

Histological aging signatures for monitoring tissue-specific aging and disease

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Aging is the primary risk factor for chronic disease and is characterized by profound structural and architectural remodeling of human tissues. Here, we present a comprehensive assessment of these changes using 25,712 whole-slide histopathological images from 40 tissue types across 983 individuals in the Genotype-Tissue Expression cohort. By leveraging deep learning, we quantified nuanced morphological alterations to develop ‘tissue clocks’, predictors of biological age that reflect tissue structural integrity and physiological fitness. These clocks correlate with established aging markers, such as telomere attrition, subclinical pathologies and comorbidities. Through a systematic evaluation of biological aging rates across organs, we identified associations of tissue-specific age acceleration with demographic, lifestyle and medical factors, highlighting potentially modifiable risk factors that affect tissue aging. Furthermore, by integrating paired histology and transcriptomic data, we developed a strategy to predict tissue-specific age gaps directly from blood samples. We validated this approach by identifying disease-relevant organ aging across independent cohorts for eight prevalent diseases, including Alzheimer’s disease, stroke and Crohn’s disease. This work positions tissue architecture as a critical integrator of molecular and cellular changes over the course of aging, demonstrates that histopathological imaging provides a robust framework for monitoring tissue-specific aging and offers a scalable foundation for understanding organ-level physiological decline in health and disease.

Aging is a fundamental biological process with far-reaching implications for human health and disease¹. Despite its inevitability, the mechanisms underlying aging and the resulting age-related changes display striking diversity across tissues^{2,3}. This heterogeneity presents a considerable challenge in elucidating the pathways through which aging influences the decline in tissue function and disease onset. Contributions from evolutionary biology^{4–6}, cellular biology and molecular genetics^{7–9} have enriched our understanding of the genetic and environmental factors that influence the human body throughout the lifespan. However, translating these insights into a coherent understanding of the aging process, which is associated with changes in physiological function at the organism level, remains a considerable challenge^{10–12}.

Research into human aging has historically faced several limitations. Animal models, despite their value, fall short of capturing the

complexity of human aging due to physiological and lifespan differences, as well as divergent environmental exposures^{13,14}. Longitudinal studies in humans tend to focus on readily accessible organs^{15,16}, which may overlook the full spectrum of aging in the body. Moreover, the current predominant focus on the cellular and molecular aspects of aging¹⁷, although essential, may neglect the intricate interplay between cellular, microanatomical and organ- and organism-level changes throughout the human lifespan. Furthermore, researching aging in humans has the added challenge of distinguishing pathological alterations¹⁸ from the normative aging process, making it difficult to pinpoint the initiation processes of age-related diseases.

To address these challenges, it is imperative to move beyond a gene or cell focus, to a holistic view of the aging organism¹⁹. Deep learning²⁰ has greatly advanced our ability to quantify and understand tissue

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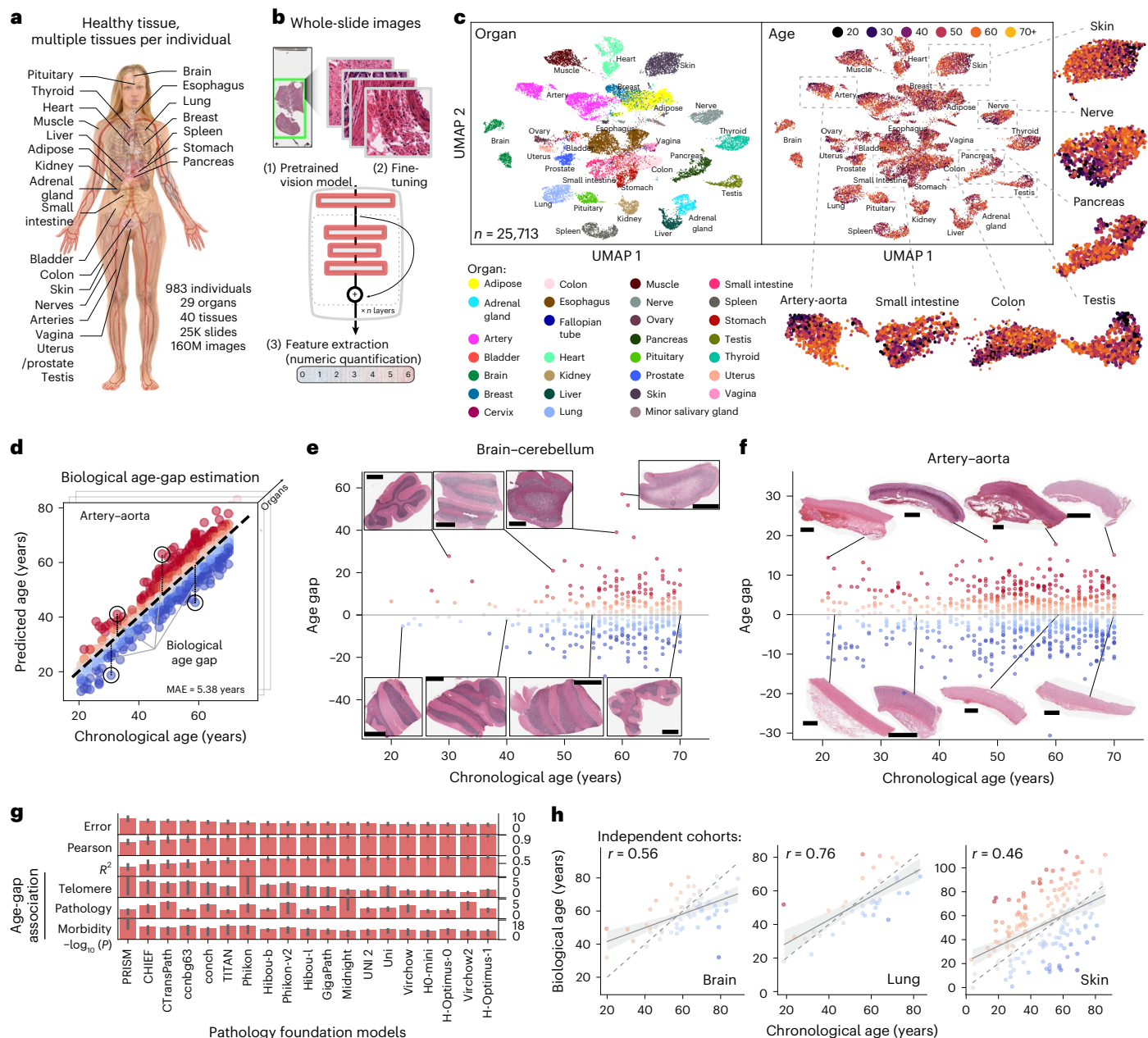


Fig. 1 | Assessment of biological age and pathological alterations in human tissues via histopathology. **a**, Overview of the cohort tissue collection approach in the GTEx project, which spans 29 organs and 40 tissues from 983 individuals; K, thousand; M, million. **b**, Image processing workflow for WSIs, illustrating the transformation of raw image data into a structured feature set for quantitative analysis. **c**, Uniform manifold approximation and projection (UMAP) visualization of the processed image data for each WSI, with samples color coded by organ type (left) and age (right). **d**, Illustration of the performance of a ‘tissue clock’ for the aorta, which produces an estimate of biological age from WSI

features. **e, f**, Scatter plot of chronological age and age gap for the cerebellum (**e**) and aorta (**f**), illustrating morphological changes associated with chronological and biological age; extreme age gaps are visibly associated with pathological alterations. **g**, Comparison of performance and enrichment metrics across foundation models for pathology; lower error and higher remaining metrics indicate increased performance. **h**, Validation of tissue clocks in independent cohorts of brain ($n = 70$), lung ($n = 40$) and skin ($n = 185$) tissues. The shaded area represents the 95% confidence interval of the regression line.

morphological and architectural patterns^{21,22} and detect and classify diseases^{23,24}. Here, we use a systematic approach to probe the interplay between aging and tissue architecture in humans and its connection to pathology, illuminating the complex relationship between tissue-specific aging patterns and their implications across the human body.

Results

Aging strongly affects healthy tissue architecture in humans

To study the impact of aging on tissue structure in humans, we used large-scale whole-slide histopathological images (WSIs) from 983

individuals in the Genotype-Tissue Expression (GTEx) project^{25–27} (Fig. 1a). The individuals profiled in this cohort died primarily from accidents, suicide or natural death, with ages ranging from 20 to 70 years (mean of 52.77 years; Supplementary Fig. 1a and Supplementary Table 1). Tissue was collected under a rapid autopsy protocol from a total of 40 different tissues in 29 organs, making up 25,713 WSIs (Supplementary Fig. 1b–e), which have been reviewed by pathologists and include a description of subclinical levels of pathology (Supplementary Fig. 1f–h), with demographic, lifestyle and clinical information also available (Supplementary Fig. 1i).

Modern artificial intelligence vision models are powerful extractors of deep features from images (Fig. 1b) that can then be linked to information such as clinical outcomes^{21–24}. For our aim, to numerically quantify the morphological features in these WSIs, we first fine-tuned vision models on a set balanced for tissue, sex and age brackets (Extended Data Fig. 1a, b) and then used them to extract a feature vector representing the morphological features of the WSI (Extended Data Fig. 1c). We observed that these features were well reflective of WSI tissue identity even in pretrained models without fine-tuning (Extended Data Fig. 1c), but fine-tuning provided better separation (Extended Data Fig. 1d). More importantly, we found that deep learning morphological features also provided information on individual-level covariates, such as age, even though they were not fine-tuned for that task (Fig. 1c and Extended Data Fig. 1d–h). Indeed, we found that age was the strongest factor driving variation across tissues (Supplementary Fig. 2), highlighting the influence of aging on tissue structure throughout the human lifespan.

Tissue clocks predict biological, pathological and clinical factors associated with age

Building on the observation that age has a marked imprint on tissue structure, we sought to develop ‘tissue clocks’, which are tissue image-based predictors of biological age, building on the concept first introduced with DNA methylation²⁸. To accomplish this, we trained regression models to predict the chronological age of each individual from the morphological features of the WSI in a cross-validated manner and observed the deviation of the predicted age from the known chronological age, that is, an age gap (Fig. 1d). This gap, in DNA methylation data, has been associated with several age-related diseases, such as Alzheimer’s²⁹, Parkinson’s³⁰ and Huntington’s³¹ diseases, amyotrophic lateral sclerosis³² and all-cause mortality³³. We used the model predictions to assess their performance and found an average mean absolute error (MAE) of 4.88 years across all tissues and a coefficient of determination of 0.69 (Extended Data Fig. 2 and Supplementary Table 2). We also assessed the model robustness by shuffling the ages across individuals and observed no evidence of overfitting; however, 4 of 40 clocks were underpowered, as fewer than 100 samples were available for these tissues (Extended Data Fig. 2a–c and Supplementary Table 2).

To understand the biological relevance of the tissue-based prediction of age and the value of the inferred age gaps, we leveraged telomere length measurements from the same tissues and individuals, available for 6,197 samples (25.2%)³⁴. We observed that, as with chronological age, there was an overall decrease in telomere length with biological age (Supplementary Fig. 3a,b). However, this trend was stronger in terms of biological age, as determined through tissue analysis, than for chronological age and was still present in the estimated age gaps (Supplementary Fig. 3a–e). This correlation was particularly pronounced for tissues such as the esophagus, stomach, kidney, prostate and pancreas (Supplementary Fig. 3c,d). Furthermore, by leveraging the annotations of subclinical levels of pathology from the same samples, we observed an enrichment of greater age gaps in samples with more pathology, which was concordant across most pathologies and, importantly, was greater in tissue-driven estimation of biological age than in chronological age alone (Supplementary Fig. 4a,b); for example, both were enriched in artery calcification. However, age gaps also recovered enrichment in pathological features not particularly present in chronological age, such as muscle atrophy (Supplementary Fig. 4c,d). Confirming the observations that higher age gaps are associated with tissue-specific pathology, we visually confirmed that WSIs with higher age gaps acquired noticeable changes in tissue-specific pathology (Fig. 1e,f). For example, independent of chronological age, cerebellar samples with greater age gaps presented discoloration associated with the loss of myelin and ischemic changes (Fig. 1e), whereas in the aorta, samples with higher age gaps presented thickening of the wall and disruption of integrity associated with atherosclerosis and other vascular disorders (Fig. 1f).

