critical to distinguish the contributions from the level at young adulthood vs. systematic differences in change to the total inter-individual differences in brain structure volumes. Importantly, different MRI measures capture ongoing brain changes to varying degrees, with some reflecting change clearly better than BAG (Smith et al., 2020; Vidal-Pineiro et al., 2021). A recent study found that controlling for intracranial volume (ICV) eliminated a major source of stable brain volume variability, and since the relative contribution of degenerative change to cross-sectional estimates gradually increased with older age, brain volume provides a better reflection of ongoing atrophy when controlling for ICV in older age (Fürtjes et al., 2024).

The degree to which accumulation of systematic differences in change eventually manifests itself in observable cross-sectional differences depends on at least three factors:

- The magnitude of the initial differences at young adulthood (level effects).

- The magnitude of the systematic inter-individual differences in change rate (change effects).

- The time span over which the differences in change rate unfolds.

Thus, individual differences in brain structure at any age will depend on a mixture of stable differences and accumulation of systematic differences in change, and the relative contribution of each is likely vary with age. Estimating how variation in these changes depends on age is also important for designing imaging studies. Several studies have shown, through either simulations (Brandmaier, Von Oertzen, et al., 2018; Brandmaier et al., 2024) or from empirical data (Vidal-Piñeiro et al., 2025), that the magnitude of the true change between measurement is essential for detection of change. Because the rate of volume change in brain structures probably varies with age, the expected signal from change will also vary.

Here, we propose to use a time-dependent stochastic dynamic model of brain volume aging to quantify the relative contributions of levels from young adulthood vs. systematic differences in change to the total variation in six major structural brain measures continuously throughout the adult lifespan. Using stochastic dynamical models to describe systems has a long tradition in physics (Einstein, 1906; Gardiner et al., 1985), finance (Föllmer & Schied, 2011; Lee, 1992), engineering (Kalman, 1960; Welch, Bishop, et al., 1995) and neuroscience (Friston, 2010). Due to recent developments in Bayesian statistical methods (Hoffman, Gelman, et al., 2014), fitting such a system directly from data is now possible within a reasonable computational time-frame (Driver & Voelkle, 2018; Sørensen & McCormick, 2025).

We hypothesize that the major part of structural brain differences can be explained by inter-individual differences, which remain stable for most of adult life, and that a gradually larger proportion of the variance can be ascribed to individual differences in change at higher ages. To our knowledge, this question has not previously been systematically investigated. We further used the dynamical model to calculate the theoretical correlation between the measurements of brain change with the true (i.e., latent) change, and from this analysis make recommendations for how best to design longitudinal studies to maximize sensitivity to ongoing brain change.

2 Methods

2.1 Data

We compiled a data sample from 14 different datasets, with a combined 8,310 subjects and a total of 18,520 sessions. Both longitudinal and cross-sectional data were included in the analysis. Table 1 lists the datasets used in this study.

Table 1: List of datasets used in the study.

Dataset	Abbreviation	Reference	N subjects	N sessions
UKBiobank	UKB	Miller et al., 2016	1287	2574
UiO LCBC	LCBC	Walhovd et al., 2018	1274	2295
OASIS-3	OASIS-3	LaMontagne et al., 2019	974	2120
The Barcelona Brain Health Initiative	BBHI	Cattaneo et al., 2018	930	1201
The Alzheimer's disease neuroimaging initiative	ADNI	Mueller et al., 2005	769	3316
Cambridge Centre for Ageing Neuroscience	Cam-CAN	Shafto et al., 2014	638	905
The Berlin Aging Study II	BASE-II	Bertram et al., 2014	430	730
The Vietnam Era Twin Study of Aging	VETSA	Kremen et al., 2019	406	1453
The Wayne State longitudinal data set	Wayne	Burgmans et al., 2010; Kennedy and Raz, 2009	313	497
PREVENT-AD	Prevent-AD	Tremblay-Mercier et al., 2021	305	1360
The BETULA project	BETULA	Nilsson et al., 1997; Nilsson et al., 2004	303	587
The University of Barcelona	UB	Abellaneda-Pérez et al., 2019; Rajaram et al., 2017; Uribe et al., 2016; Vidal-Piñeiro et al., 2014	288	421
Harvard Aging Brain Study	HABS*	Dagley et al., 2017	281	673
COGNORM	COGNORM	Idland et al., 2017	113	388

*HABS data release 2.20, retrieved in August 2022 via habs.mgh.harvard.edu.

The age distribution of the datasets is shown in Fig. 1. See Supplementary information of Vidal-Piñeiro et al., 2025 for a detailed overview of each dataset.

The T1-weighted MRI brain scans of each individual were processed with longitudinal FreeSurfer v.7.1.0

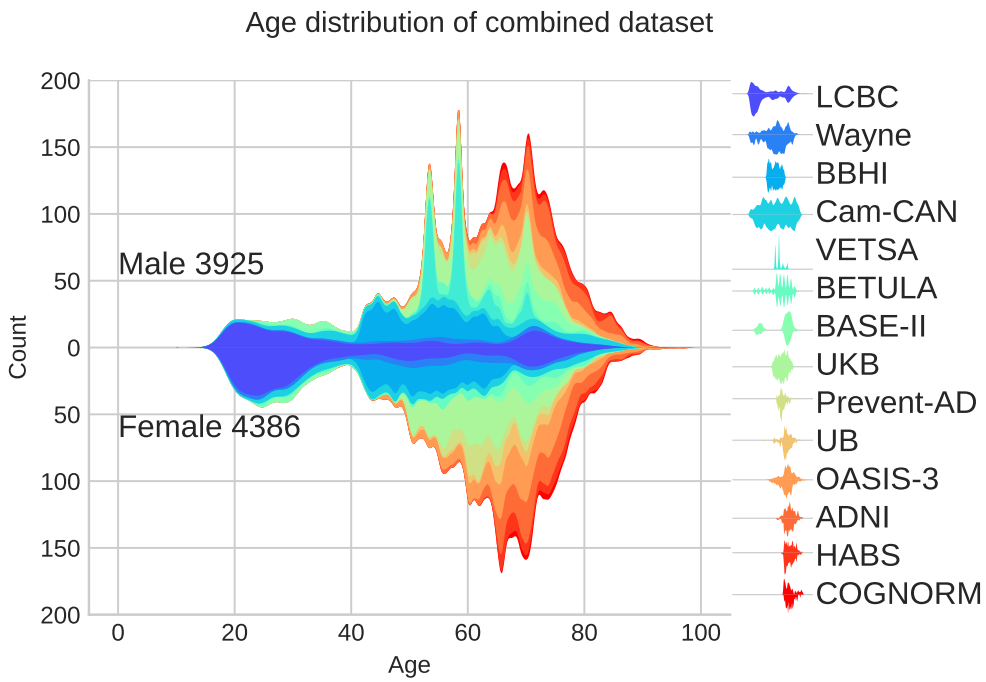

Figure 1: Left: Age distribution of the combined sample. The histogram shows the number of male and female participants at each age, with colors denoting different datasets. Right: Age histogram for each dataset with corresponding color.

stream (Reuter et al., 2012). The volume of combined hippocampus, gray matter, white matter, supratentorial regions (excluding ventricles), combined lateral ventricles, and the brainstem was extracted. We also used the imaging site as a covariate in our model. In the ADNI dataset, some sites have very few participants; we therefore constructed combined sites for ADNI after scanner type. This reduces the total number of imaging sites from 125 to 39.

2.2 Model

2.2.1 Informal description

No study follows individuals longitudinally from early adulthood to old age. Therefore, we construct a dynamical model to understand brain development over the lifespan. Our approach is based on several assumptions that enable us to characterize the evolution of brain structure volumes under both systematic trends and random variations. Brain structures, such as the hippocampus, change gradually over time as an individual age; abrupt changes in volume are not expected. We also expect the change rate of each structure to be stable over a short time span. However, over a lifetime, an individual may change their

change rate relative to the population, due to external factors such as lifestyle, illness, or other random influences. The change rate therefore changes according to an acceleration (i.e the change rate of the change rate). This acceleration is assumed to have a random individualized component and a systematic influence dependent on age. An individual's change rate at any age then reflects the accumulated effect of the acceleration up to that age. Furthermore, we assume that the acceleration itself is not directly driven by the current volume or the current change rate. We argue that this assumption is justified in adult populations where the rapid growth phase has already concluded. We address differences among cohorts by considering the intracranial volume (ICV). There is evidence that ICV, and by extension, brain volume, has increased over the last century (DeCarli et al., 2024; Kim et al., 2018). Adjusting for ICV may also correct for other factors such as environmental factors during development and genetics that might bias some of the datasets. To account for these cohort effects, we model the initial brain structure volume at age 18 to be proportional to the ICV. Finally, recognizing that measurements of brain structures are subject to considerable noise and site bias, especially compared to the subtle changes observed over a few years (Vidal-Piñeiro et al., 2025), we explicitly incorporate measurement noise and site bias into our model. We assume that this noise is independent of the other factors influencing brain development, and that each imaging site adds a bias to the volumetric measurement. With these assumptions, the brain development of each volume is modeled as a stochastic dynamical system evolving under the influence of both systematic trends and random factors.

2.2.2 Formal Description

We model the system dynamics using the latent state $\boldsymbol{z}(t)$ defined as:

$$\boldsymbol{z}(t) = \begin{bmatrix} s(t) \\ v(t) \end{bmatrix}, \tag{1}$$

with $s(t)$ representing the true volume of the brain structure when removing measurement noise and site bias, and $v(t)$ is the first derivative with respect to time of the volume, which we refer to as change rate. The time variable t denotes the age of the individual, with initial age of t_0 being set somewhat arbitrary to approximately the end of development at age 18. Based on the assumption in the previous section the stochastic time-dependent dynamical model is given by

$$\begin{aligned} \dot{s}(t) &= v(t), \\ \ddot{s}(t) = \dot{v}(t) &= b(t) + w_q(t), \end{aligned} \tag{2a}$$

where $(\cdot)$ and $(\cdot\cdot)$ denote the first and second time derivative operation. $b(t)$ is an age dependent bias, and w_q is Gaussian white noise with an age dependent variance $\sigma_q^2(t)$.

The observed volume measurement $\hat{s}(t)$ is modeled as,

$$\hat{s}(t) = s(t) + \beta(\text{site}) + w_r(t), \tag{2b}$$

where $\beta(\text{site})$ is a site dependent-bias term and w_r is Gaussian white noise with variance σ_r^2. $\beta(\text{site})$ accounts for different imaging sites having different scanners and scanning protocols that may cause a bias in the volume measurement (X. Han et al., 2006). β is constrained such that $\sum_{j \in \text{sites}} \beta_j := 0$, ensuring that $\hat{s}(t)$ is an unbiased estimator of $s(t)$. At time t_0 the population latent volume and change rate is modeled as two independent Gaussian distributions,

$$\begin{aligned} s(t_0) &\sim \mathcal{N}(\mu_{s0}(\text{sex}, \text{ICV}), \sigma_{s0}^2) \\ v(t_0) &\sim \mathcal{N}(\mu_{v0}(\text{sex}, \text{ICV}), \sigma_{v0}^2) \end{aligned} \tag{2c}$$

where the initial means μ_{s0} and μ_{v0} is assumed to be linearly dependent on both the sex and the ICV of the individuals. The variance of the initial distribution of the latent volume and latent change rate is given by σ_{s0} and σ_{v0}. In summary the following parameters are fitted

- Intercept and sex- and ICV-coefficient for mean initial latent volume
  $\mu_{s0} = \beta_{s0} + \beta_{s0,sex}\text{sex} + \beta_{s0,ICV}\text{ICV}$.
- Intercept and sex- and ICV-coefficient for mean initial change rate
  $\mu_{v0} = \beta_{v0} + \beta_{v0,sex}\text{sex} + \beta_{v0,ICV}\text{ICV}$.
- Variance term σ_{s0}^2 for initial latent volume.
- Variance term σ_{v0}^2 for initial change rate.
- Age dependent bias $b(t)$ for the acceleration parametrized as a cubic spline with 9 checkpoints.
- Age dependent variance $\sigma_q^2(t)$ for the acceleration parametrized as a cubic spline with 9 checkpoints.
- A bias for each site $\beta(\text{site})$.
- Variance term σ_r^2 for the measurement noise.

This gives a total 12 parameters when counting the weights of the splines and each site bias as one parameter. When counting all the weights of the splines and the bias for each site there is a total of 66 fitted parameters.

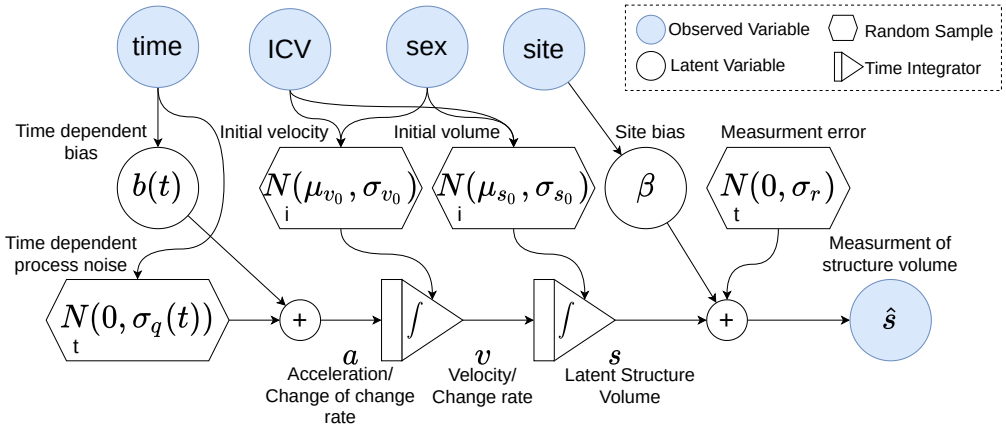

Figure 2: State-space diagram showing the dynamical model of the brain structure volume. The i in the hexagon indicates that the variable is iid for each individual, while a t indicates iid for each time step.

2.2.3 Properties of the Stochastic Linear Dynamical System

The model can be expressed compactly in matrix form as:

$$\dot{\boldsymbol{z}}(t) = \boldsymbol{F}\boldsymbol{z}(t) + \boldsymbol{B}(t) + \boldsymbol{w}_{\boldsymbol{Q}}(t), \qquad \boldsymbol{w}_{\boldsymbol{Q}}(t) \sim \mathcal{N}\left(\boldsymbol{0}, \boldsymbol{Q}(t)\right) \tag{3a}$$

$$\boldsymbol{y}(t) = \boldsymbol{H}\boldsymbol{z}(t) + \boldsymbol{D} + \boldsymbol{w}_{\boldsymbol{R}}(t), \qquad \boldsymbol{w}_{\boldsymbol{R}}(t) \sim \mathcal{N}(\boldsymbol{0}, \boldsymbol{R}) \tag{3b}$$

$$\dot{\boldsymbol{z}}(t) = \begin{bmatrix} 0 & 1 \\ 0 & 0 \end{bmatrix} \boldsymbol{z}(t) + \begin{bmatrix} 0 \\ b(t) \end{bmatrix} + \boldsymbol{w}_{\boldsymbol{Q}}(t), \qquad \boldsymbol{w}_{\boldsymbol{Q}}(t) \sim \mathcal{N}\left(\boldsymbol{0}, \begin{bmatrix} 0 & 0 \\ 0 & \sigma_q^2(t) \end{bmatrix}\right), \tag{4a}$$

$$\hat{s}(t) = \boldsymbol{y}(t) = \begin{bmatrix} 1 & 0 \end{bmatrix} \boldsymbol{z}(t) + \begin{bmatrix} \beta(\text{site}) \end{bmatrix} + \boldsymbol{w}_{\boldsymbol{R}}(t), \qquad \boldsymbol{w}_{\boldsymbol{R}}(t) \sim \mathcal{N}\left(\begin{bmatrix} 0 \end{bmatrix}, \begin{bmatrix} \sigma_r^2 \end{bmatrix}\right), \tag{4b}$$

where $\boldsymbol{y}(t)$ is the measurement vector which in our case is just the measured volume $\hat{s}(t)$. A state-space diagram of the model is shown in Fig. 2.

The continuous model can be time discretized analytically with a sampling period of Δ (Driver & Voelkle, 2018). We assume a zero-order-hold for the time dependent parameters $b(t)$ and $\sigma_q(t)$ within each period Δ (Simon, 2006), meaning these parameters remain constant within this period. Discrete variables are denoted with a star ($*$), and time steps are indexed by k, such that $\boldsymbol{F}^*$ represent the time discrete version

of $\boldsymbol{F}$ and $b_k := b(t_0 + k\Delta)$. The time discrete model is given by

$$\boldsymbol{z}_{k+1} = \boldsymbol{F}^* \boldsymbol{z}_k + \boldsymbol{B}_k^* + \boldsymbol{w}_{\boldsymbol{Q}k}^*, \qquad \boldsymbol{w}_{\boldsymbol{Q}^*k} \sim \mathcal{N}\left(\boldsymbol{0}, \boldsymbol{Q}_k^*\right) \tag{5a}$$

$$\boldsymbol{y}_k = \boldsymbol{H}\boldsymbol{z}_k + \boldsymbol{D} + \boldsymbol{w}_{\boldsymbol{R}k} \qquad \boldsymbol{w}_{\boldsymbol{R}k} \sim \mathcal{N}\left(\boldsymbol{0}, \boldsymbol{R}\right) \tag{5b}$$

$$\boldsymbol{z}_{k+1} = \begin{bmatrix} 1 & \Delta \\ 0 & 1 \end{bmatrix} \boldsymbol{z}_k + \begin{bmatrix} \frac{\Delta^2}{2} b_k \\ \Delta b_k \end{bmatrix} + \boldsymbol{w}_{\boldsymbol{Q}^*k}, \qquad \boldsymbol{w}_{\boldsymbol{Q}^*k} \sim \mathcal{N}\left(\boldsymbol{0}, \begin{bmatrix} \frac{\Delta^3}{3}\sigma_{qk}^2 & \frac{\Delta^2}{2}\sigma_{qk}^2 \\ \frac{\Delta^2}{2}\sigma_{qk}^2 & \Delta\sigma_{qk}^2 \end{bmatrix}\right) \tag{6a}$$

$$\boldsymbol{y}_k = \begin{bmatrix} 1 & 0 \end{bmatrix} \boldsymbol{z}_k + \begin{bmatrix} \beta(\text{site}) \end{bmatrix} + \boldsymbol{w}_{\boldsymbol{R}k}, \qquad \boldsymbol{w}_{\boldsymbol{R}k} \sim \mathcal{N}\left(0, \begin{bmatrix} \sigma_r^2 \end{bmatrix}\right) \tag{6b}$$

The initial conditions remain as specified in Eq. 2c.

Assume that at time step k the latent state is estimated as $\boldsymbol{z}_k \sim \mathcal{N}(\boldsymbol{\mu}_k, \boldsymbol{\Sigma}_k)$. $\boldsymbol{\mu}_k$ represents the state mean (which can be both the population norm or the mean of an individual's posterior distribution after measurements) and $\boldsymbol{\Sigma}_k$ denotes the associated uncertainty. The distribution for the subsequent time step is given by

$$\boldsymbol{\mu}_{k+1} = \boldsymbol{F}^* \boldsymbol{\mu}_k + \boldsymbol{B}_k^* \tag{7}$$

$$\boldsymbol{\Sigma}_{k+1} = \boldsymbol{F}^* \boldsymbol{\Sigma}_k \boldsymbol{F}^{*T} + \boldsymbol{Q}_k^* \tag{8}$$

which for n time steps becomes:

$$\boldsymbol{\mu}_{k+n} = \boldsymbol{F}^{*(n)} \boldsymbol{\mu}_k + \sum_{i=0}^{n-1} \boldsymbol{F}^{*(n-1-i)} \boldsymbol{B}_{k+i}^* \tag{9}$$

$$\boldsymbol{\Sigma}_{k+n} = \boldsymbol{F}^{*(n)} \boldsymbol{\Sigma}_k \boldsymbol{F}^{*(n)T} + \sum_{i=0}^{n-1} \boldsymbol{F}^{*(n-1-i)} \boldsymbol{Q}_{k+i}^* \boldsymbol{F}^{*(n-1-i)T} \tag{10}$$

This model puts an important constraint on the system. Since we are assuming no correlation between $s(t)$ and $v(t)$ at t_0, and no feedback, the variance of $s(t)$ and $v(t)$ will always increase with age. This can easily be verified by writing out the update function of $\boldsymbol{\Sigma}_k$ in Eq. 8 for $\boldsymbol{\Sigma}_k$ with positive off-diagonal terms.

2.2.4 Correlation Characteristics of the Stochastic Dynamical System

Our goal is to quantify the explained variance of brain structure volume in adulthood given the initial volume at young adulthood t_0. To do so, we use the auto-correlation (AC) which is the normalized auto-covariance.

The auto-covariance $\boldsymbol{K}$ with lag n is defined as

$$\boldsymbol{K}(\boldsymbol{x}_k, \boldsymbol{x}'_{k+n}) = E\left[(\boldsymbol{x}_k - E\left[\boldsymbol{x}_k\right])\left(\boldsymbol{x}'_{k+n} - E\left[\boldsymbol{x}'_{k+n}\right]\right)\right], \tag{11}$$

for the random variables $\boldsymbol{x}_k$ and $\boldsymbol{x}'_k$. We will only consider the case where $n \geq 0$, since the auto-covariance is symmetric for negative n and this simplifies the equations a little. Let $\boldsymbol{d}(\boldsymbol{\Sigma})$ be the vector of the diagonal of a matrix $\boldsymbol{\Sigma}$. We define the standard deviation vector as $\boldsymbol{\sigma} = \sqrt{\boldsymbol{d}(\boldsymbol{\Sigma})}$ and the outer product of this vector as $\overline{\boldsymbol{\Sigma}} = \boldsymbol{\sigma}\boldsymbol{\sigma}^T$. The auto-correlation $\boldsymbol{\rho}_{\mathsf{AC}}$ is given by

$$\boldsymbol{\rho}_{\mathsf{AC}}(\boldsymbol{x}_k, \boldsymbol{x}'_{k+n}) = \frac{\boldsymbol{K}(\boldsymbol{x}_k, \boldsymbol{x}'_{k+n})}{\sqrt{\overline{\boldsymbol{K}}(\boldsymbol{x}_k, \boldsymbol{x}_k)\overline{\boldsymbol{K}}(\boldsymbol{x}'_{k+n}, \boldsymbol{x}'_{k+n})}}, \tag{12}$$

where the division is performed element-wise. Note that the auto-correlation $\boldsymbol{\rho}_{\mathsf{AC}}$ reduces to the correlation $\boldsymbol{\rho}$ when $n = 0$.