To assess the generalization of our tissue-based predictors of biological age, we used 7 classical deep learning models and 18 foundation models for pathology in feature extraction, building predictors from them (Fig. 1g, Supplementary Fig. 5 and Extended Data Fig. 3). The classical models, which were never trained on tissue images, showed predictive power but were not on par with our model (Extended Data Fig. 3a; mean MAE across organs and models of 8.67), whereas the performance of foundation models was more comparable to our own model (Extended Data Fig. 3b; mean MAE across organs and models of 5.74). However, the age gaps inferred by all types of models also showed significant associations with shorter telomeres and increases in comorbidities (Extended Data Fig. 3b–d). We also showed that models with markedly different architectures, such as graph neural networks (GNNs) with attention mechanisms, can learn to predict biological age (Supplementary Fig. 6a), with the advantage that their attention maps can be used to further locate areas in tissue most associated with biological aging (Supplementary Fig. 6b). We noted that a subset of the foundation models were pretrained on datasets that include GTEx histopathological images, which could favor their internal performance. To address this, we validated the histological predictors in external cohorts of brain ($n = 70$), lung ($n = 40$) and skin ($n = 185$) donors (Supplementary Table 3) by applying tissue clocks trained on the GTEx cohort to their histopathological images. In these cohorts, GTEx clocks predicted biological age with specificity depending on the tissue they were trained in (Pearson correlation coefficients of 0.56, 0.76 and 0.46 for brain, lung and skin, respectively; Fig. 1h, Extended Data Fig. 4 and Supplementary Table 4). In these external cohorts, we also evaluated the ability of multiple regressors to generalize (Supplementary Fig. 7) and found that both regularized linear models, as well as ensemble methods, performed comparably, but were superior to deep learning or unregularized models. Finally, to assess whether the estimated age gaps were meaningful, we compared them to biological age and age gap estimates derived from DNA methylation in the lung cohort and observed good agreement (Pearson correlation coefficient from 0.3 to 0.47 depending on the DNA methylation clock; Extended Data Fig. 5).

Histological and molecular interpretation of tissue aging

To characterize the histopathological features associated with the aging of tissues more systematically, we leveraged a pretrained self-contrasting multimodal model trained on many pathological images and their natural language descriptions³⁵ (Fig. 2a). With this model, we queried the similarity of each image to a set of histological and pathological terms ($n = 150$), generating a highly interpretable numerical vector to further describe the images. The histological text terms showed high organ- and tissue-specific enrichment, with terms such as ‘adipose tissue’ high in breast tissue and visceral and subcutaneous adipose tissue or ‘neurons’ in the brain (Fig. 2b and Extended Data Fig. 6a). We then characterized the association of each term with aging in each organ (Extended Data Fig. 6b,c) and found that terms such as atrophy, microvascular rarefaction and fibrosis increased across multiple organs, whereas the most common reduction in text terms across organs was related to the epithelium and hyperplasia (Fig. 2c). In addition to these common trends across organs, we also found some more specific trends in certain organs, such as fat infiltration in skeletal muscle (Fig. 2d), which we could confirm visually. Similarly, we also visually confirmed additional associations, such as microvascular rarefaction in the uterus (Fig. 2e) and peripheral nerve atrophy (Fig. 2f). Finally, we verified using another vision-language model³⁶ that there was no systematic bias for terms that were changing with age to be specific to one model or the other (Supplementary Fig. 8). These findings support our deep learning-driven analysis of tissue and enable a histological interpretation of age-associated changes in healthy tissue at a large scale.

To further interpret the observed morphological insights, we leveraged paired samples from the same tissues in the same

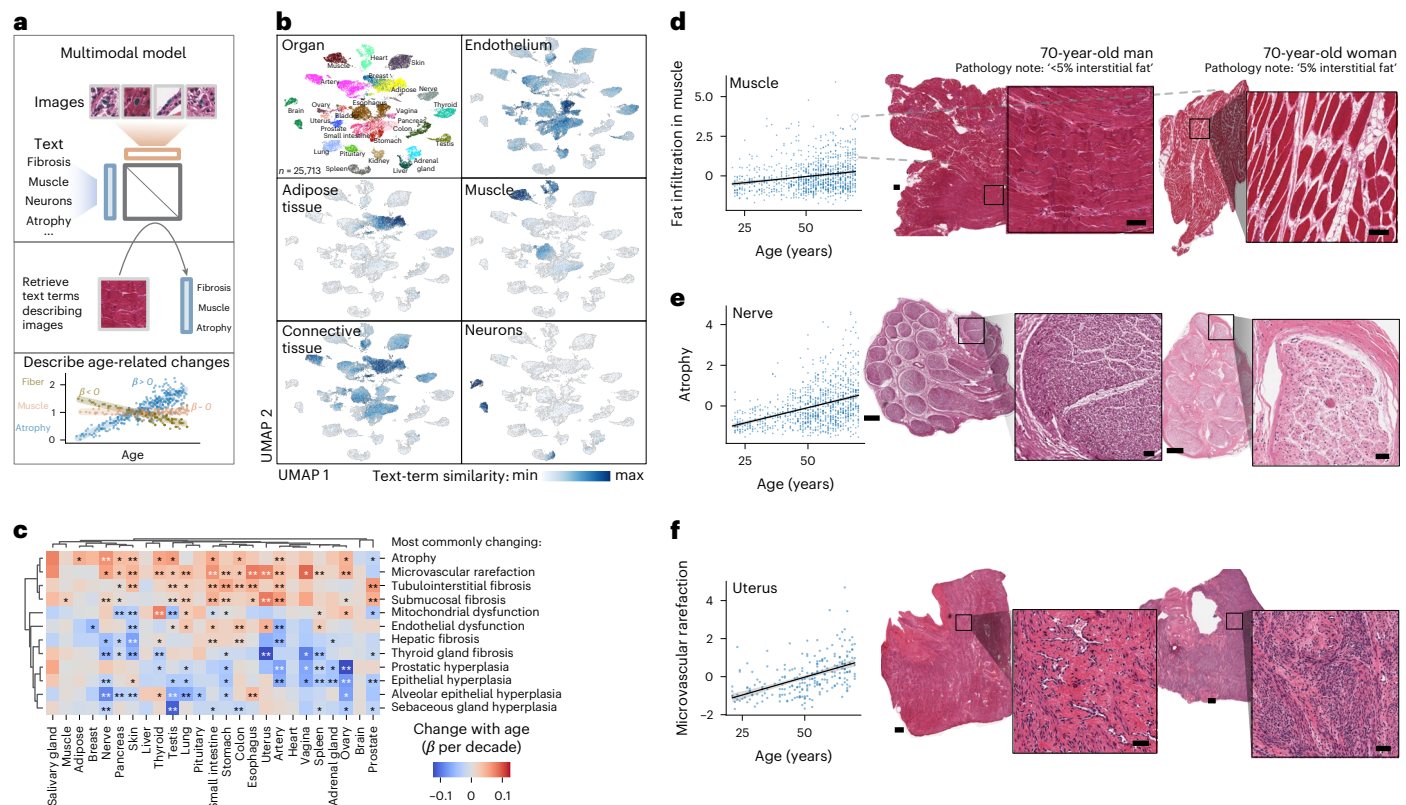


Fig. 2 | Characterization of age-associated changes in tissue using vision-language models. a, Representation of the strategy for querying text-image multimodal pathological models; a pretrained model is used to embed text terms, and the similarity of each term to images is measured, followed by the investigation of text terms whose similarity changes with age in the images. **b**, Illustration of histological text terms characterizing various organs using the

UMAP representation from Fig. 1c. **c**, Heat map showing the most commonly changing text terms colored according to the magnitude and direction of change for each organ. **d–f**, Examples of text terms with changes associated with age (left), with example tissue sections (right); scale bars, 500 μ m and 50 μ m (insets). The shaded area represents the 95% confidence interval of the regression line.

donors in the GTEx project. First, we sought to understand the relationship between estimates of biological age derived from DNA methylation^{28,37–41} and those derived from histological images (tissue clocks; Extended Data Fig. 7). In the GTEx cohort, 987 samples from 8 tissues had available DNA methylation data⁴², which we used to derive a range of biological age estimates via established biological age clocks (Extended Data Fig. 7a,b). In a systematic comparison of 28 DNA methylation clocks and 19 histological clocks on the same GTEx donors (Extended Data Fig. 8 and Supplementary Table 5), we found that neither modality was uniformly superior across biologically relevant outcomes. For comorbidity burden, histological age gaps showed more consistent associations (89% and 79% of models significant in the colon and lung, respectively) than DNA methylation clocks (7% and 50%), with greater directional consistency and narrower confidence intervals. For telomere length, DNA methylation clocks performed comparably or better (18% and 43% significant in the colon and lung, respectively) than histological clocks (0% and 37%). For tissue pathologies, both modalities performed comparably in the lung (47% versus 25%), whereas neither achieved robust associations in the colon. Histology- and DNA methylation-derived age gap estimates showed no direct agreement (Pearson correlation coefficient of 0.09; Extended Data Fig. 7e–g), consistent with the two modalities capturing partially overlapping but distinct dimensions of the aging process.

Second, leveraging over 17,000 matched bulk RNA-sequencing (RNA-seq) samples, we investigated how gene expression changes with chronological age and histologically derived biological age (Fig. 3). We used regularized regression models to associate the expression of all genes with varying degrees of deviation from chronological

age in the same samples (Fig. 3a). We observed that many more genes were associated with changes in chronological age than with age gaps (thousands versus hundreds; Supplementary Fig. 9c–e) but that the degree of association was not necessarily driven by the performance of the tissue clock or sample size (Supplementary Fig. 9c), suggesting that tissue-specific factors may also affect biological age. We found that genes associated with tissue-specific age gaps were overall also tissue-specific (Fig. 3b and Supplementary Fig. 9f) but also included genes not usually expressed in the tissue. For example, we detected the upregulation of EYA transcriptional coactivator and phosphatase 4 (*EYA4*) in adipose tissue during aging (Fig. 3c), which is usually restricted to the muscle, tongue and brain and was previously associated with hearing loss⁴³. Insulin-like growth factor binding protein 2 (*IGFBP2*), which is usually restricted to the liver, pancreas and stomach and promotes oncogenic processes, was also found to be upregulated in the adrenal gland with increasing age (Fig. 3c). These gene expression profiles offer potential biomarkers for aging and highlight the kind of gene-specific shifts that may contribute to the aging process.