For a linear system such as Eq. 5, the auto-covariance has a closed-form solution given by propagating the initial covariance through the system transfer matrix $\boldsymbol{F}$ n times, which gives

$$\boldsymbol{K}(\boldsymbol{z}_k, \boldsymbol{z}_{k+n}) = \boldsymbol{F}^{*(n)}\boldsymbol{\Sigma}_k, \tag{13}$$

and

$$\boldsymbol{K}(\hat{s}_k, \hat{s}_{k+n}) = \begin{cases} \boldsymbol{H}\boldsymbol{F}^{*(n)}\boldsymbol{\Sigma}_k\boldsymbol{H}^T, & n \neq 0 \\ \boldsymbol{H}\boldsymbol{\Sigma}_k\boldsymbol{H}^T + \boldsymbol{R}, & n = 0. \end{cases} \tag{14}$$

The measured volume has the same co-variance with the latent variables (including the latent volume) as the latent volume itself, which gives,

$$\boldsymbol{K}(\hat{s}_k, \boldsymbol{z}_{k+n}) = \boldsymbol{K}(s_k, \boldsymbol{z}_{k+n}) \tag{15a}$$

$$\boldsymbol{K}(\boldsymbol{z}_k, \hat{s}_{k+n}) = \boldsymbol{K}(\boldsymbol{z}_k, s_{k+n}). \tag{15b}$$

$\boldsymbol{\rho}_{\mathsf{AC}}$ for the latent variables can be written compactly as

$$\boldsymbol{\rho}_{\mathsf{AC}}(\boldsymbol{z}_k, \boldsymbol{z}_{k+n}) = \frac{\boldsymbol{F}^{*(n)}\boldsymbol{\Sigma}_k}{\sqrt{\overline{\boldsymbol{\Sigma}}_{k+n}\overline{\boldsymbol{\Sigma}}_k}}. \tag{16}$$

For the measured volume, the measurement noise must be added to the total variance. Thus, $\boldsymbol{\rho}_{\mathsf{AC}}$ for the measurements with $n > 0$ becomes

$$\boldsymbol{\rho}_{\mathsf{AC}}(\hat{s}_k, \hat{s}_{k+n}) = \frac{\boldsymbol{H}\boldsymbol{F}^{*(n)}\boldsymbol{\Sigma}_k\boldsymbol{H}^T}{\sqrt{\left(\boldsymbol{H}\overline{\boldsymbol{\Sigma}}_k\boldsymbol{H}^T + \boldsymbol{R}\right)\left(\boldsymbol{H}\overline{\boldsymbol{\Sigma}}_{k+n}\boldsymbol{H}^T + \boldsymbol{R}\right)}}. \tag{17}$$

By using Eq. 15 one can obtain similar correlations between $\hat{s}_k$ and $\boldsymbol{z}_{k+n}$.

We assign names to the elements of Eq. 16 according to their interpretation as correlation coefficients:

$$\boldsymbol{\rho}_{\mathsf{AC}}(\boldsymbol{z}_k, \boldsymbol{z}_{k+n}) = \begin{bmatrix} \rho_{s_k s_{k+n}} & \rho_{v_k s_{k+n}} \\ \rho_{s_k v_{k+n}} & \rho_{v_k v_{k+n}} \end{bmatrix} \tag{18}$$

An intuitive explanation of these coefficients, assuming comparison between time points k and $k+n$, is as follows:

- $\rho_{s_k s_{k+n}}$ is the correlation coefficient of the structure volume at time step k and at the later time step $k+n$.
- $\rho_{v_k s_{k+n}}$ is the correlation coefficient of the change rate at time step k and the volume at the later time step $k+n$.
- $\rho_{s_k v_{k+n}}$ is the correlation coefficient of the volume at time step k and the change rate at the later time step $k+n$.
- $\rho_{v_k v_{k+n}}$ is the correlation coefficient of the change rate at time step k and at the later time step $k+n$.

2.2.5 Estimates of Change Rate from Measurements

As the brain ages, accumulated differences in anatomical changes affect the volume of the brain structures. Consequently, a single volume measurement, when compared to the age-group norm, can serve as an estimate of the current rate of change. However, earlier changes may not accurately reflect the current rate, and the accumulated changes might be too small compared to measurement noise for the volume

to be related to the current change rate. To evaluate how well a single volume measurement of brain volume can act as a proxy for the current change rate, we compute the correlation between the measured volume at a given age and the latent change rate given by $\rho_{\hat{s}_k v_{k+n}}$.

An alternative method for obtaining an estimate of the change rate is to take the difference between two volume measurements, which we call a delta estimate and denote $\hat{v}_{k+n}$. This is given by

$$\hat{v}_{k+n} = \frac{1}{n\Delta}\left(\hat{s}_{k+n} - \hat{s}_k\right). \tag{19}$$

The question is whether this is a good measurement of the true change rate at the last time step $k+n$ of the two measurements. We quantify this by calculating the correlation ρ between $\hat{v}_{k+n}$ and v_{k+n} which is given by

$$\rho(\hat{v}_{k+n}, v_{k+n}) = \frac{\boldsymbol{K}(\hat{v}_{k+n}, v_{k+n})}{\sqrt{\boldsymbol{K}(\hat{v}_{k+n}, \hat{v}_{k+n})\boldsymbol{K}(v_{k+n}, v_{k+n})}} \tag{20}$$

A little of mathematical manipulations results in the following expression for the normalized correlation:

$$\rho(\hat{v}_{k+n}, v_{k+n}) = \frac{\boldsymbol{K}(s_{k+n}, v_{k+n}) - \boldsymbol{K}(s_k, v_{k+n})}{\sqrt{(\boldsymbol{K}(\hat{s}_{k+n}, \hat{s}_{k+n}) + \boldsymbol{K}(\hat{s}_k, \hat{s}_k) - 2\boldsymbol{K}(\hat{s}_{k+n}, \hat{s}_k))\boldsymbol{K}(v_{k+n}, v_{k+n})}} \tag{21}$$

which are all quantities that can be calculated from Eq. 13 and Eq. 14.

Another common approach to estimate the change rate, is to do many samples within a period, and use the slope of a linear model as the estimate. Let $\hat{\boldsymbol{s}}_{k:k+n} = \left[\hat{s}_k, \hat{s}_{k+1}, ..., \hat{s}_{k+n}\right]$ be the vector of the equally spaced measurements. It can be shown that the slope $\alpha(\hat{\boldsymbol{s}}_{k:k+n})$ is given by

$$\alpha(\hat{\boldsymbol{s}}_{k:k+n}) = \boldsymbol{\Lambda}\hat{\boldsymbol{s}}_{k:k+n}, \quad \boldsymbol{\Lambda} = \frac{12}{n(n+1)(n+2)}\left[0 - \tfrac{n}{2}, 1 - \tfrac{n}{2}, ..., n - \tfrac{n}{2}\right]. \tag{22}$$

One can thus calculate the correlation as

$$\rho(\alpha(\hat{\boldsymbol{s}}_{k:k+n}), v_{k+n}) = \frac{\boldsymbol{K}(\alpha(\hat{\boldsymbol{s}}_{k:k+n}), v_{k+n})}{\sqrt{\boldsymbol{K}(\alpha(\hat{\boldsymbol{s}}_{k:k+n}), \alpha(\hat{\boldsymbol{s}}_{k:k+n}))\boldsymbol{K}(v_{k+n}, v_{k+n})}} \tag{23}$$

which again with a little mathematical manipulation can be shown to be

$$\rho(\alpha(\hat{\boldsymbol{s}}_{k:k+n}), v_{k+n}) = \frac{\boldsymbol{\Lambda}\boldsymbol{K}(\hat{\boldsymbol{s}}_{k:k+n}, v_{k+n})}{\sqrt{\boldsymbol{\Lambda}\boldsymbol{K}(\hat{\boldsymbol{s}}_{k:k+n}, \hat{\boldsymbol{s}}_{k:k+n})\boldsymbol{\Lambda}^T\boldsymbol{K}(v_{k+n}, v_{k+n})}} \tag{24}$$

Note that each measurement's contribution to the overall slope is linearly dependent on that measurment's distance in time from the middle time point within the time interval. Therefore, for odd number

of observations the middle observations has no contribution to the slope.

2.2.6 Implementation details

The posterior distribution of the latent variables $p(\boldsymbol{z}_k|y_1...y_K)$ for each individual can be calculated analytically using a Kalman/RTS smoother (Kalman, 1960; Murphy, 2023; Rauch et al., 1965).

Similarly, the exact model likelihood of the longitudinal observations,

$$p(y_0...y_K) = p(y_0) \prod_{k=1}^{K-1} p(y_k|y_0, ..., y_{k-1}) \tag{25}$$

can be evaluated by marginalizing out $\boldsymbol{z}$ analytically. The model therefore naturally handles both one and multiple observations by calculating the joint probability of all the observations.

In our model we parameterize $\sigma_q^2(t_k)$ and $b(t_k)$ as cubic splines with 9 control points, one for every 10 year in the interval 18 to 100. We also tested using 5 and 18 control-points for the splines, without this resulting in any major changes to the results. The volume data was discretized to a sampling interval Δ of 1.0 year. Here we also tested for intervals of 0.5 years and 2 years, which gave the same results. The priors of the variance terms are parameterized as a squared softplus (Dugas et al., 2000) transformed Gaussian distribution.

We use Markov Chain Monte Carlo (MCMC) with a No-U-Turn (NUTS) sampler (Hoffman, Gelman, et al., 2014) in order to get the posterior distribution over the model parameters. The model is implemented using the python package Pyro (Bingham et al., 2019). The model was first fitted with MAP estimate with a Limited-memory Broyden-Fletcher-Goldfarb-Shanno (L-BFGS) algorithm (Nocedal & Wright, 2006). The MCMC sampler was initialized to the MAP estimates, as recommended by Geyer, 2011, and 3000 samples was dawned after a warm-up of 500 samples. The trace plots can be examined in Appendix B.

To improve statistical power and convergence rate of the MCMC sampler, we used strong priors on the measurement errors of the structures derived from controlled experiments in Vidal-Piñeiro et al., 2025. That is, we centered the priors of σ_r around the estimated standard error for each structure, and set the prior standard deviation to 5.0 % of the absolute value of the estimated standard error. For the other variables, we used weak priors that can be examined in Appendix A.

The combined sample has a high density of individuals at the age between 50 and 70. To ensure that the analysis was invariant to the age distribution, we fitted the model to the data of only LCBC and Cam-CAN, which have a more even age distribution. This resulted in the same general results as using

the full dataset, but with larger uncertainty in the estimates. These results can be seen in Appendix D.

3 Results

3.1 Dynamical Aging Norm Curves for Brain Structures

Fig. 3 provides an overview of the normative aging dynamics of the brain structures across the adult lifespan. The mean and two standard deviations around the mean are plotted for both the latent volume and the change rate. The mean trajectories of the volumes show distinct shapes. The hippocampal and the supratentorial volume gradually decrease until around 55 years of age, followed by an acceleration of change rate and therefore faster shrinkage after age 60 years. The white matter and the brain stem volume follow similar mean trajectories, with an increase in volume up to the age of 50 years, followed by decline. Gray matter volume shows a steady, close to linear, shrinkage throughout life. The lateral ventricles follow a very different trajectory. Most people start with small lateral ventricles at the age of 18 and there is a small but measurable increase up to 50 years. After that, the rate of growth accelerates, leading to a rapid increase in size.

Although the mean trajectories differ across structures, the variation in change rate follows a similar pattern. For all structures, the variation in change rate is very small up to the age of approximately 45 to 50 years. This implies that the inter-individual differences in change for an age can be small even though the change rate might be high, as seen for instance in gray matter. After the age of 50 years, the variation in change rate increases, which after a few decades results in a moderate spread of the observed volumes. The lateral ventricles follow a different pattern. Already from young age there are observable inter-individual differences in change rate, and later in life there is large spread of both the change rate and the volume.