To study how transcriptional pathways and signatures are altered with aging, we leveraged the Hallmark pathways from the molecular signatures database (MSigDB; Supplementary Fig. 10 and Supplementary Table 6). The most common significantly upregulated pathways were related to apoptosis and inflammation, whereas the downregulated pathways were most related to metabolism (Supplementary Fig. 10b,c). We also observed that among extracellular matrix/matrisome genes, the group of structural collagens was the most downregulated, followed by the basement membrane proteins, whereas elastic fiber components were the most upregulated

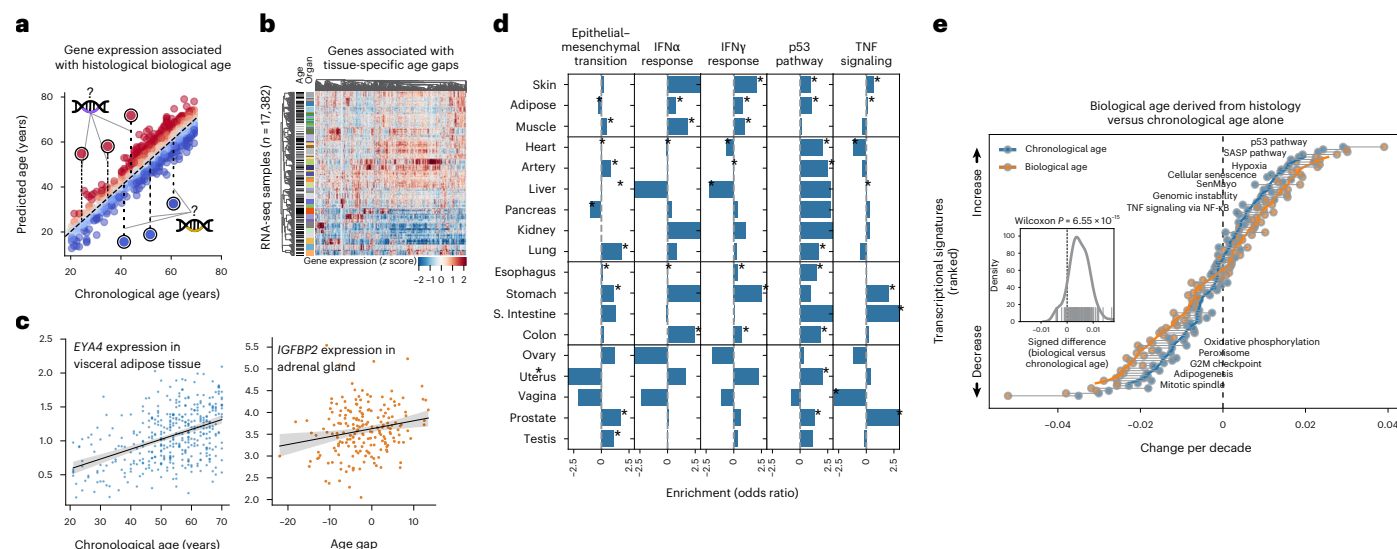


Fig. 3 | Transcriptional changes associated with tissue aging. **a**, Schematic representation of the approach for the integration of histological and gene expression data to determine gene associations with age gaps; genes whose expression changes in coordination with age gaps are identified via linear regression. **b**, Expression of genes associated with age gaps across multiple tissue samples, clustered by expression values. **c**, Examples showing the association of gene expression with chronological age (left) or age gap (right). The shaded area represents the 95% confidence interval of the regression line. **d**, Examples of signaling pathways associated with age in different tissues. The sign and

magnitude of the enrichment are given by the signed odds ratio, and pathways whose association with age is statistically significant are indicated with an asterisk (* $P < 0.05$, hypergeometric enrichment test, Benjamini–Hochberg false discovery rate-adjusted); IFN, interferon; S. intestine, small intestine. **e**, The mean amount of change (x axis) in each transcriptional signature (y axis) across organs is illustrated for chronological age (blue) and histologically derived biological age (orange). The distribution of absolute differences between chronological and biological ages is displayed as an inset, determined using a two-sided Wilcoxon test.

(Supplementary Fig. 11). However, each organ showed specific changes, likely related to its specific physiological function (Fig. 3d and Supplementary Figs. 10b,c and 11d,e). When analyzing these data, we observed that changes with biological age were consistently stronger than those with chronological age, regardless of direction (Fig. 3e). Pathways such as p53 signaling, cellular senescence, senescence-associated secretory phenotype, hypoxia, genomic instability and TNF signaling were upregulated with both measures of age but more strongly with biological age. Conversely, the mitotic spindle, G2M checkpoint, adipogenesis, peroxisome and oxidative phosphorylation pathways showed greater downregulation. On average, the slope between biological and chronological age was 1.26 (compared to the expectation of 0), indicating that histologically derived biological age captured a greater degree of transcriptional dysregulation and provided a refined view of the molecular–morphological interplay in aging.

Demographic and clinical factors modulating tissue-specific aging

The morphological and molecular analyses above captured the general landscape of aging across human tissues, yet aging unfolds differently across individuals. To understand what drives this heterogeneity, we investigated patterns of coordinated and discordant aging across tissues and their association with demographic and clinical variables. By leveraging age gaps estimated for various tissues from the same individual (Fig. 4a), we identified several patterns of cross-tissue aging within individuals: consistently below-average age gaps across tissues ('resilient agers'), consistently average age gaps ('average agers'), single- and multiple-tissue agers (one or a few tissues with greater age than others) and a group of individuals who consistently demonstrated greater predicted age gaps in most tissues ('systemic agers'). To visualize the pattern of aging across many individuals, we focused on a set of 303 individuals with greater than average age gaps in at least one tissue and identified various groups of individuals on the basis of their internal organ synchronicity in aging rates (Fig. 4b). We observed that most individuals with at least one high age gap tended to have several

organs with large age gaps (Fig. 4b, pan-tissue cluster). However, we detected several individuals with one particularly prominently aged organ, such as the heart, lung or stomach (Fig. 4c).

To provide an overview of the landscape of factors potentially underlying a specific deviation in the aging of one organ compared to others among the 983 individuals, we devised a strategy to associate tissue-specific age gaps with demographic, clinical and lifestyle variables^{25–27}. This analysis sought to characterize broad association patterns across tissues, serving as an exploratory framework rather than a formal test of specific hypotheses. These included 184 variables, from which we identified 80 that were recurrent enough to assess in light of the tissue-specific age gaps (Supplementary Fig. 1i). We discovered that, by and large, most factors tended to affect several or most tissues (Fig. 4d and Extended Data Fig. 9a,b) but also revealed several associations that were tissue and sex specific. One of the most prominent observations was the association of renal failure with accelerated aging across several tissues (Fig. 4d). Interestingly, the strongest association was not found in the kidney but was detected in tissues such as adipose tissue, pituitary, spleen and tibial nerve tissue (Fig. 4e). In women, the association between tibial nerve aging and kidney failure could be related to the fact that more than 90% of individuals with chronic kidney disease who undergo dialysis suffer from peripheral neuropathy⁴⁴. With respect to variations across tissues, we confirmed several known associations, such as chronic respiratory disease most prominently affecting deviations in lung tissue biological age from chronological age⁴⁵ (Fig. 4d), type 2 diabetes associated with pancreatic aging⁴⁶ (Fig. 4d,e), heart disease associated with adipose tissue aging⁴⁷ (Fig. 4d) and the effects of steroid use on the spleen⁴⁸ (Fig. 4d). However, we also found other less well-known associations that have not yet been linked to an explicit morphological manifestation of the aging process, such as higher rates of aging in the cerebellum associated with unexplained seizures⁴⁹ (Fig. 4d) or accelerated prostate aging and hypertension in men (Extended Data Fig. 9b), even though there are reports that link hypertension with prostate hyperplasia^{50,51}.

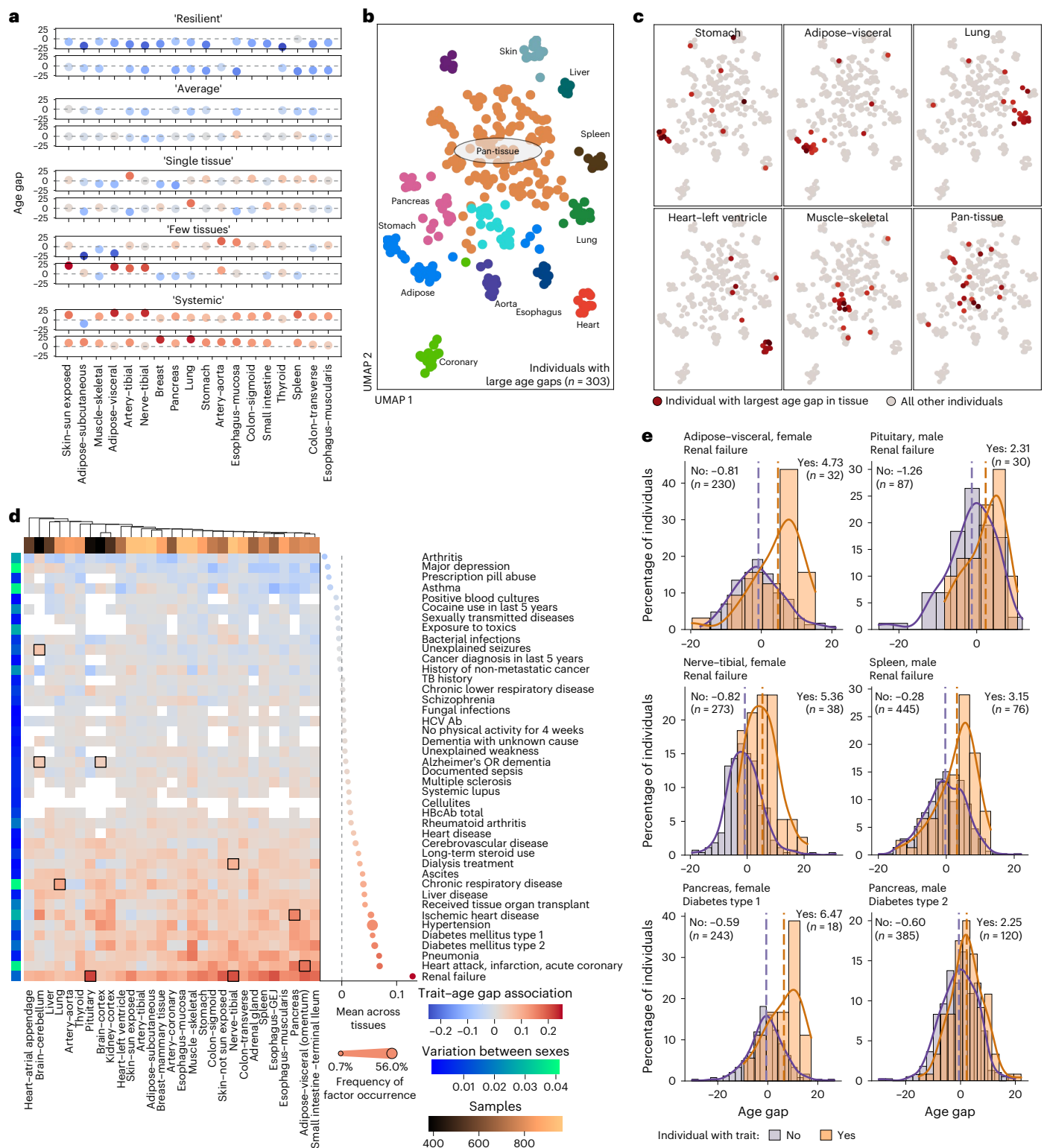
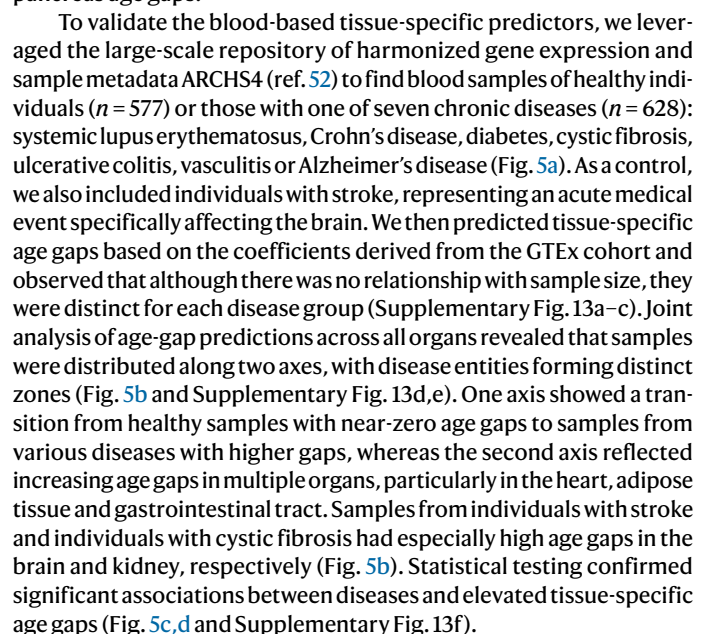


Fig. 4 | Diversity of aging within and between individuals. a, Age gaps for tissues from GTEx donors showing five different patterns of aging. Each row indicates a different donor. **b, c**, UMAP plots demonstrating the variation in age gaps across tissues for each individual. Individuals are colored according to the pattern of intertissue variation during aging (**b**) or according to the tissue with the largest age gap (**c**). **d**, Associations of various demographic, clinical and lifestyle factors with tissue-specific age differences. Boxes highlight known

associations, are highlighted in **e** or are described in the text. No statistical testing was performed; GEJ, gastroesophageal junction; HBcAb, hepatitis B core antibody; HCV Ab, antibodies to hepatitis C virus; TB, tuberculosis. **e**, Histograms comparing inferred tissue-specific age gaps depending on clinical factors. Individuals with a trait showed higher age gaps than those without it. The mean age gap and sample size are indicated.