3.2 Explained Variance from Young Adult Levels vs. Systematic Change

We quantified how much variance in brain-structure volume at later ages can be explained by the volume measured at age 18. From the fitted model we calculated the squared correlation, corresponding to the proportion of explained variance, R^2, between individuals at age 18 with the same individuals later in life. To maximize sensitivity to true change, ICV and sex were regressed out. The calculations were performed both with and without measurement noise. That is; without noise the R^2 reflects the explained variance of the *latent* volume in life given the sex, ICV and *latent* volume at 18 years. With noise, the R^2 reflects

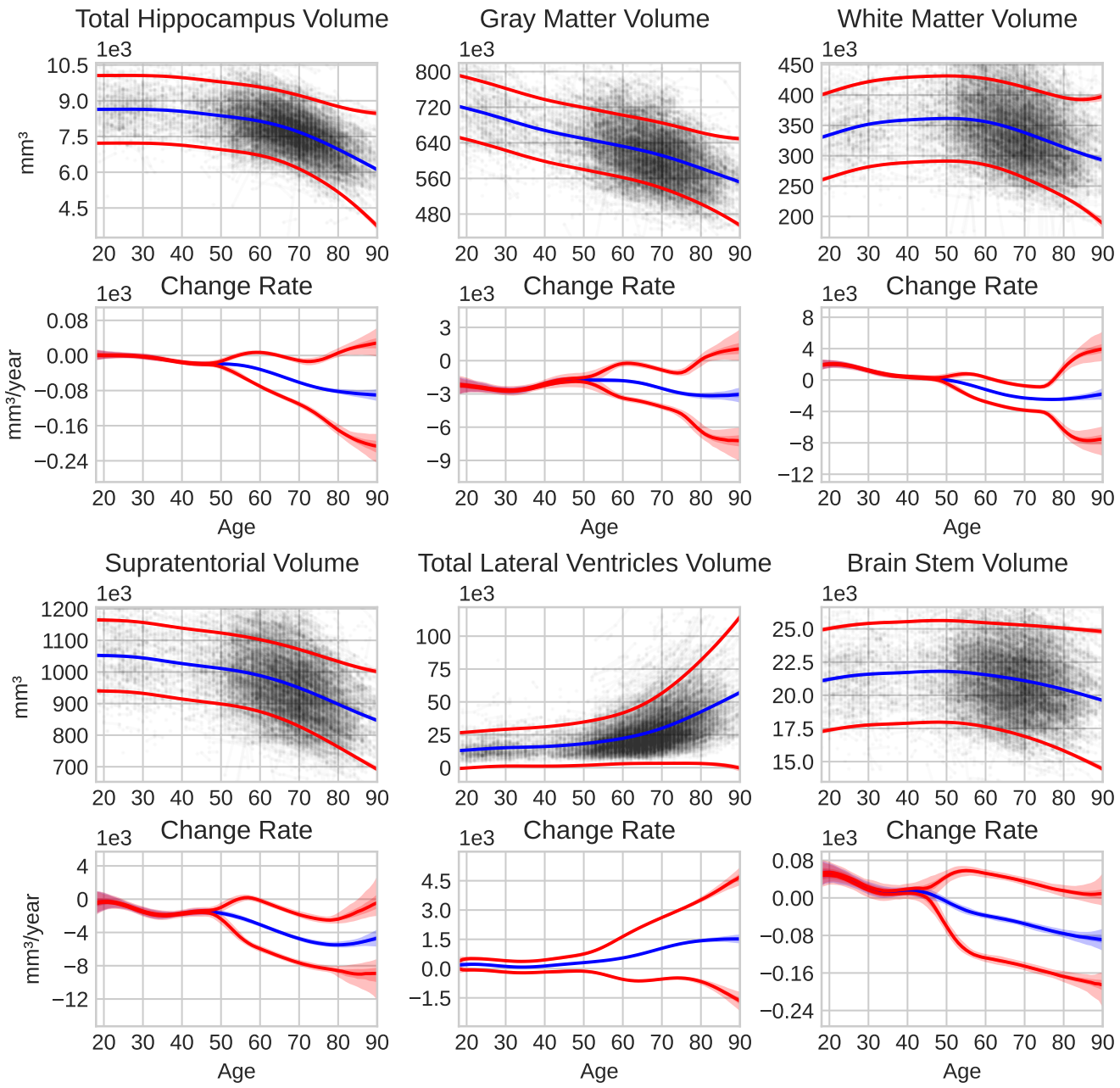

Figure 3: Norm curves for the dynamics of selected brain structures. For each structure the top plot shows the latent structure volume for the population from age 18 to 90, and the bottom plot the change rate of the latent volume. The observed data is plotted in the background. The blue curves indicates the population mean and the red curves show two standard deviations from the population mean, meaning ∼95% of the population is expected to have volumes and change rates within this region. The shaded region indicate the 50% and the 95% confidence interval (CI) for each curve. For some curves the CI are small, and therefore the CI regions appears as a single line.

the explained variance of the *measured* volume later in life given the sex, ICV and *measured* at age 18.

The proportion of explained variance is shown in Fig. 4. We observe that up to the age of 60 years, the initial volumes explained nearly all of the variance. For instance for hippocampal volume at age 50 years, the model predicts that the initial latent volume explains 99.9% of the variance, while a measured volume explained 92.4%. At age 60 years, 97.9% of the explained variance in the latent volume is from young adult levels. This number then drops rapidly with the large increase in systematic differences in volumetric change to age 90 years where only 35.8% of the variance is explained by young adult levels.

The other structures show similar trends. The exception is again the lateral ventricles which shows a steady decrease in correlation with the initial volume throughout the age-range, i.e. effects of differences in change are observed at earlier ages. At age 40 years, the explained variance from the ventricle volume at age 18 years is 83.0 % which drops steadily to age 90 years where the initial volume only accounts for 5.6% of the variance.

3.3 Stability of Individual Change Rates Over the Lifespan

The change rate of an individual is often assumed to be stable over time. Changes earlier in life are also often assumed to predict changes later in life. We tested whether an individual's rate of brain-volume change remains stable over time by calculating the AC of latent change rates. AC reflects the correlation between a person's change rate at one age and the same person's change rate at a later age. This indicates the extent to which a perfect measurement of latent change at one age can predict the rate of latent change later in life.

We calculated the AC between the ages of $[18, 35, 50, 60, 70]$ and all subsequent ages (Fig. 5). Under the age of 40 years, the CI of the AC is wide, indicating that we lack sufficient statistical power to estimate the AC for these ages. However, we observe that there is no correlation between the change rate at 35 years and that of later ages, indicating that a change measurement at 35 has little predictive value for later life. At age 50 years, the change rate has a weak correlation with the change rate at later ages. For instance, the AC of hippocampal change rate between age 50 and 70 is around 0.15. This means that even with a perfect measure of change rate, prediction of change 20 years later is poor. At higher ages and with shorter intervals, the correlations are substantially higher—around 0.80 from 60 to 70 years, and 0.40 from 60 to 80 years for the hippocampus. For the supratentorial and brain stem volumes, the change rates at age 60 years show near-perfect correlation with the change rate at 80 years. As we will discuss later, this may likely be a model artifact, due to the lack of feedback in the model. We therefore highlight that these correlations are likely inflated.

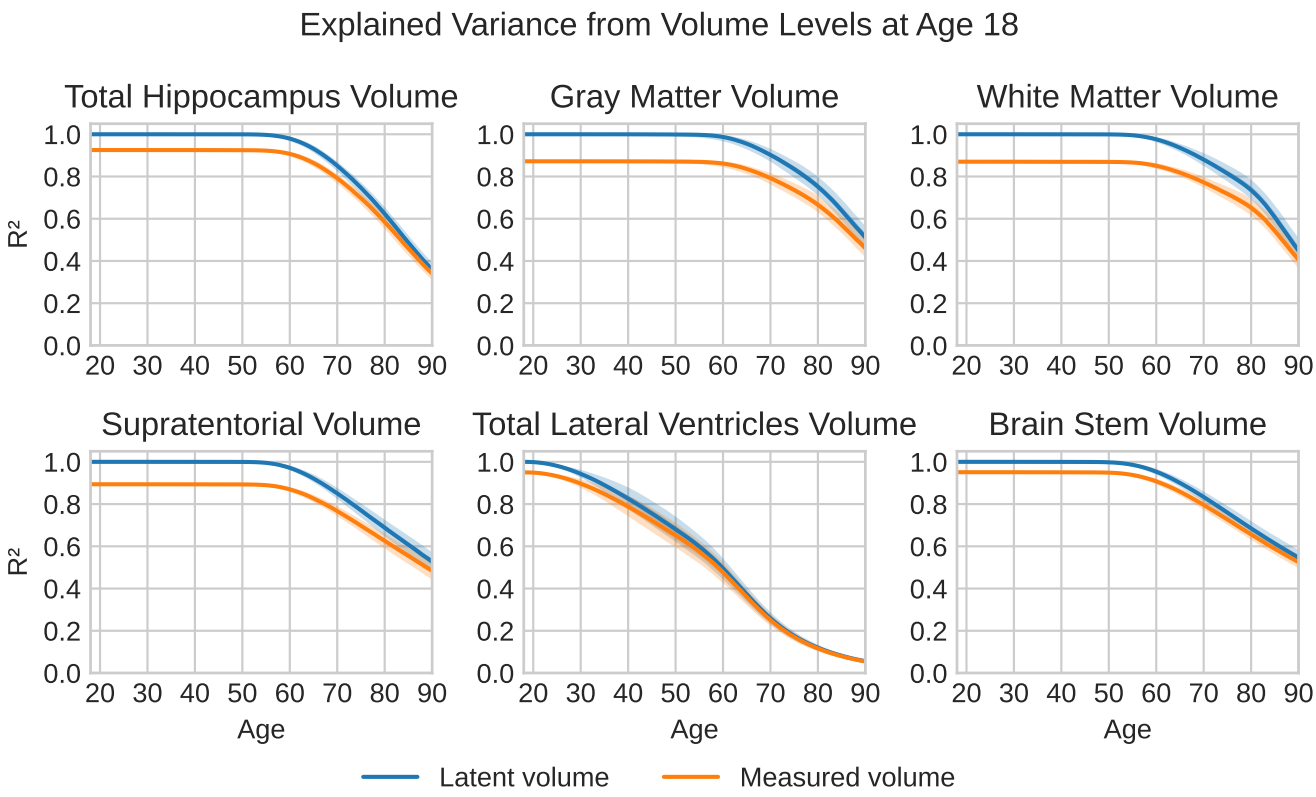

Figure 4: The ratio of explained variance R^2 in brain structure volumes across the lifespan, given the structure volume at age 18 years. A value of 1 indicates perfect correlation later in life with the volume at age 18 years. The blue line shows the explained variance of the latent volumes without measurement noise, while the orange line includes measurement noise. Both lines are calculated from the fitted model. Confidence intervals are shown as shaded regions around each line; however, in most graphs, the intervals are narrow and appear as lines rather than shaded areas. We refer to the Methods and Materials where the calculations are explained in detail. In this plot $\rho^2_{s_k s_{k+n}}$ and $\rho^2_{\hat{s}_k \hat{s}_{k+n}}$ with $t_k = 18$ years of Eq. 18 are visualized.