Notably, individuals with stroke showed the most pronounced age-gap deviation specifically in the brain (Fig. 5c–e), in alignment with the affected tissue in this acute event. Moreover, all seven chronic diseases were significantly associated with tissue-specific accelerated aging in at least one organ (Fig. 5d). For example, Crohn's disease was associated with increased predicted age gaps in the gastrointestinal tract (esophagus, stomach, small intestine and colon), whereas vasculitis exhibited higher age gaps in the kidney, liver and heart (Fig. 5e), which are highly vascularized organs and primary targets of inflammatory processes in this disease. In some diseases, fewer and milder but specific associations were detected; for example, the brain was the only organ with significantly higher age gaps in Alzheimer's disease (Fig. 5d). Interestingly, we also found associations of age gaps with organs that are not the primary site of disease action. These associations could be revealing of how treatment of a primary condition may affect other organs⁵³, as detected by significantly higher age gaps for individuals with stroke in the kidney and liver, or of secondary effects of disease, such as changes in the brain due to chronic hypoxia in cystic fibrosis⁵⁴, for which we also detected significantly higher age gaps than healthy individuals (Fig. 5e). Leveraging a subset of blood samples for which the chronological age of the donors was available, we could also verify that the inferred age gaps from blood were not associated with chronological age (Supplementary Fig. 14). Finally, to assess the potential clinical utility of blood-based tissue-specific age gaps in detecting disease, we evaluated the performance of thresholded age gaps (Supplementary Fig. 15). The models demonstrated moderate to strong classification performance, as assessed by the area under the receiver operating characteristic curve, and positive predictive values above 0.3 in several cases suggested potential applicability for population-level screening.

Overall, this approach demonstrates the feasibility of inferring tissue-specific biological age and disease-related aging signatures from minimally invasive blood samples, underscoring its potential utility in early disease detection and monitoring aging in clinical settings.

Discussion

This study presents a comprehensive analysis of human aging from the perspective of tissue histology, highlighting the complexities of tissue-specific age variation across tissues and within individuals. The use of GTEx project data has provided an unprecedented view of the histopathological hallmarks of aging in healthy tissue or tissue with subclinical pathology and, at the same time, has enabled us to correlate tissue-specific aging phenotypes with molecular data and demographic and clinical factors.

The morphological assessment of tissue underscored the profound impact of aging on tissue architecture. Despite the commonality of aging as a universal process, we revealed a multitude of factors modulating it and a remarkable variation in the rates of aging across tissues during the human lifespan. The development of 'tissue clocks' stands, therefore, as a pivotal advance, following the paradigm first established with DNA methylation studies^{28,37–41} and continuing to be developed through new generations of clocks^{55,56}, while bringing a highly tissue- and organ-specific context that is deeply connected to physiological fitness. Through validation in independent cohorts of histopathological images and multiple types of models, we also demonstrated that the tissue-based imprints of biological aging are a general feature of human tissue and are transferable across cohorts.

The generalizability of image-based predictors across institutions remains an important consideration. Unlike molecular assays, where standardized protocols yield comparable readouts across laboratories, histopathological images are subject to variation in staining, scanner optics and tissue preparation, a challenge broadly recognized in computational pathology^{57,58}. In our external validation, tissue-matched clocks consistently outperformed mismatched clocks across all calibration metrics (Bland–Altman bias, limits of agreement and calibration slope), confirming tissue specificity of the aging signal.

Performance varied across cohorts (Pearson correlation coefficients of 0.46, 0.56 and 0.76 for the skin, brain and lung, respectively), with calibration slopes below 1.0 reflecting the regression-to-the-mean compression expected under domain shift. We also found that regularized linear models, ensemble methods and kernel-based approaches all generalized comparably well to independent data, whereas neural network-based regressors showed substantially worse external performance, consistent with recent observations in biomedical age prediction in other modalities⁵⁹. These findings indicate that, although the tissue-specific aging signal is robust and reproducible across some model architectures, broader deployment will benefit from careful selection of the most generalizable models for the task, harmonization of imaging protocols and domain adaptation strategies⁶⁰.

Leveraging the largest dataset of paired histological images, RNA-seq and DNA methylation data from noncancerous tissue and multimodal deep learning models, we systematically characterized the histological features of tissue aging and identified loss of epithelial proliferation and an increase in tissue atrophy, microvascular rarefaction and fibrosis as some of the most common aging features across organs. The observation that changes in pathways and transcriptional signatures were more strongly recovered with histologically derived biological age than with chronological age suggests that histological analysis captures a more pronounced molecular aging signal, potentially reflecting the cumulative burden of microanatomical alterations to tissue that are not fully accounted for by intrinsic cellular changes alone. We observed agreement between the age estimates derived from DNA methylation and histology only in biological age, although both methods resulted in low errors and associations of age gaps with pathological features. Moreover, it is noteworthy that histological measures of biological age and its gap with chronological age align with telomere attrition rates, particularly in tissues of the gastrointestinal tract, lung, pancreas and kidney. Although agreement between epigenetic aging clocks can be fairly low⁶¹, the lack of agreement we observed between tissue clocks and DNA methylation estimates in GTEx data likely reflects both biological and technical factors. Biologically, DNA methylation clocks leverage the accumulation of stochastic changes in DNA⁶², whereas tissue morphology is conditioned by physiological and external factors that diverge from those driving epigenetic drift. Technically, the GTEx DNA methylation and histopathological data were not necessarily derived from the same tissue blocks, and the predominantly healthy GTEx donors provided limited dynamic range in age-gap estimates, reducing the power to detect cross-modal agreement. Consistent with this interpretation, in our lung validation cohort, where both modalities were profiled from the same tissue blocks and donors spanned a wider range of physiological states, we observed good agreement between histological and epigenetic age estimates (Pearson correlation coefficient from 0.3 to 0.47 depending on the clock).

With the increasing efforts of large-scale histopathological⁶³ repositories providing an avenue for the large-scale validation of tissue clocks, it is conceivable that they may be applicable in tissues with routine sampling, such as during colonoscopy. However, physiologically relevant, tissue image-based clocks have the disadvantage of requiring the invasive procurement of tissue. In the search for accurate biomarkers of aging, noninvasive or minimally invasive methods, such as thermal facial imaging⁶⁴ or plasma proteomics, are desirable. The latter has recently shown the ability to make organ-specific inferences by making assumptions about the origin of circulating proteins in plasma⁶⁵. In our work, we used the observed changes in tissue morphology to train a blood-based predictor of tissue-specific aging rates, which was enriched in tissue-specific pathologies and was validated in independent cohorts of individuals with eight different diseases. This analysis uncovered specific signal for affected organs in acute events (stroke) and even in remarkably heterogeneous chronic diseases, such as significantly higher age gaps for the brain in individuals with Alzheimer's disease. Furthermore, we also found significant associations of

tissue-specific age gaps with organs that are not the primary focus of the disease, such as the pervasive accelerated aging of the kidney and liver across multiple chronic diseases compared to in healthy individuals. This ability to detect both organ-specific and systemic aging patterns from a minimally invasive blood test underscores the potential of this approach as a valuable tool for early disease detection and as a future prognostic marker. However, we note that the absolute calibration of predicted tissue-specific age gaps from blood cannot be verified in external cohorts without paired tissue histology, and that our validation was performed on individuals with prevalent disease, demonstrating association with existing conditions. Whether elevated tissue-specific age gaps in blood precede disease onset and can therefore serve as predictive biomarkers of incident disease remains to be established in prospective longitudinal cohorts with prediagnostic blood samples and subsequent clinical follow-up.

Beyond these considerations, several additional limitations should be noted. (1) An important aspect is the sex imbalance within the GTEx cohort (a female:male ratio of 1:2). This disproportion is reflected in the performance of aging clocks, with 3 of 4 (from a total of 40) underperforming clocks being from female reproductive system tissues. (2) The use of postmortem samples poses a challenge owing to the variable onset of tissue autolysis between death and the start of autopsy. Due to the excellent annotation of this factor, we have adjusted for this to reduce its potential impact, but we cannot exclude that this has reduced the power for discovery in some tissues. (3) Due to the use of cross-sectional data collected postmortem, our analysis is not well powered to address questions about the timing of disease onset and manifestation or causal relationships, but it currently recovers only correlations and must be limited to an exploratory mapping of associations. In future endeavors, combining genetic data with approaches such as genome-wide association studies and Mendelian randomization, similar to studies conducted in larger cohorts without tissue-level data⁶⁶, may provide avenues to infer causal relationships.

Despite these limitations, our study stands as a testament to the potential of tissue analysis in aging research and supports the view of aging as a dynamic interplay of molecular, cellular and histological changes that are intricately influenced by an individual's life trajectory^{3,19}. Furthermore, by connecting quantitative tissue-derived aging phenotypes to molecular data from blood, we provide a window to fingerprint the physiological state of multiple organs from a clinically amenable blood sample in health and in age-associated diseases.

Online content

Any methods, additional references, Nature Portfolio reporting summaries, source data, extended data, supplementary information, acknowledgements, peer review information, details of author contributions and competing interests and statements of data and code availability are available at <https://doi.org/10.1038/s41591-026-04566-5>.

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Methods

Data reporting

No statistical methods were used to predetermine sample size due to the predetermined sample availability of the GTEx project²⁷. Three samples were excluded from the study as they were annotated with the wrong tissue label.

Data acquisition

GTEx WSIs were downloaded from the public portal²⁷. All slides were acquired with a Leica Biosystems Aperio ScanScope with a $\times 20$ objective (effective resolution of $\sim 0.4942 \mu\text{m}$ per pixel). Demographic data (including the exact chronological age of the individuals), lifestyle information, clinical information for the participants and gene expression data were downloaded from dbGaP because they are under protected access.