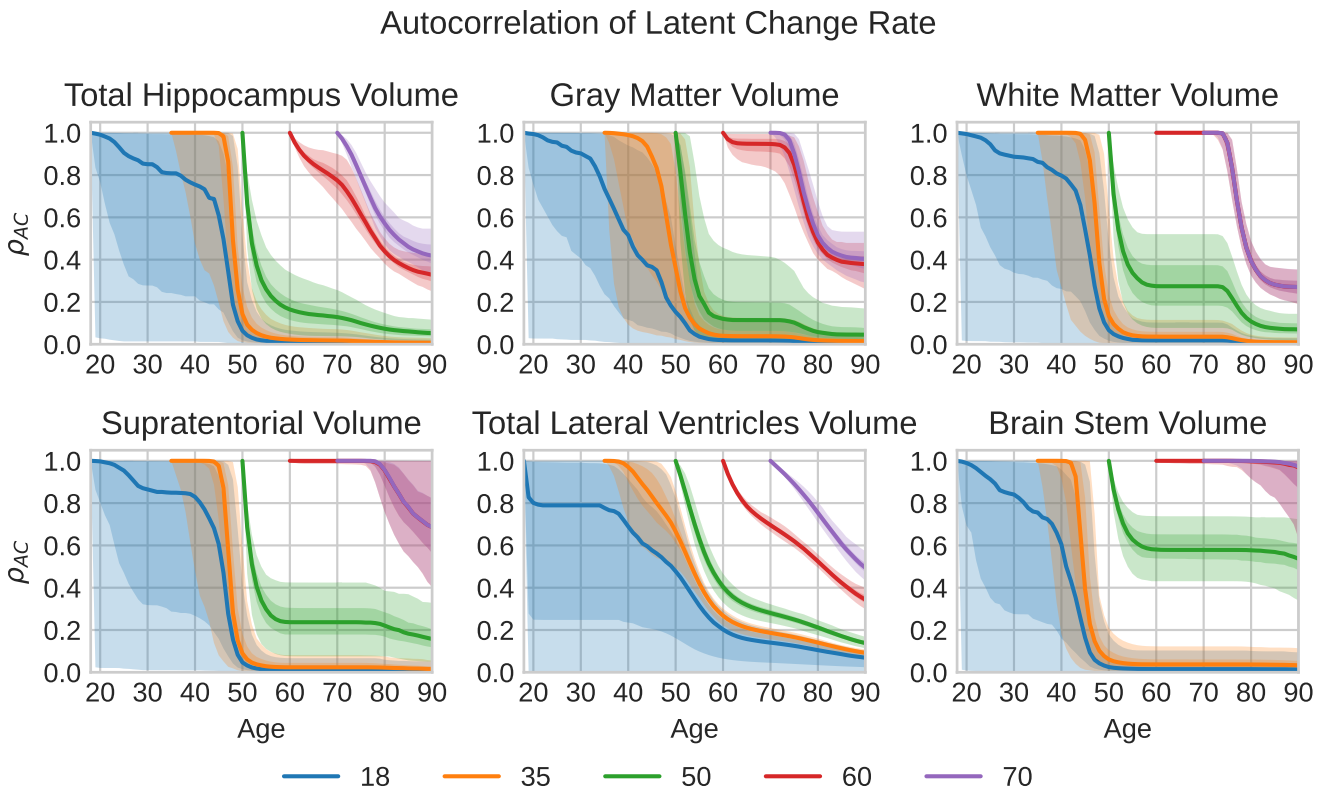

Figure 5: Auto-correlation ρ_{AC} of latent brain volume change rates across the lifespan. AC reflects the correlation between an individual's change rate at a given baseline age and their change rate at later ages. Each colored line represents a different baseline age (t_k), as indicated in the legend. By definition, all lines start at AC $= 1.0$ at their baseline age and then decline as the temporal gap increases. A steeper decline and lower values indicates less stability in individual change rates over time. The shaded regions show the 95% and 50% confidence intervals for each estimate. See Methods and Materials for details on the AC calculation, which corresponds to $\rho_{v_k v_{k+n}}$ in Eq. 18 where each line represents a different t_k.

3.4 Estimation of Change Rate

Next we examine how well one can estimate the volumetric change of a brain structure. We examine three methods for obtaining an estimate of change. i) Use a single measurement of the volume of a structure and compare that to the norm accounting for age, ICV and sex. Volumes deviating from the norm are likely to have experienced, and still experience individualized change. ii) Using the time-normalized difference in volume between two time points gives the delta estimate of the change rate. iii) Measurements from more than two sessions can be used by fitting a line using linear regression to the measurements and using the slope as an estimate of change rate.

The correlations of the volume with change rate are shown as black lines in Fig. 6. Up to the age of 50 years, there is no correlation between measured volume and change rate, except for the lateral ventricles where the correlation is approx. 0.4 already at age 40 years. At older age, the measured volume is moderately correlated with the change rate. For instance, at age 80 years, a measurement of the hippocampus volume has a 0.45 correlation with change rate.

The delta estimates of change rate show a similar trend with no correlation up to age 50. After this age, delta estimate for 1 year and 2 year between-scanning intervals show in general a lower correlation with the latent change rate than a volume measurement. For instance, a 2 year delta estimate of hippocampus at age 70 years has a correlation of about 0.25 with the latent change rate, while a volume measurement has a correlation of about 0.35. This means that if the follow-up interval between MRIs at age 70 is 2 years or less, a cross-sectional scan may give slightly better estimates of ongoing atrophy than using estimates from the longitudinal scans. With 8 years or more between scans, however, the delta estimate of change does in general outperform the single volume estimate of change. Interestingly, we see the largest benefit from longitudinal observations compared to a single observation at the age of the beginning of accumulation of inter-individual differences in change, between 50 and 60 years. Here, while still having a low correlation with true change rate, a two-year observation interval captures the change rate more accurately than a single volume measurement. The reason is likely that at this age, we are able to measure individual differences in change with a certain degree of accuracy, while the effects of accumulated change on the observed volumes are still too small compared to the stable individual differences to be detected in a cross-sectional analysis. When differences in change accumulate over time, however, effects on volume increase to a level where they can be measured with higher accuracy than actual longitudinal changes.

In Fig. 7 the correlation between estimates of change and true change when using multiple sessions. We observe that increasing the number of sessions only shows a moderate increase in correlation compared

to increasing the time between the first and the last session. For instance, for a 2-year measurement interval for hippocampal volume at age 80 years, the correlation with the change rate is 0.38 using 2 measurements and 0.47 using 12 measurements within the same scanning interval. This improvement is lower than for going from 2 to 4 year intervals with only two scans, where the correlation improves from 0.38 to 0.62.

From our calculations, increasing the number of sessions from 2 to 12 is almost never as good as doubling the time between two measurements. The take-home message is that increasing the signal, i.e. the absolute amount of change, is more efficient than adding more measurements. Note that these calculations assume equal spacing between each measurement, and the situation will be different if multiple measurements are performed close to the first and the last time point.

4 Discussion

The present analyses yielded three main results. First, we are not able to detect systematic inter-individual differences in volumetric brain change before age 50 years in a large cross-cohort sample of cognitively healthy adults. This indicates that in cognitively healthy adults, morphometric differences prior to age 50 years largely reflect stable individual differences, and cannot be ascribed to differences in change rate. From about 60 years, individuals started to follow detectable different trajectories, and differences in change gradually explained more variance with higher age. Second, because the variation appears to be dominated by stable individual differences, a model trained to predict cross-sectional age will be sensitive to age, but not differences in aging. The only measure partially reflecting individual differences in change before age 60 was the ventricles, which are known to be sensitive to age-related changes, but typically do not dominate in brain age calculations. Finally, the reliability to detect differences in change was very low before age 50 years, even with many samples and up to 16 years between first and last measurement. From the age of 50 years, reliability increases with longer follow-up times having the largest effects, while adding more intermediate time points comparatively affected reliability to a very modest degree. For example, two scans 4 years apart yielded similar or higher reliability to detect change than 12 scans evenly distributed over 2 years. The implications of the findings are discussed below.

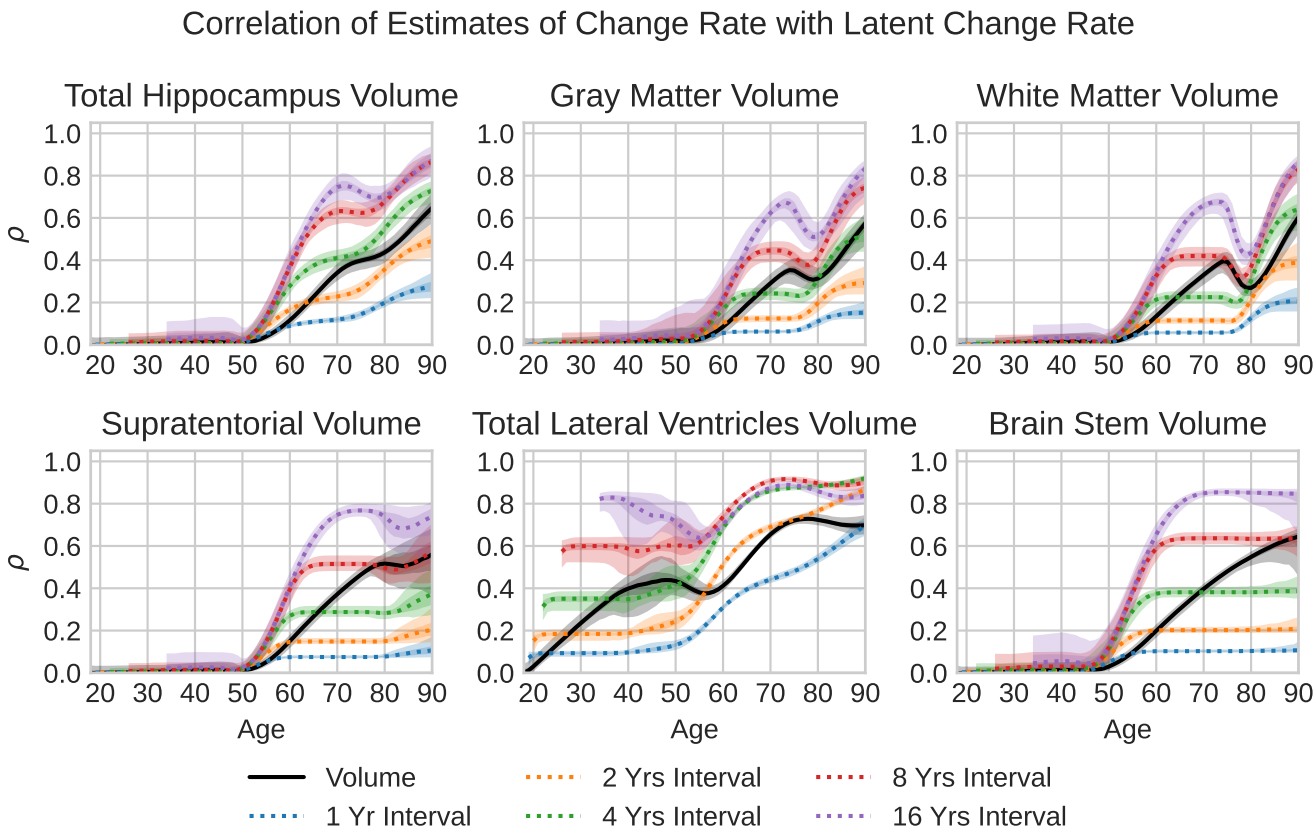

Figure 6: The correlation ρ between measured volume with the latent change rate, and the correlation of the delta estimate with latent change rate. The black line indicate the how much a measurement of the volume of a brain structure correlates with the latent change rate of that volume at that time point. The colored lines indicates how much the the slope between two longitudinal measurements of brain volume correlates with the latent change rate of that volume at the last session. Each color indicate the time between the sessions. The shaded regions show the 95% and 50% confidence interval of each line. In the Methods and Materials section the black lines corresponds to $\rho_{v_k s_k}$ of Eq. 18 with $n = 0$ and the colored lines corresponds to $\rho(\hat{v}_{k+n}, v_{k+n})$ of Eq. 21.

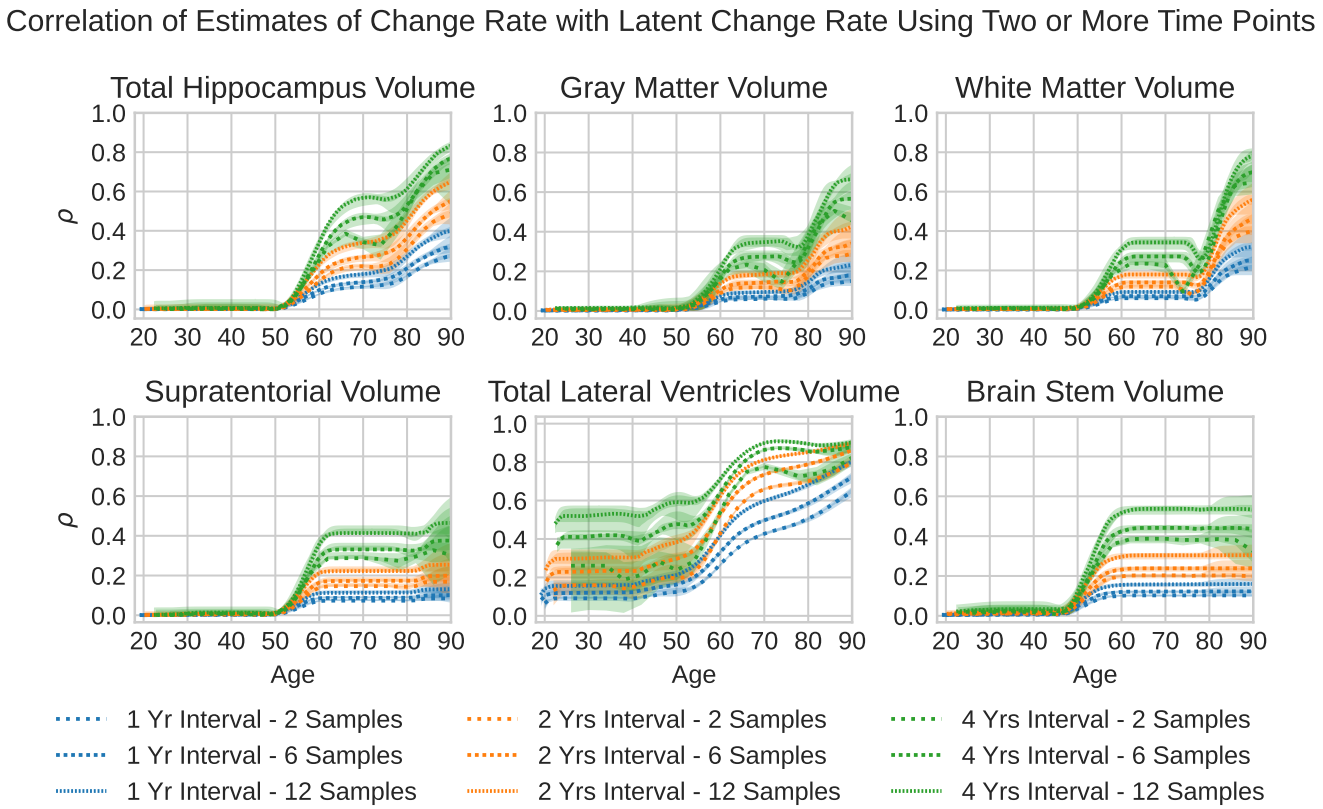

Figure 7: The correlation ρ between slope estimates of change rate from 2, 6 and 12 sessions with the latent change rate. The 2 samples lines are the same as the colored lines in Fig. 6 while the other lines indicate the correlation between the slope estimate with the latent change rate when including more intermediate sessions. In the Methods and Materials section these correlations are calculated from Eq. 24.

4.1 Cross-sectional differences mostly do not reflect differences in brain change

The aging norm trajectories of the different brain structures replicate previous aging studies (Fjell et al., 2013). All the structures showed age-related decline, but followed distinct patterns. The hippocampus remains relatively stable until around 60 years of age, after that accelerated decline is observed. In contrast, total gray matter volume exhibits almost linear reductions, with a slight acceleration from age 60 onward. White matter and brain stem are the only structures not showing monotonic decline, instead apparently increasing until middle age, which is a well-established pattern (Allen et al., 2005; Walhovd et al., 2005). The lateral ventricles display the most unique trajectory, with a small increase in volume until around 50 years, followed by a rapid increase throughout the rest of the lifespan.

Importantly, as was recently demonstrated in a study of the UK Biobank database, high cross-sectional age correlations do not necessarily translate to high sensitivity to brain change (Smith et al., 2025). This means that if individuals have smaller volume of an age-sensitive brain structure, this does not imply that they have undergone greater age-related changes than others. The present results clearly confirm that while brain regions may be age-sensitive at the group level, this does not reflect the existence of systematic differences in age-related rates of change (Vidal-Piñeiro et al., 2025). We observe substantial age-related changes in all tested neuroanatomical volumes, with some, particularly total gray matter volume and supratentorial volume, changing continuously from early adulthood. Nevertheless, the variance attributable to baseline differences surpasses the variance associated with individual differences in change by far, at least until advanced ages.

As shown in Figure 4, until around 60 years of age, nearly all differences in neuroanatomical volumes reflect stable, individual differences established in early adulthood. From approximately 50 years, systematic differences in change rates between participants become detectable. These differences accumulate over time, and by 60 years, their impact is sufficiently large to be observed as smaller volumes, but only a minor proportion of individual variation is still due to systematic differences in change. This proportion steadily increases at different rates across structures, reaching approximately 20% at 70 years and up to 50% or more at 90 years for most structures. It is crucial to note that these findings represent group-level effects and cannot be directly translated into considerations on level versus systematic change in the brains of individual participants.

The reason for the small proportion of variance attributed to systematic differences in change is that absolute volumetric differences between individuals are substantial, while inter-individual variation in change is relatively small. Consequently, only after several decades do volumetric differences significantly

reflect change. However, the ventricles deviated from this pattern, and we are able to detect small individual changes during the first 30 years of adulthood before expanding rapidly from around 50 years. The relatively minor individual differences in baseline volume, combined with systematic variation in individual change rates, also at young age, result in a situation where a much larger proportion of volume variation can be attributed to change. Even at 50 years, more than a quarter of the volumetric differences between individuals can be explained by differences in change, a proportion that reaches nearly 95% at 90 years. This means that ventricular size is the only tested brain measure that reflects actual age-related variability when measured at a single time point throughout life. This observation was previously reported by Vidal-Pineiro et al., 2021.

Thus, measures where the rate of change later in life is large relative to inter-individual variation in young adulthood will, by this reasoning, reflect proportionally more change than baseline effects when measured in aging. Another good example is white matter hypointensities, not measured here, where variation appears to reflect change to a greater extent than most other brain measures (Smith et al., 2025). However, this also means that for other brain measures, cross-sectional comparisons do not inform us about individual differences in aging in cognitively healthy normal populations. Hence, typical brain age models, trained to predict chronological age, will typically be dominated by cross-sectional variance and consequently very insensitive to individual differences in rate of aging (Smith et al., 2025).

4.2 Impact of levels vs. change will depend on the sample

An important consideration is that the proportion of variance at a given age that can be attributed to levels at young adulthood vs. systematic differences in change will depend on the type of samples included. For example, we find that about 40% of the individual differences in hippocampal volume at age 80 years can be ascribed to differences in change, but this number is likely much higher in neurodegenerative disorders like AD. While we estimate annual change in hippocampal volume to be around 1% after 60 years, this number often exceeds 3.5% in AD patients (Fjell et al., 2009). Consequently, such a large difference in rate of atrophy will eventually manifest in lower hippocampal volume in AD patients, regardless of the variation at young adulthood. Although large baseline hippocampal volume may be a protective factor, volumetric differences between patients with progressed AD and age-matched controls will likely to a larger extent reflect accumulated higher atrophy rates in the patients. How much of the variance that can be ascribed to each remains to be tested. Similarly, comparing other patient groups having conditions associated with magnified volumetric change rates may also be expected to yield a higher proportion of volumetric differences ascribed to change.

Still, AD and some other age-related dementias are extreme cases, as they are characterized by massive neurodegeneration. For many other conditions where neuroanatomical differences are found — such as neuropsychiatric disorders like schizophrenia (Constantinides et al., 2023; Van Erp et al., 2018; Zhu et al., 2023) or major depression (L. K. Han et al., 2021), differences in change rates are usually much smaller (Abé et al., 2022; Vita et al., 2012) than in AD. In such cases, the present results suggest that volumetric differences largely reflect stable levels, likely originating early in life and possibly partly due to developmental differences.

For example, a large multi-sample study of bipolar disorder did not find substantial differences in change rates of neuroanatomical volume between patients and controls (Abé et al., 2022). Therefore, a cross-sectional comparison would be expected to reveal primarily level differences between groups, regardless of the age at testing. However, this study included several middle-aged and older participants and higher ventricular expansion was observed in the patient group. This finding is particularly relevant, as ventricular expansion was the one variable in the present study that reflected the most systematic differences in change.

Other cross-sectional studies of schizophrenia have found that patients have higher predicted brain age than controls (Constantinides et al., 2023). As argued above, brain age prediction models depend on age relationships and, therefore, primarily reflect the features of brain structures that are most reliably linked to age. For example, total gray matter volume would typically be assigned high weight in brain age models, and has been reported to be the measure most predictive of brain age differences between patients with schizophrenia and controls (Ballester et al., 2023). However, as low inter-individual differences in change give more precise brain age predictions, such measures are likely insensitive to aging (Smith et al., 2025). An implication is that cross-sectional studies of aging differences between neuropsychiatric groups run a high risk of confounding stable levels with true aging effects.

Education, sometimes regarded as one of the strongest protective factors for dementia (Livingston et al., 2024), has recently been shown to correlate with larger brain volumes but not differences in brain change (Nyberg et al., 2021). Longitudinal and cross-sectional brain structural measures are also found to relate differently to cognitive function (Walhovd et al., 2022). These results fit well with the present observation that differences in regional brain volumes mostly reflect stable individual differences also in relatively high age.

Conversely, when comparing groups with different clearly defined developmental risk factors, such as prenatal drug or alcohol exposure, very low birth weight or premature birth, brain volumetric differences will probably for even longer reflect effects present early in life. Consistent with this, a review showed that reported effect sizes on neuronataomical volumes from fetal life risk factors were several times larger than

later-life risk factors such as hypertension, overweight and heavy alcohol consumption (Walhovd et al., 2023). We expect the same to be the case with neurodevelopmental psychiatric diagnoses associated with brain morphometric differences, such as attention deficit hyperactivity disorder (Hoogman et al., 2017). Since these differences also originate from early in life, adult comparisons will be expected to primarily reflect stable levels even in old age (Walhovd et al., 2012).

4.3 Implications for studies of brain aging

The results confirm a growing body of evidence suggesting that deviation from "age-expected" lifespan brain trajectories cannot be used to make inferences about brain aging, at least not before the age of 60. Cross-sectional studies can provide important information about the brain basis for cognitive function in aging, but brain aging per se is better studied using longitudinal designs. Interestingly, the results suggest that we have very little signal to detect systematic differences in brain change before the age of 50 years, although this will ultimately depend on the reliability of the measurements (signal-noise ratio) (Brandmaier, Wenger, et al., 2018; Vidal-Piñeiro et al., 2025) and the sample in question.

As has been shown previously using simulations (Brandmaier et al., 2024; Ghisletta et al., 2020) and computations based on empirical data (Hertzog et al., 2008; Vidal-Piñeiro et al., 2025), the results show that time between measurements is much more important for reliability than the number of observations. Except for the lateral ventricles, reliability was low even with 12 scanning session evenly spaced across 12 months. In contrast, a 4 year follow-up interval increased reliability greatly. This demonstrates that more signal is the most important factor for reliable measures of longitudinal brain change. Since change rates increase with age, the reliability also increased greatly with aging, reaching a correlation of about 0.70 for hippocampal change over four years even with only two scans. Hence, an implication for aging studies is to maximize follow-up time even at the expense of more time points.

An exception to this conclusion is of course when special events are of interest, such as in intervention and experimental studies, which differ from observational studies of naturally occurring aging processes. For example, intervention studies have detected systematic effects of cognitive training over a few weeks in younger and older participants (Bråthen et al., 2022; Engvig et al., 2010; Wenger et al., 2012, 2017). In these cases, post-intervention differences reflect change due to the experimental intervention. Another reason to prefer many imaging sessions is that participants are likely to drop out of the study, and acquiring intermediate sessions might be necessary to ensure some data before participants potentially drop out.