Independent histopathological image datasets were used to validate the tissue clocks. Postmortem brains of individuals aged 35 to 99 years were identified from the archives of the Institute of Neuropathology and Neuromolecular Pathology at the Medical University of Innsbruck. Ethical approval for the use of formalin-fixed and paraffin-embedded (FFPE) tissues for research studies, along with a waiver of the requirement for informed consent, was granted by the ethical committee of the Medical University of Innsbruck (EK 1387/2025). FFPE tissues of frontal and cerebellar cortex were retrieved, and hematoxylin and eosin-stained sections were assessed for central nervous system pathology. The sections were then digitized in $\times 20$ magnification using an Aperio GT 450 DX automated digital pathology slide scanner, and whole-slide scans were saved in .svs format. Skin samples were obtained at the Department of Plastic and Reconstructive Surgery or the Department of Dermatology of the Medical University of Vienna. The study complied with national law and was approved by the Medical University of Vienna Ethics Committee (ECS 1969/2021 and ECS 1877/2024), with informed consent obtained from participants. Skin biopsies were fixed in formalin, embedded in paraffin and stored at -20°C to preserve tissue structure and RNA for morphological and molecular analyses. For histology, FFPE blocks were sectioned into $6\text{-}\mu\text{m}$ slices using a microtome (Leica RM2235) onto SuperFrost Plus slides (VWR, 6310108) and stained with hematoxylin and eosin using a Dako Cover Stainer with standard reagents (Agilent). Slides were digitized in $\times 40$ magnification using a Hamamatsu C9600-12 automated digital pathology slide scanner, and whole-slide scans were saved in .ndpi format. Lung samples were obtained under approval by the ethics committee of UZ Leuven/KU Leuven (S52174), with signed informed consent from participants. The study was conducted in accordance with the Declaration of Helsinki. Whole lungs were excised, air inflated and snap frozen, with all samples derived from the same anatomical region. Slides were scanned on an Axioscan 7 with an EC Plan-Neofluar $\times 20/0.50\text{-NA}$ M27 objective (effective resolution of $\sim 0.1725 \mu\text{m}$ per pixel) and saved in .czi format.

WSI processing

WSIs were segmented into foreground tissue and background regions using computer vision algorithms adapted from the pre-processing utilities of the CLAM repository⁶⁷. Only the image pre-processing components were reused; the CLAM multiple-instance learning and attention-based models were not used. We repurposed and modularized the preprocessing code into a general-purpose WSI library that is model agnostic and now open sourced at <https://github.com/rendeirolab/wsi>. Briefly, signal from a WSI thumbnail was converted to HED color space, Otsu-thresholded and dilated, and small objects (<500 pixels) were removed. To produce a tissue mask, the holes were filled, and a separate mask for the holes (>0.5 and <50 pixels) was used. Contours were stored in .h5 format, and slides were tiled in the tissue area with square patches of 224 pixels (effective size of $\sim 112 \mu\text{m}$).

Vision model fine-tuning

To capture histological features better, we fine-tuned a variety of vision model architectures in a tissue classification task. Importantly, we created a balanced dataset comprising equal numbers of slides and tile patches from different tissues, age brackets and sexes. We built upon well-established and pretrained models (AlexNet, VGG16, ResNet50, ResNet152, ResNet50, ConvNeXt tiny and ConvNeXt base), with a classifier head corresponding to the tissue classes. To train the new classifier head layer, we first froze all layers of the pretrained model and trained one epoch, followed by up to 100 epochs of fine-tuning the whole model via the AdamW optimizer with cosine annealing. We started with an empirically discovered learning rate by measuring the loss at incremental steps and choosing one-tenth of the minimum (learner.lrfind). Model fine-tuning was performed with PyTorch and Fast.ai, either on TPUs through Google Colab or on a workstation with two NVIDIA RTX A6000 GPUs.

Feature extraction and unsupervised analysis

Inference was run on a high-performance computing cluster using CPUs for all tiles in all slides at three levels of magnification (~ 480 million tiles). We worked with three different tile widths (224, 448 and 896 pixels at $\sim 0.5 \mu\text{m}$ per pixel) but centered at the same location, such that the tile centroids across different widths were matched and represented different, progressively wider views of the same tissue location. Features were extracted with a variety of models as described earlier, and for downstream analysis, feature values were aggregated across tiles by means and concatenated across different tile widths to generate a single feature vector for each WSI. We used AnnData and Scanpy⁶⁸ to perform dimensionality reduction with principal component analysis (PCA), compute neighbors and compute a UMAP for visualization, each step with default parameters (PCA: 50 principal components, neighbor graph: 15 neighbors on the basis of PCA representation, UMAP: 0.5 min_dist, 1.0 spread).

Analysis of total variance explained

To provide a global measure of the importance of various factors in explaining the observed range of morphological heterogeneity across tissue samples, we implemented linear models that use those factors to predict the variability of samples in the principal components. We collected 86 variables related to demography, lifestyle, serology, morbidity and circumstances of death for each participant. Regression was based on an ordinary least squares regression model (statsmodels⁶⁹) and was fit for each tissue and principal component at a time. The full model was fit first, and models missing each of the 86 variables (leave one out) were subsequently fit and compared to the full model on the basis of the adjusted coefficient of determination. These values were weighted by the variance ratio of each principal component in the data and summed across components to generate a value of total variance explained for the factor.

Tissue clocks and estimation of age gaps

We used linear models implemented in scikit-learn⁷⁰, including Linear Regression, Ridge, RidgeCV and RandomForestRegressor, using GroupKFold ($k = 5$) cross-validation, where the group was an individual, to ensure that the training and validation splits did not contain the same individual. Models were trained for each tissue separately using the features from the vision models as inputs, age as the target and sex, cohort type and minutes of ischemic time as covariates. To assess potential overfitting, we also fitted the models on shuffled age labels as target. We computed the coefficient of determination and MAE as metrics. Adjustment for regression to the mean was performed by regressing out the coefficient of age from the observed residuals as previously described¹⁶. All the results reported downstream were obtained for tissue clocks trained with a Ridge model, as it exhibited good performance and was fast.

The 'Bladder', 'Cervix - Ectocervix', 'Cervix - Endocervix', 'Fallopian Tube' and 'Kidney - Medulla' tissues had fewer than 100 samples available and overall showed poor performance (for example, MAE > 9 years) and were excluded from further analysis. We also noticed that three samples had extreme age-gap values ('GTEx-IGMR2-0426', 'GTEx-IS82U-0426' and 'GTEx-11ZTS-0426'), which, upon inspection, were found to be annotated with the wrong tissue type.

Classic vision and foundation models

To validate and assess the generalization of findings with our fine-tuned model, we used 6 classic vision models trained on ImageNet (Supplementary Fig. 5) and 18 pathology foundation models (Extended Data Fig. 3)^{21,22,35,36,71–94}. We performed feature extraction using LazySlide⁹⁵ on NVIDIA H100 GPUs, using square patches of 224 pixels and aggregating features within each slide by the mean (as done previously for our fine-tuned model). Age predictors were fitted as described in the section above using the Ridge model with GroupK-Fold ($k = 5$) cross-validation, and metrics were calculated based on the chronological age of the individuals.

GNNs

To further validate the choice of feature aggregation across patches of the same slide, and to enable the visualization of weights associated with biological age on tissue images, we also used GNNs for biological age prediction from histopathological images (Supplementary Fig. 7). Here, tissue patches were used as nodes with features from the convNeXt fine-tuned model. A k -d tree was used for quick nearest-neighbor lookup with a radius of patch size $\times$ the square root of 2 to connect adjacent tissue tiles.

The model architecture was composed of a dropout layer (with a probability of 0.1, 0.25 or 0.5), a variable number (2, 4 or 8) of graph convolutional layers (torch_geometric.nn.conv.GCNConv) with batch normalization and ReLU activation. The convolutional layers had a variable number of hidden dimensions (32, 64, 128 or 256) and were aggregated via jumping knowledge (torch_geometric.nn.models.JumpingKnowledge) across all layers, upon which an attention aggregation layer (torch_geometric.nn.aggr.AttentionalAggregation) with sigmoid activation was added. Finally, a fully connected linear layer was added to output a scalar value.

The target value was chronological age, and GNNs were trained per organ for 80 epochs on an NVIDIA A6000 using an 80–20 dataset split, MAE loss, the AdamW optimizer with cosine annealing, with a starting learning rate of 1×10^{-3} , and weight decay of 1×10^{-4} . We assessed performance in the validation set using MAE, Pearson correlation and coefficient of determination in relation to the known chronological age of the donors.

To visualize attention weights on tissue (Supplementary Fig. 9d), we extracted node-level attention scores from the best-trained GNNs for each tissue. For each patch (node), we obtained the raw gate outputs and normalized them into per-node attention weights using scatter-based softmax over the batch dimension. The outputs were aligned back to the spatial positions of the original patches, and the normalized attention weights were overlaid on the corresponding histological tissue images as heat maps. This enabled spatial visualization of regions that contributed most strongly to the graph-level age prediction.

Telomere lengths and annotated levels of tissue pathology

We leveraged the telomere quantity index values measured for tissue blocks from the same tissues and individuals in the GTEx cohort³⁴. We z scored these values per tissue to account for intertissue variability in the mean values. Only tissues with at least 100 paired WSIs and telomere length samples were used for analysis.

We also leveraged the pathological notes available in the GTEx cohort, in particular the discretized set of 57 text categories describing

the WSIs, which comprised 11,016 instances of a term annotating an image. For the purpose of associating particular pathological annotations with histological age gaps, we excluded 'clean_specimens', 'no_abnormalities' and 'tma'. For pathologies common across more than one tissue, we also derived an overall 'body pathology burden', which is a composite measure of the number of pathologies annotated in all tissues of an individual.

Text term characterization of age gaps

We used the pathology language and image pretraining (PLIP) model³⁵ to embed 512-pixel-wide (at $0.5 \mu\text{m}$ per pixel) tiles from every slide in the GTEx project and used them to query the similarity to a set of histological and pathological terms. The terms were selected to represent equal parts of the histological components and features of the various tissues under study (for example, epithelium, muscle, neurons, adipose tissue and myofiber degeneration). The values were aggregated by means per slide, and associations with histological age gaps were derived via regularized linear regression (Ridge).

To assess the agreement between vision-language models in their interpretation of histopathological images of aging, we compared the outputs of PLIP and CONCH using slides from the colon, lung and skin tissues in the GTEx dataset ($n = 4,368$). For each slide, we computed the cosine similarity of image features to a curated set of 150 histological and pathological text terms using both models. The resulting slide-level similarity matrices were used to compute, for each text term, the Pearson correlation coefficient between the PLIP- and CONCH-derived similarity values, yielding a distribution of model agreement across terms. To identify factors underlying this agreement, we extracted a set of text-level features describing the linguistic structure of each term, including character and word composition (for example, number of characters, word length, punctuation, uppercase and lowercase usage, lexical diversity and character entropy). In addition, we included the mean and standard deviation of the PLIP and CONCH similarity values for each term. These features were standardized and used as predictors in a linear regression model explaining the correlation between models. Finally, we quantified, for each tissue, the association of change in text-term similarity with donor age and the agreement of terms between the vision-language models.

DNA methylation clocks

We used the PyAging package⁹⁶ to predict the biological age of the DNA methylation samples matched to the histological images of the tissue. DNA methylation data⁴² were measured via the Infinium HumanMethylationEPIC bead chip, which measures approximately 850,000 CpG sites. We then derived age gaps by comparing them to the real chronological age of the samples and compared both the predicted values and the DNA methylation-derived age-gap values to the histological predictions using Pearson correlation coefficient.

Gene expression analysis

We used bulk gene expression data from the GTEx project that were matched to the same tissues as the histopathology images. We converted gene-level counts to log counts per million (log (CPM)), and any technical replicates were aggregated by means. To explain both aging and tissue-specific rates of age acceleration (age gaps) with gene expression of the corresponding tissues, we implemented Ridge regression using, as previously described, sex, cohort and minutes of ischemic time as covariates. Genes with an absolute coefficient value above 0.005 ($> 5\%$ change per decade) were selected. Finally, we used Enrichr⁹⁷ through the GSEAPy package⁹⁸ for gene set enrichment with the MSigDB database separately for the up- and downregulated gene sets.

Similarly, we also used the 50 MSigDB pathways together with a set of 50 age-related signatures previously compiled (available at <https://github.com/WJPina/HUSI/>), as well as a set of genes related to extracellular matrix biology, and quantified them in the transcriptomes using the

from the postmortem brain, skin and lung samples that were used retrospectively for this project with institutional permission and are, thus, not publicly available. Data from the validation cohorts are available from Gene Expression Omnibus under accessions [GSE66573](#), [GSE72420](#), [GSE72509](#), [GSE84891](#), [GSE89403](#), [GSE102114](#), [GSE109313](#), [GSE110685](#), [GSE111459](#), [GSE112087](#), [GSE113386](#), [GSE120691](#), [GSE123658](#), [GSE123786](#), [GSE123787](#), [GSE124548](#), [GSE125512](#), [GSE129752](#), [GSE131475](#), [GSE134080](#), [GSE136053](#), [GSE136371](#), [GSE143507](#), [GSE147931](#), [GSE147933](#), [GSE151282](#), [GSE159121](#), [GSE160268](#), [GSE161196](#), [GSE161731](#), [GSE162828](#), [GSE169687](#), [GSE171770](#), [GSE174056](#), [GSE184050](#), [GSE184876](#), [GSE184877](#), [GSE185263](#), [GSE186593](#), [GSE187429](#), [GSE199819](#), [GSE206250](#), [GSE206648](#), [GSE208405](#), [GSE212610](#) and [GSE222408](#).

Code availability

Source code is publicly available at the GitHub repository <https://github.com/rendeirolab/tissue-clocks> (<https://doi.org/10.5281/zenodo.20671352>)¹⁰¹. The package for the analysis of WSIs is available open source at <https://github.com/rendeirolab/wsi>, which is based on the ‘CLAM’ repository from the Mahmood lab⁶⁷. LazySlide⁹⁵, a new framework for accessible and interoperable work with WSIs, is available at <https://github.com/rendeirolab/lazyslide>.

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Author contributions

E.A., I.B., Y.Z. and A.F.R. conceptualized the study. L.K., S. Klotz, R.K., A.M., S. Kadri, M.P., M.D., P.T., B.S., L.J.D.S., W.W., B.V., L.J.C., D.D.B., L.J.F., G.S., A.W. and H.B.S. provided samples and generated histopathological images for validation cohorts. R.K., A.M., S. Kadri and M.H. performed DNA methylation analysis. M.N., W.H., Y.T. and A.W. provided pathology expertise and valuable input for data quality and interpretation. E.A., I.B., Y.Z. and A.F.R. performed computational analysis, with support from T.V., Z.W., A.M., S.M., M.H. and P.T. E.A., I.B., Y.Z. and A.F.R. prepared the paper with input from all coauthors. P.T., M.H., L.J.C., D.D.B., L.J.F., G.S., Y.T., A.W., H.B.S. and A.F.R. supervised the research.

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Competing interests

E.A., I.B., Y.Z. and A.F.R. declare competing financial interests in the form of a patent (PCT/EP2025/078696 and WO/2026/074209). L.J.D.S. reports travel grants from Boehringer Ingelheim, speaker's fees from Boehringer Ingelheim and research collaborations with Endeavor Medicines and Alentis Therapeutics. A.W. received honoraria for lectures by Servier. The remaining authors declare no competing interests.

Additional information

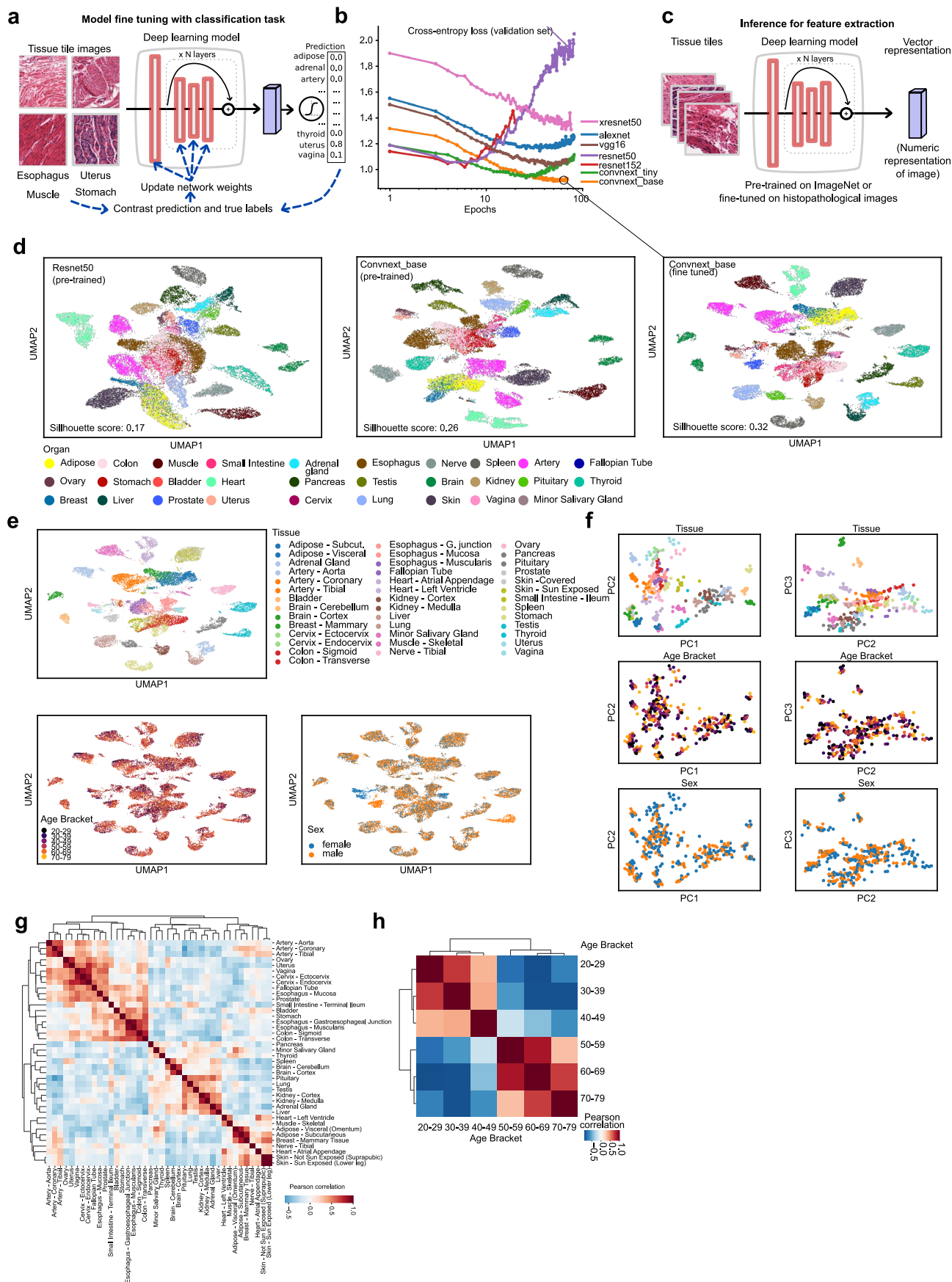
Extended data is available for this paper at <https://doi.org/10.1038/s41591-026-04566-5>.

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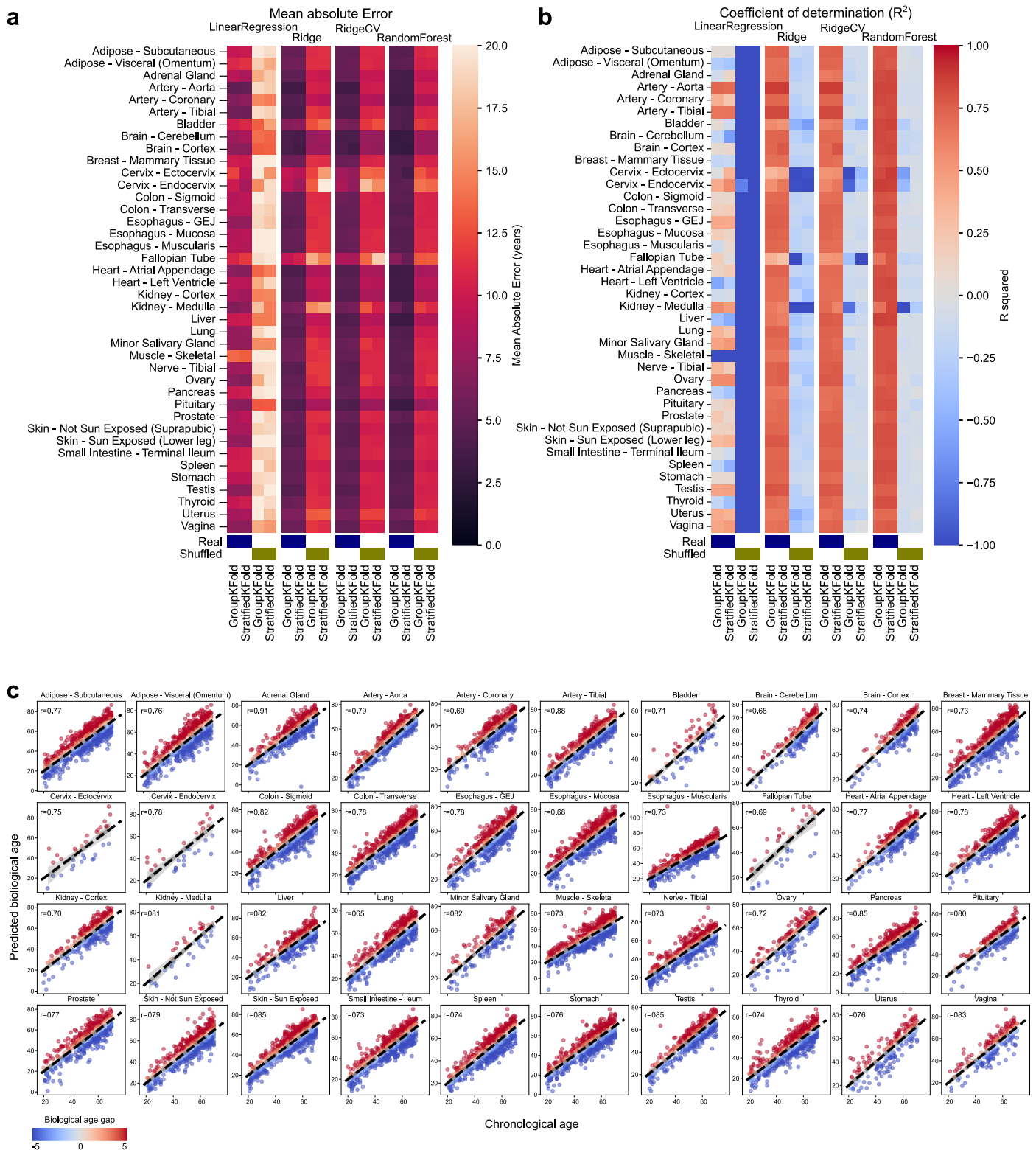
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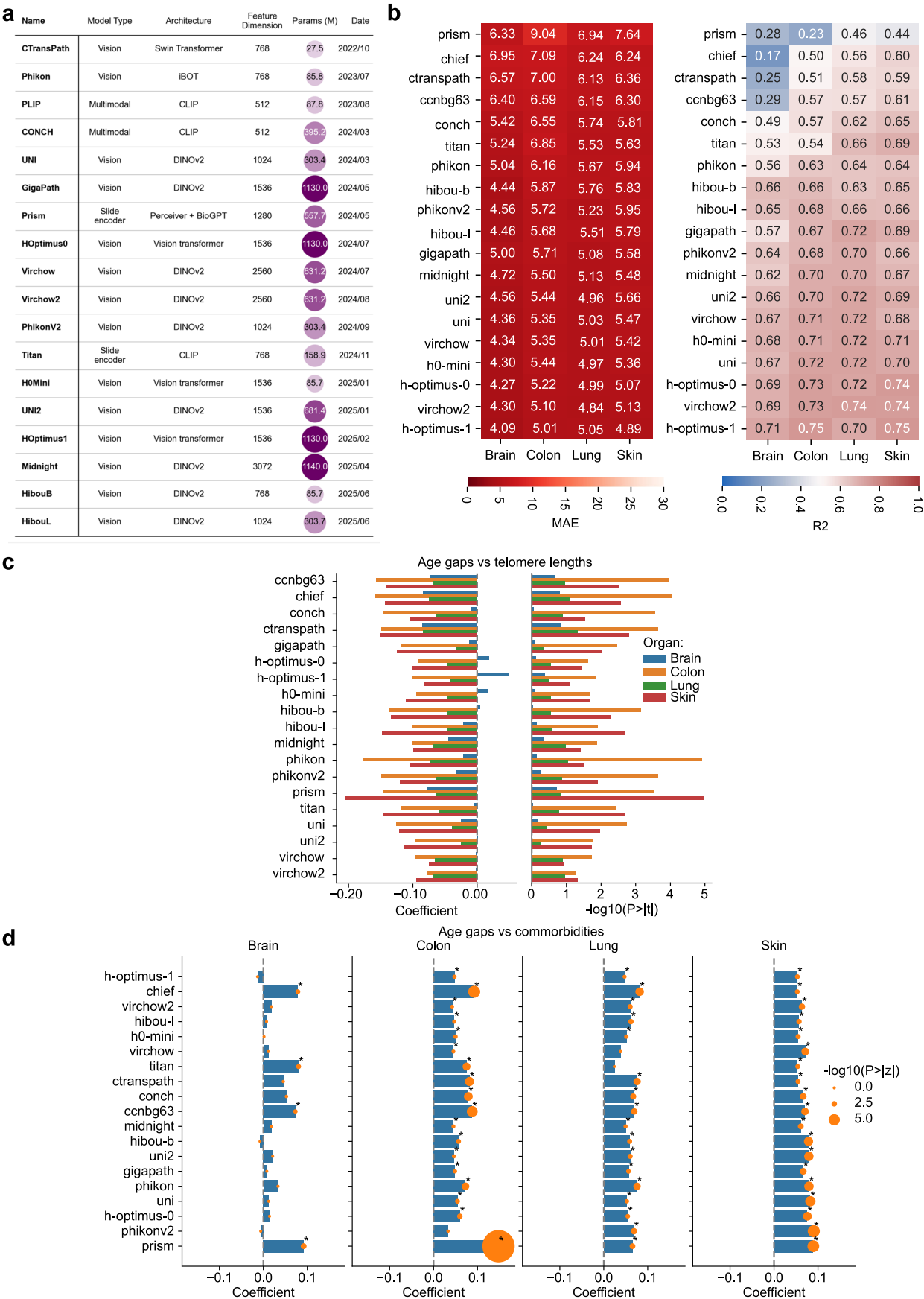
Extended Data Fig. 1 | See next page for caption.