Another implication is that if only cross-sectional data are available, aging studies should focus on

brain measures reflecting differences in change to a larger degree, e.g. the lateral ventricles and WM hypointensities (Smith et al., 2025; Vidal-Pineiro et al., 2021). Similarly, residualizing total brain volumes for ICV has been shown to correlate with ongoing atrophy (Fürtjes et al., 2024), because these measures are very highly correlated in adolescence and young adulthood, and residual scores therefore partially reflect accumulated change since lifetime peak brain size. In any case, the results underscore the need to consider early-life developmental processes to understand and account for individual differences in brain structure at all later stages in life (Walhovd et al., 2016).

4.4 Considerations and limitations

Our results rely on the accuracy of the assumptions we use to construct our model. First, we assume that the measurement noise is Gaussian distributed and independent of all variables. This may not be true as older individuals are harder to scan due to factors such as movement (Vidal-Piñeiro et al., 2025). Second, we also assume the noise driving the stochastic part of the acceleration to be Gaussian distributed. It is likely that the true distribution of change rate and acceleration is skewed as is shown in Vidal-Piñeiro et al., 2025. Third, similar concerns can be raised for the initial distributions of structure volume and change rate, which we assumed are Gaussian distributed. For the lateral ventricles, it is especially evident that this does not hold, which can be seen in Fig. 3, where the 95% CI of the population also includes negative ventricle volumes.

However, there are also good reasons for assuming a Gaussian distribution. First, this makes the model analytical, such that the probability of multiple observations of a single individual as well as all the results presented in Fig 3 to 7 can be calculated directly from the model parameters. Second, Gaussian distributions can also be considered the base assumption. Keep in in mind that most other models, such as Latent Growth Curve Models (Preacher, 2008) and the model used by Smith et al., 2025 are based on Gaussian distributions.

We are also assuming that the dataset population is representative, also for each age group. We have attempted to compensate for cohort effects by regressing out ICV, however, some cohort effects between datasets and age groups may still exist.

The small variance of the population change rate up to the age of 50 years may seem unlikely, as this suggests that all brain structures are changing at the same rate between individuals. Since we assume that acceleration is independent of change rate and volume, this implies that the population variance must increase over time(see the Materials and Method sections for details). A visual inspection of Fig. 3 as well as Appendix E Fig 12 shows that the variance at age 50 years is similar to that of age 18,

and therefore, according to our assumption, there must be little individual differences in change rate. In reality there might be some interaction between acceleration and change rate, for instance is it observed that an increase in regional brain volume is followed by a decrease later (Bråthen et al., 2022; Engvig et al., 2010; Wenger et al., 2012, 2017), which would correspond to a negative feedback effect from change rate or volume to acceleration. This would allow individuals to have larger differences in change rates, with smaller increases in the volume population variance than what is possible in our model. In Fig. 5 we see that there is perfect correlation between the change rate of the supratentorial volume at age 60 years and all the way to age 75. This is an also an unlikely scenario, that we believe also rises from the lack of feedback. The model observes little acceleration of the spread of the data, and the most probable fit is therefore that the change rate at 60 is maintained to the age of 75. With feedback the volume change rate of individual would fluctuate towards the population mean, while the correlation the change rate between two ages would go down.

We must therefore emphasis that these results only hold as long as the model assumptions hold. The correlations are likely to be slightly inflated dude to the lack of feedback. However, due to the small amount of widening of the variance with age we believe that the results still largely gives an accurate description of the proportion of variance in brain volumes contributed from adulthood change.

4.5 Conclusion and further research

The present results show that at up to age 50, there are small systematic differences in change for brain structures between individuals. After age 50, larger systematic differences in changes begin to accumulate, resulting in a gradual increase in brain neuroanatomical differences, and in observed volumetric differences at age 60. Therefore, before the age of 60 years, differences in brain volumes primarily reflect stable levels from young adulthood. The proportion of variance attributable to systematic differences in change increases at higher ages, typically reaching 30-40% at age 80 years and 50-65% at age 90 years. The exception is ventricular volume, with more than 70% of the individual differences in volume at age 70 years reflecting differences in change, a proportion increasing to 90% at age 80. Further research should extend these findings to include different populations, including neuropsychiatric conditions, groups with different risk factors, and diseases known to affect brain structure. It will be important to assess how the relative contributions from levels of young adult vs. differences in change varies as a function of various diseases and conditions.

Ethics

Each contributing dataset was approved by its local Research Ethics Committee, and data were shared with us under the terms specified by the respective data-use agreements. Analyses were performed on secure institutional servers with restricted access, and no attempt was made to re-identify participants.

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Data and Code Availability

The raw data were gathered from many different datasets. Different agreements are required for each dataset. Most datasets are openly available with prespecified data usage agreements. For some datasets, such as UKB, fees may apply. Requests for LCBC, UB, and COGNORM should be submitted to the corresponding principal investigator. The code to fit the model and generate the figures is available at https://github.com/EdvardGrodem/brain-trajectories.

Author Contributions

Conceptualization: AF, DP and EG. Data curation: DP. Formal analysis: EG, DP and ØS. Funding acquisition: AF and AB. Investigation: DB-F, AB, GC, SD, RH, SK, UL, LN, AP-L, CS-P, JS, LW and KW. Methodology: EG, AD, DP, SS, BM and PG. Supervision: BM, AF and AB. Project administration: AF and AB. Resources: AF and AB. Visualization: EG. Writing – original draft: EG, AF and DP. Writing – review and editing: All authors

Declaration of Competing Interests

The authors declare no competing interests.

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Table 2: Priors for the model parameters.

Parameter	Prior Distribution	Comments
$b(t)$	$\mathcal{N}(0, 10)$	
$\sigma_q(t)$	$\text{Softplus}\Big(\mathcal{N}(a, b)\Big)$	such that $E[\sigma_q] \approx 10$, $Std[\sigma_q] \approx 10$
β_{s0}	$\mathcal{N}(0, 5)$	
β_{v0}	$\mathcal{N}(0, 5)$	
σ_{s0}	$\text{Softplus}\Big(\mathcal{N}(a, b)\Big)$	such that $E[\sigma_{s0}] \approx 2$, $Std[\sigma_{s0}] \approx 2$
σ_{v0}	$\text{Softplus}\Big(\mathcal{N}(a, b)\Big)$	such that $E[\sigma_{v0}] \approx 2$, $Std[\sigma_{v0}] \approx 2$
$\beta_{s0,\text{sex}}$	$\mathcal{N}(0, 0.2)$	
$\beta_{s0,\text{ICV}}$	$\mathcal{N}(0, 1.0)$	
$\beta_{v0,\text{sex}}$	$\mathcal{N}(0, 0.01)$	
$\beta_{v0,\text{ICV}}$	$\mathcal{N}(0, 0.01)$	
σ_r	$\text{Softplus}\Big(\mathcal{N}(a, b)\Big)$	such that $E[\sigma_r] \approx \sigma_{r,\text{emp}}$, $Std[\sigma_r] \approx 0.05\,\sigma_{r,\text{emp}}$
$\beta(\text{site})$	$\mathcal{N}(0, 0.3)$	with $\sum_{site \in \text{sites}} \beta(site) = 0$

A Priors

Before fitting the model each structure volume is z-scored such that the whole dataset population has a mean of 0 and a std of 1. The priors are set in the z-scored units such that the same priors relative to the scale of each structure is used. The time is normalized to [0, 1] such that a for instance the prior of initial change rate $\beta_{v0} \sim \mathcal{N}(0, 5)$ corresponds to a prior covering the change rates from -10 std to $+10$ std over the life span, when considering the 95% CI. Notice that the priors on the $b(t)$ corresponds to the common L2 smoothing priors for splines.

B Trace Plots

The trace plots of our MCMC runs, to show proper convergence and coverage of the posterior distribution Geyer, 2011.

Figure 8: Trace plot of the MCMC runs. The parameters of the initial conditions are grouped together such that the first plot shows the latent structure volume parameter and the second the change rate.

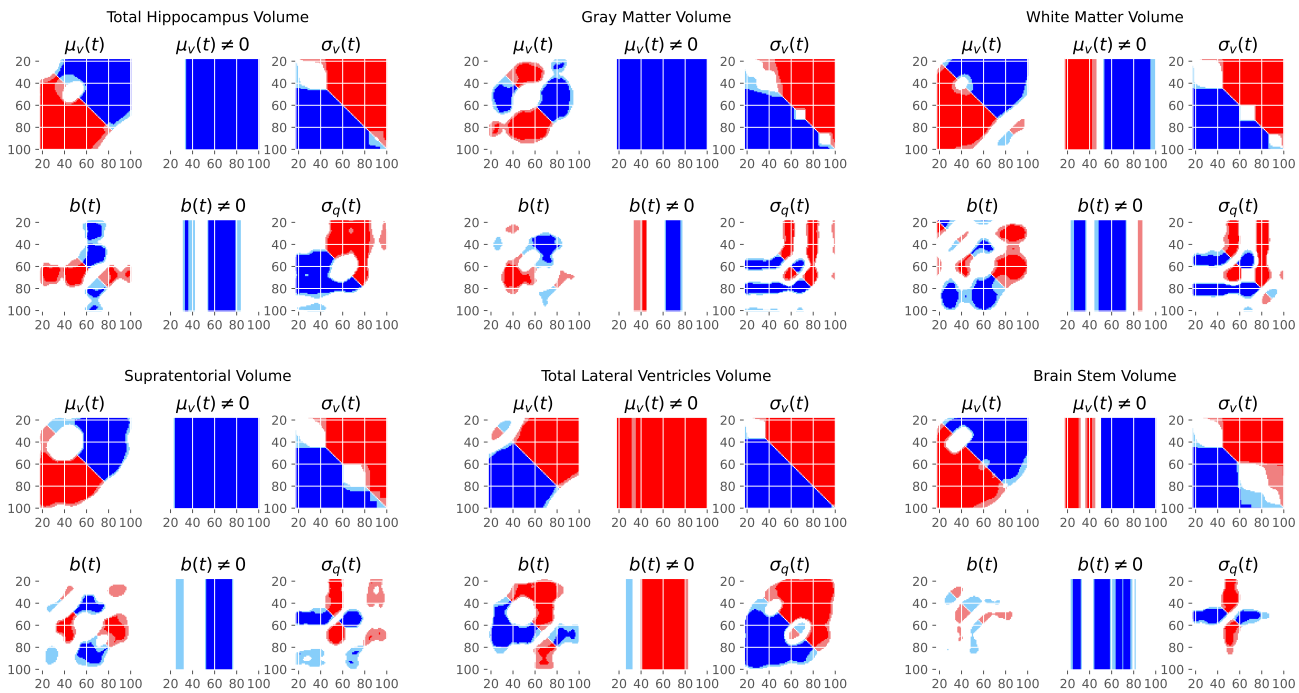

Figure 9: Significance plots for the time dependent parameters. The x-axes indicate the age to compare from and the y-axes the age to compare to. Blue indicate significantly smaller, and red significantly larger. Light colors show $0.025 > p > 0.001$ and saturated colors $p < 0.001$ Example on how to read: take $b(t)$ for white matter. We choose to compare the age of 60 to all other ages. We then look at the vertical line up from 60, and we see that at 60 the mean acceleration $b(t)$ is significantly smaller than the acceleration at 80 to 90 and the acceleration at 40. There is no significant differences between the acceleration at 60 and the acceleration at for instance 30.

C Significance Tests

In order to make statements on properties of the shape of the population trajectories we performed statistical test for significance. For all ages we test for significant differences in values for the change rate and acceleration of the model. For each sample of the MCMC trace we compared if more than 97.5% or 99.9% of the samples where either over or under that of another age. Similar tests was performed for $b(t)$ being different from zero. For the structure volume curves, the uncertainty was so low that we have not included them in this plot, but a visual inspection of Fig. 3 can verify this.