Extended Data Fig. 1 | Vision models for the analysis of histopathological images across tissues. **a)** Strategy for the supervised fine-tuning of vision models by classifying tissue types. Datasets were balanced per tissue, age bracket and sex. **b)** Performance of various model architectures during fine-tuning. **c)** Strategy to use vision models for feature extraction. **d)** UMAP plot of all WSIs comparing 3 models: a pre-trained Resnet50 and Convnext base, and a fine-tuned

ConvNeXt base. WSIs were colored by organ. **e)** UMAP for a fine-tuned ConvNeXt base model as in **d)** but with WSIs colored by tissue, age bracket and sex. **f)** PCA plots for the fine-tuned ConvNeXt base model with WSI features aggregated by tissue, age and sex. **g-h)** Pairwise correlation plots for the WSI features aggregated by tissue (**g**), or age bracket (**h**).



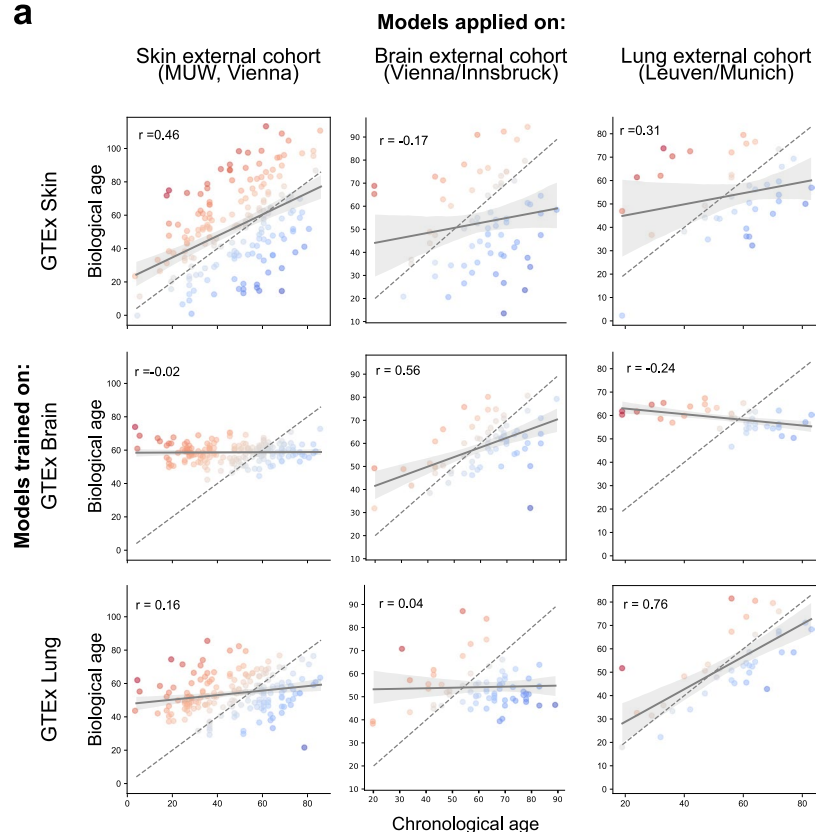
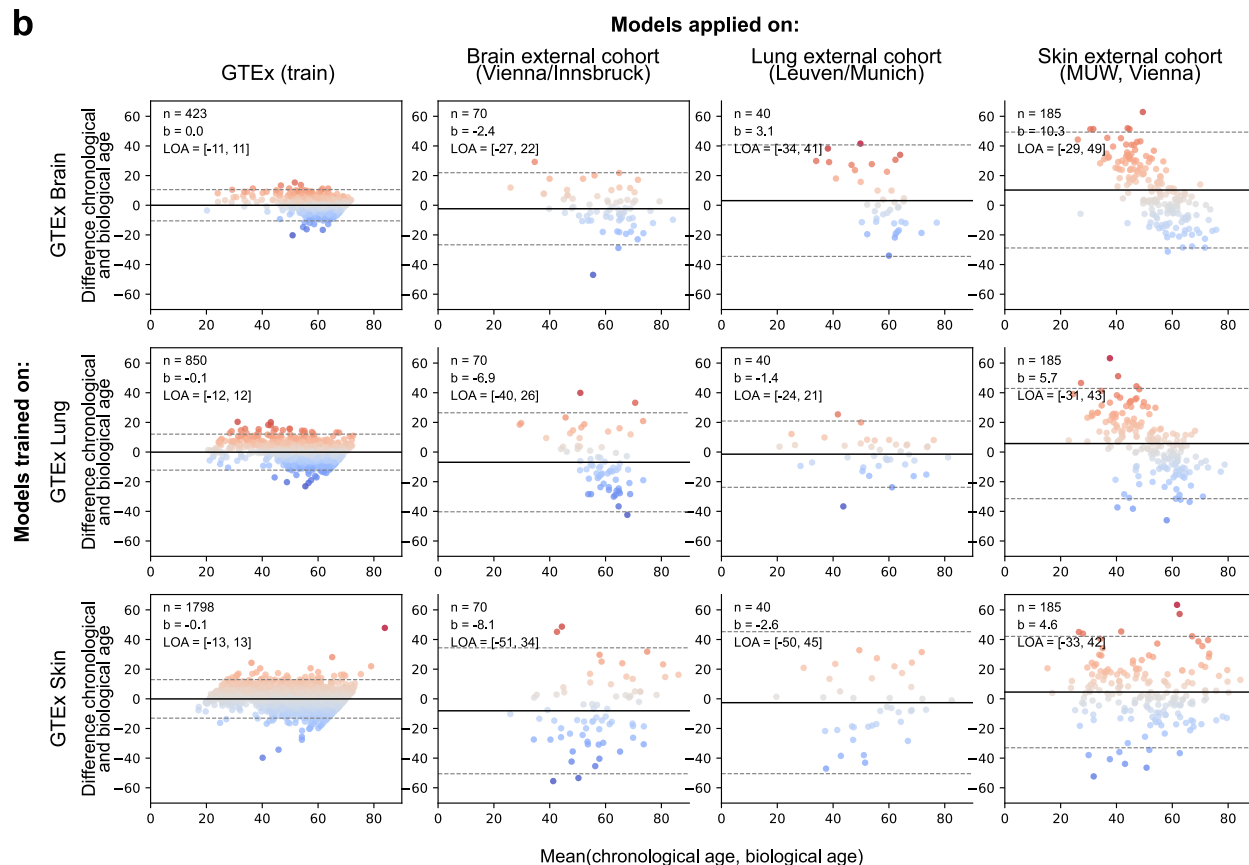
Extended Data Fig. 2 | Performance of tissue clocks. a-b) Assessed with the mean absolute error (a) and coefficient of determination (b) metrics for each tissue using different predictors and cross validation strategies. **c)** Visualization of the predicted biological age (y-axis) contrasted with chronological age (x-axis) of each individual in each tissue.



Extended Data Fig. 3 | See next page for caption.