D Verification of Invariance to Dataset Distribution

In Fig. 3 as well as in Fig. 1 one can notice that the age group from 50 to 70 has a higher representation than the younger age group. We also see that the spread of the variance in change rate happens at the beginning of this high density of data. To make sure that this is not an artifact of the age distribution of the sample we performed a second fit to a subsample for the data. The subsample consisted of the LCBC dataset and Cam-CAN dataset, which both have even age distribution. We observe that the confidence intervals for the normative curves are wider than for the full dataset, as expected, however we see no significant differences to the conclusions drawn from the full dataset. We therefore conclude that the the spread of change rate variance at age 50 is not due to an artifact of age distribution.

E Standard Deviation of the Brain structure Volumes

We plotted the standard deviation (SD) for age bins of 1 year throughout the adult lifespan. We observe that for all structures, except the ventricles, the SD is stable throughout the lifespan, with possibly a small tendency to shrink after the age of 60 years in the case of the Total Gray Matter Volume and the Supratentorial Volume. If individuals have large variation in trajectories one would expect the SD to increase with time, not remain stable as seen here. As discussed in the discussion, when the model is fitted to the data, this is likely some of the evidence that is taken into account when estimating the model parameters, and hence low variation in change is a likely senario given the model.

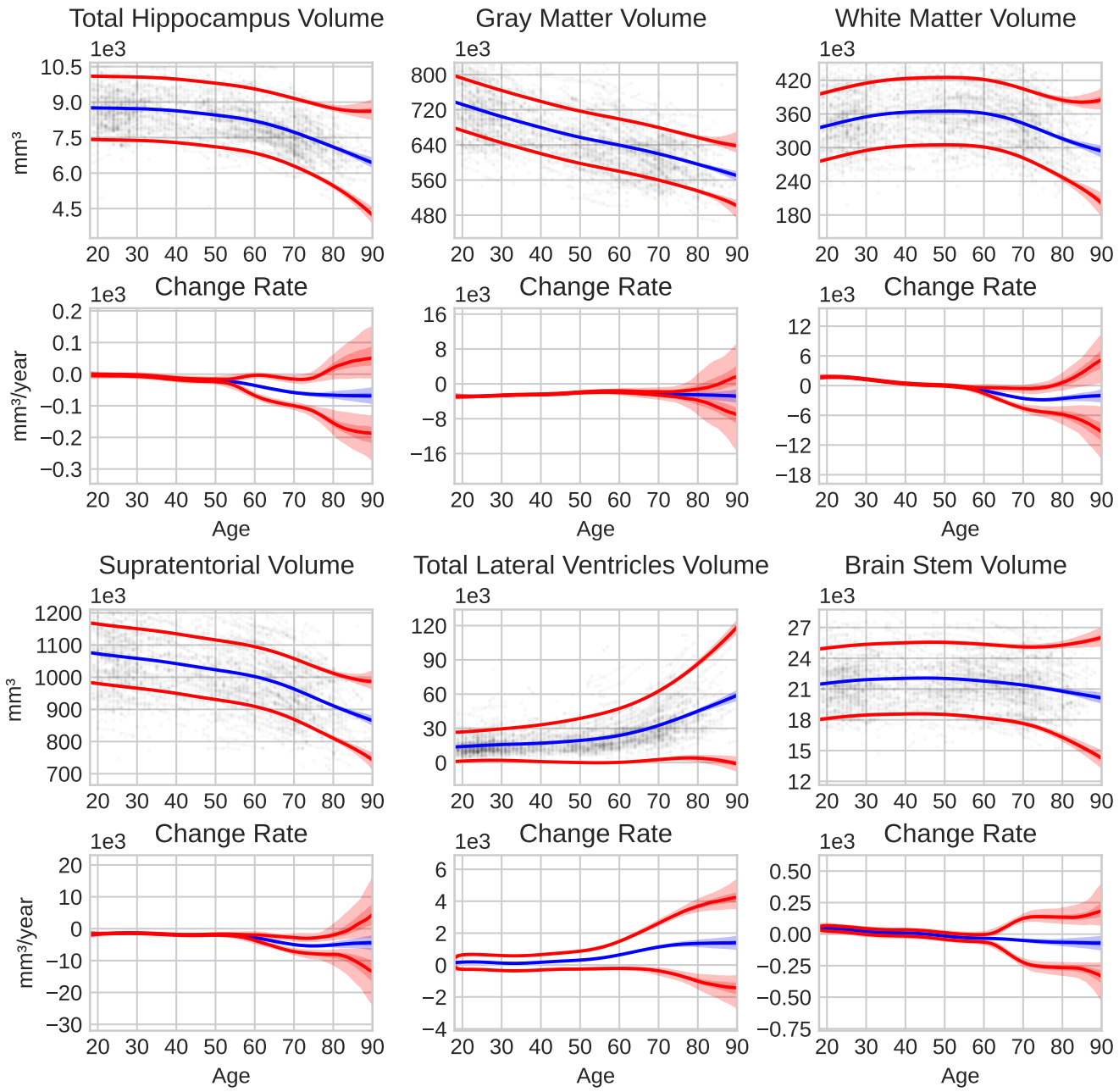

Figure 10: Reproduction of the Fig. 3 however here only data from the LCBC dataset and Cam-CAN is used to fit the model such that the the age distribution is more uniform. The CI around the lines are much wider, especially for older ages and the axis are adjusted to include the full CI.

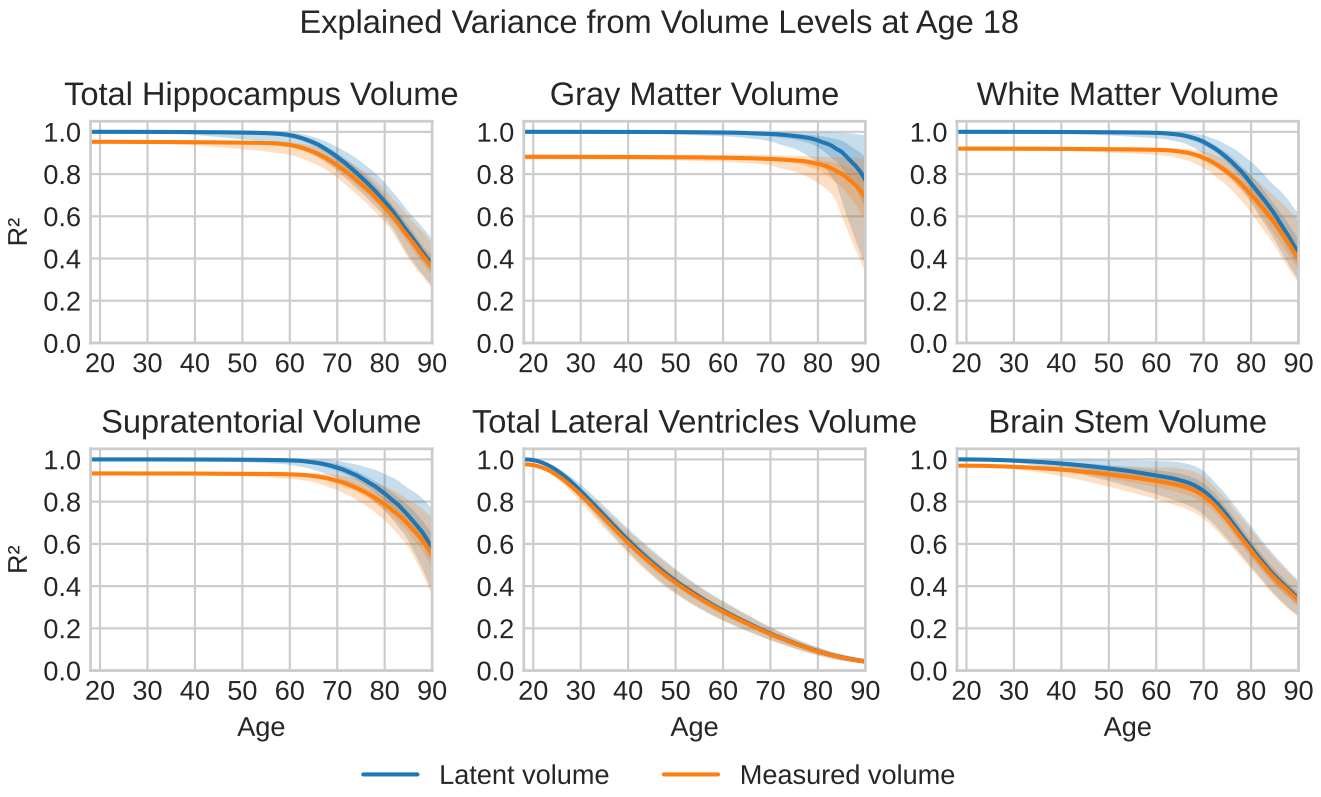

Figure 11: Reproduction of the Fig. 4 however here only data from the LCBC dataset and Cam-CAN is used to fit the model.

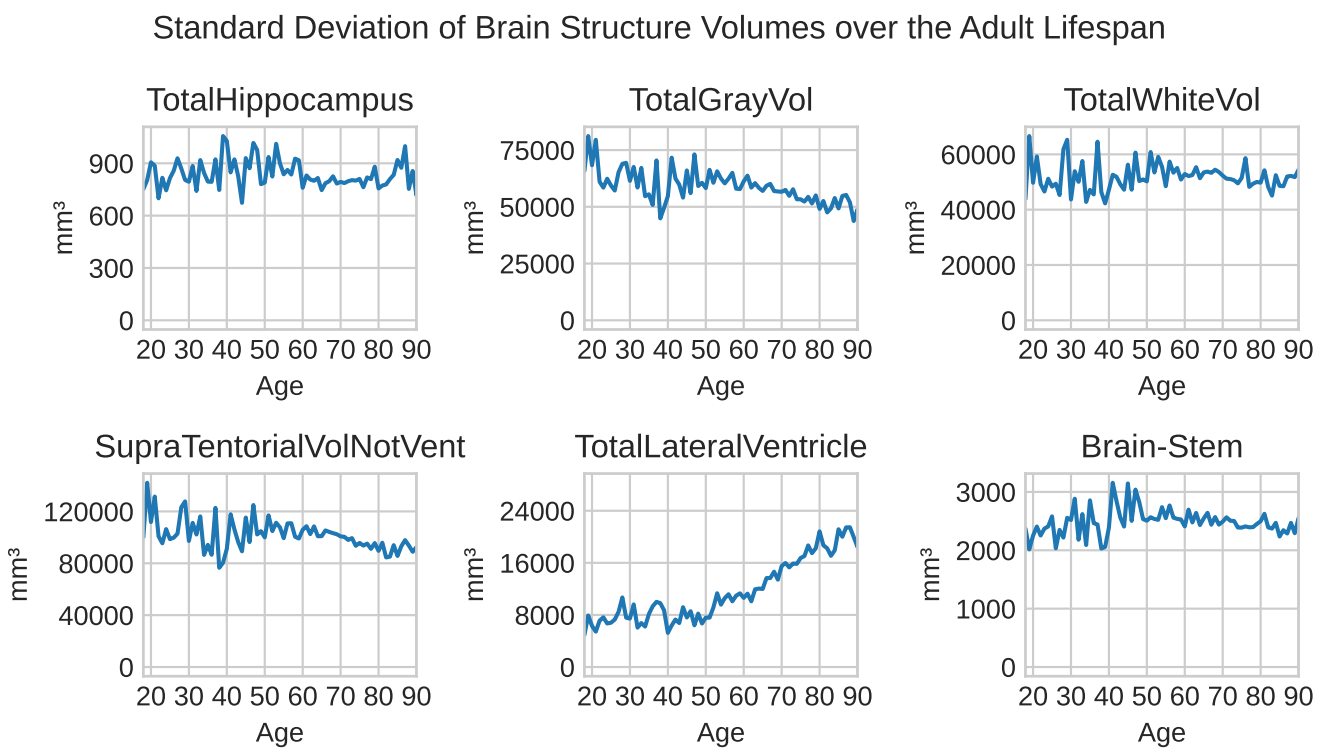

Figure 12: Standard deviation of the volume of the brain structures throughout the adult lifespan.