Extended Data Fig. 3 | Demonstration of the generalization of tissue clocks across various pathology foundation models. a) Description of the main characteristics of the models used. **b)** Performance of the pathology foundation models (mean absolute error, top; coefficient of determination, bottom) in prediction of age from WSIs. **c)** Association between age gaps and the length of

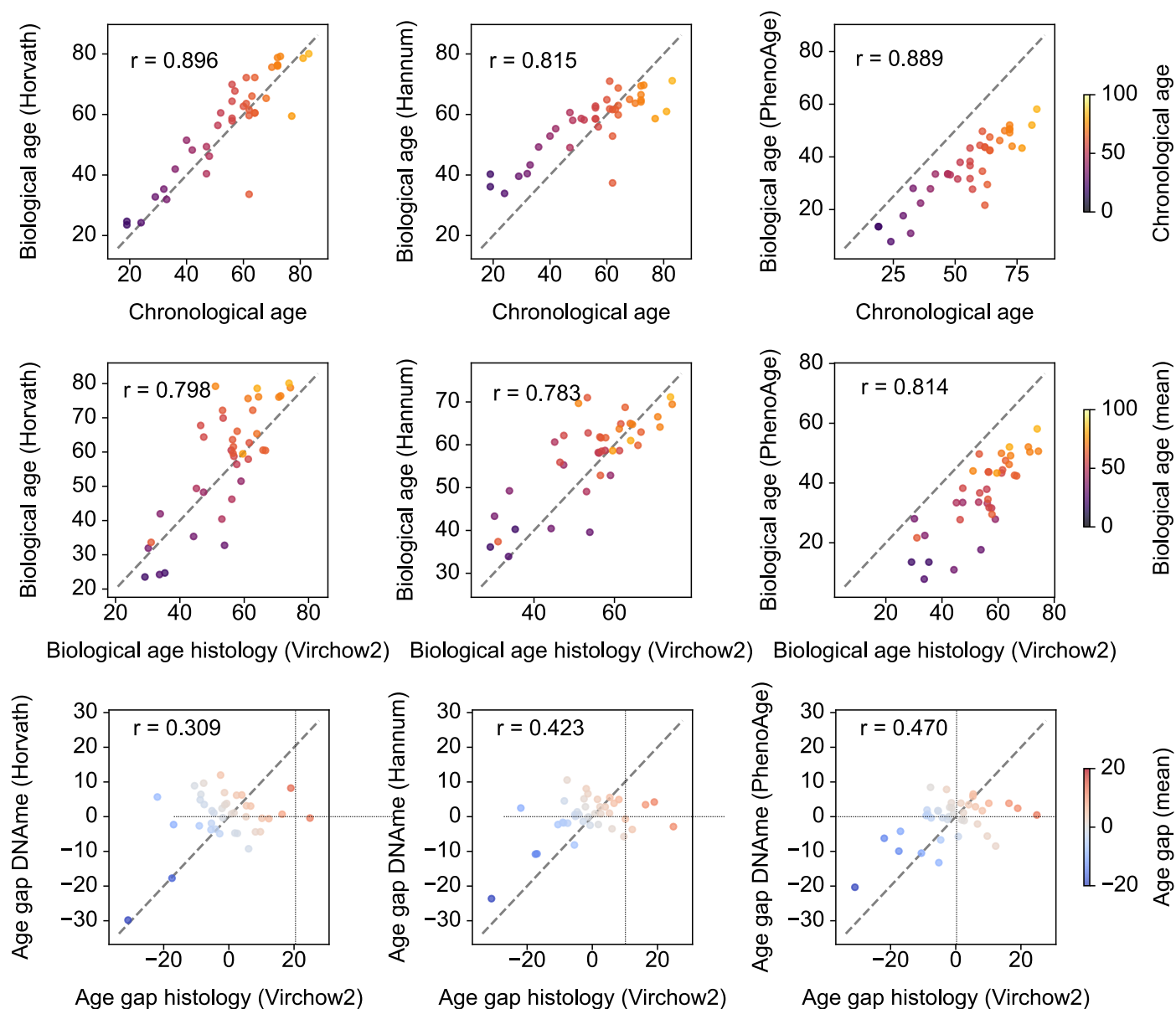
telomeres in the same samples. A negative coefficient denotes that with higher age telomeres tend to be shorter. Two-sided t-test for the regression coefficient, unadjusted p-value. **d)** Association between age gaps and the incidence of comorbidity. Two-sided t-test for the regression coefficient, unadjusted p-value. * p-value < 0.05.

a**b**

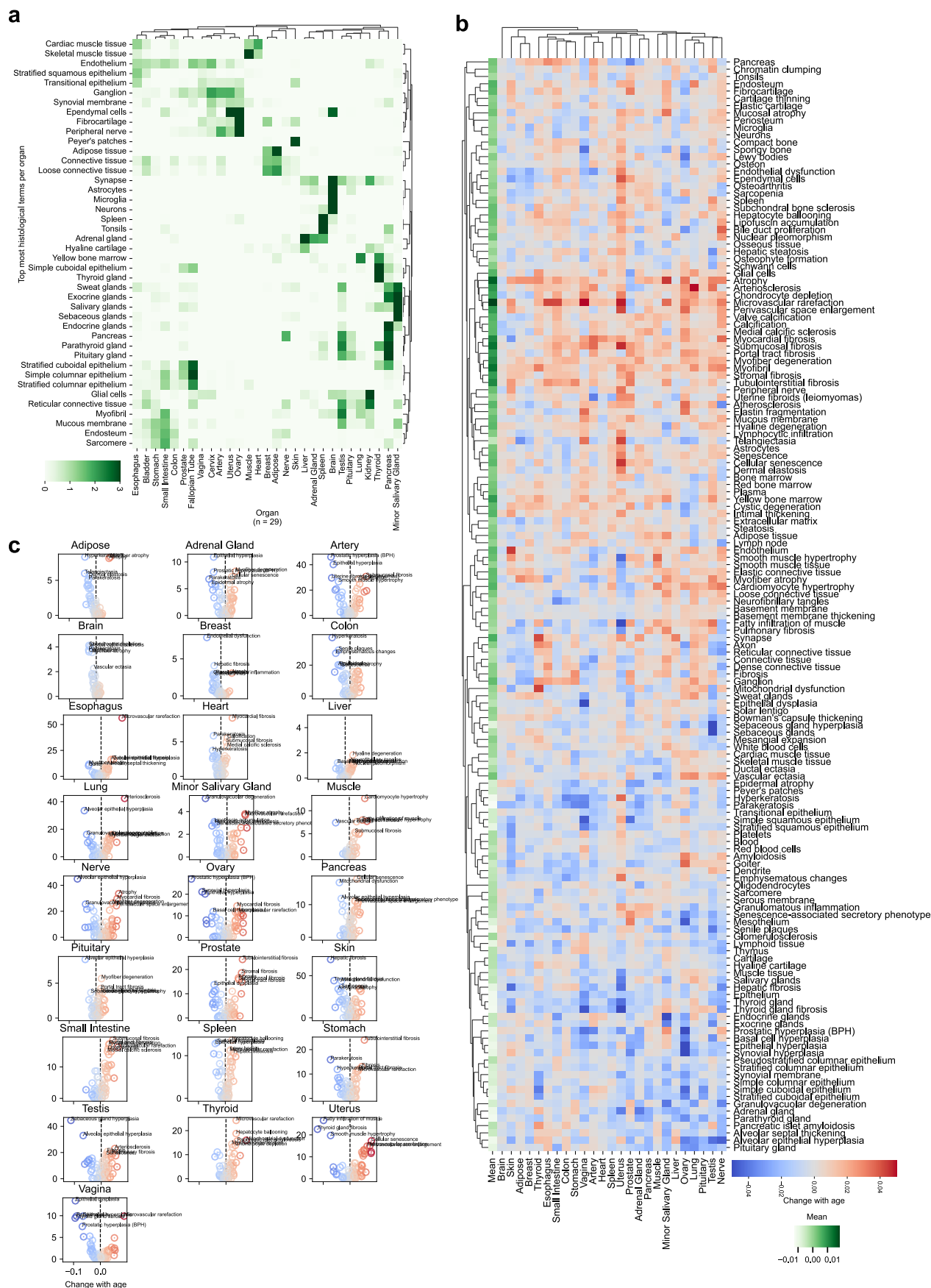
Extended Data Fig. 4 | See next page for caption.

Extended Data Fig. 4 | Application of histological tissue-clocks in independent cohorts. a) Cross-application of clocks derived from the GTEx cohort on the independent cohorts. Note that clocks trained on the corresponding tissue (diagonal) show the highest degree of agreement between estimated and true chronological age of the donors. The shaded area represents 95% CI of the regression line. **b)** Bland-Altman plots to assess agreement between

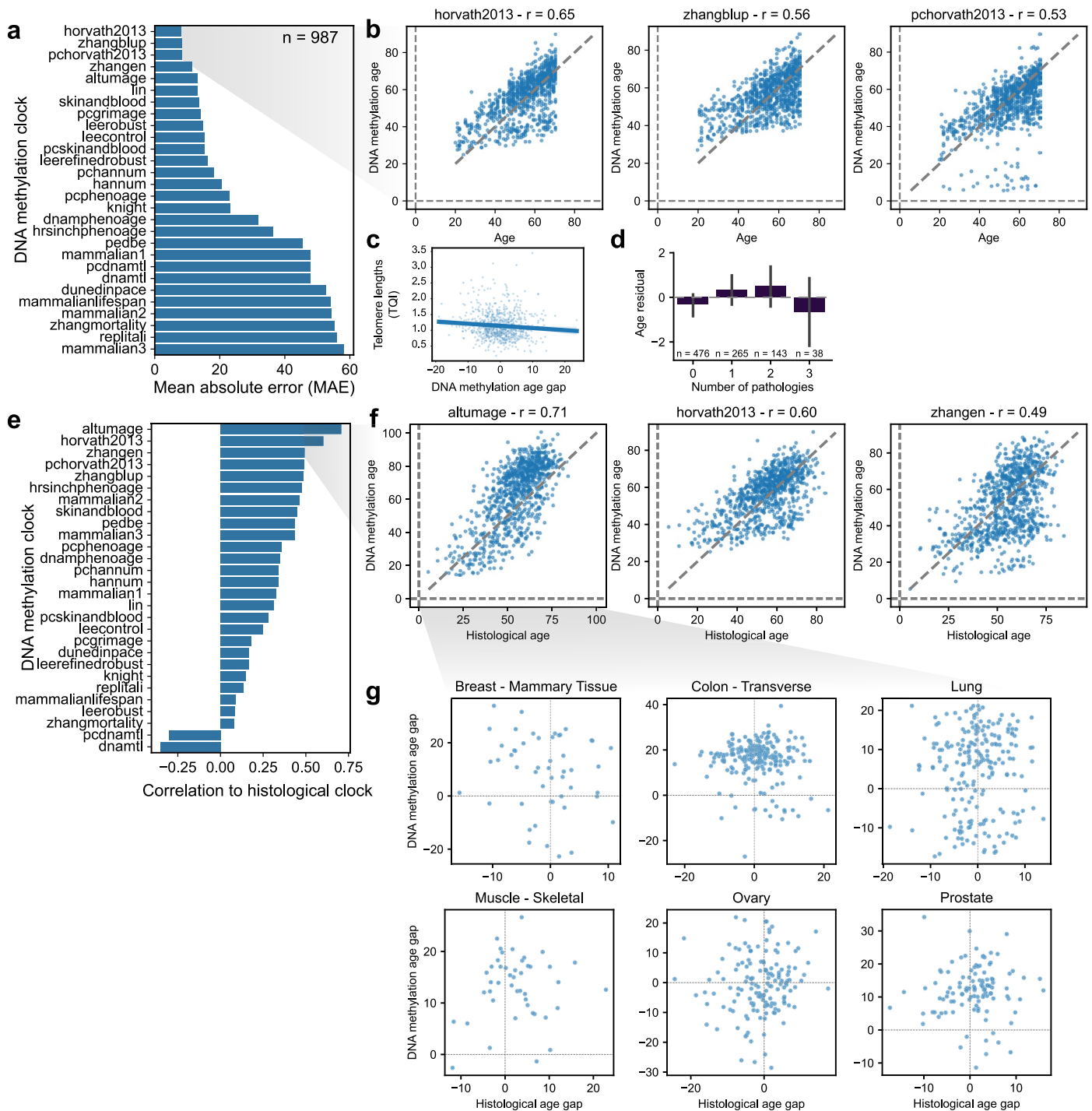
predicted biological age and chronological age. The x-axis indicates the mean agreement between chronological and biological age, whereas the y-axis indicates the bias (**b**), defined as the mean difference between predicted and chronological age, with 95% confidence interval. Limits of agreement (LOA) computed as $\text{bias} \pm 1.96 \times \text{standard deviation of differences}$ are indicated.



Extended Data Fig. 5 | Relationship between histologically derived biological age and age gaps and DNA methylation for an independent cohort of lung samples. Scatter plot with estimated biological age or age gaps for either of the two methods. We note considerable agreement between histological and DNAm-derived estimates.

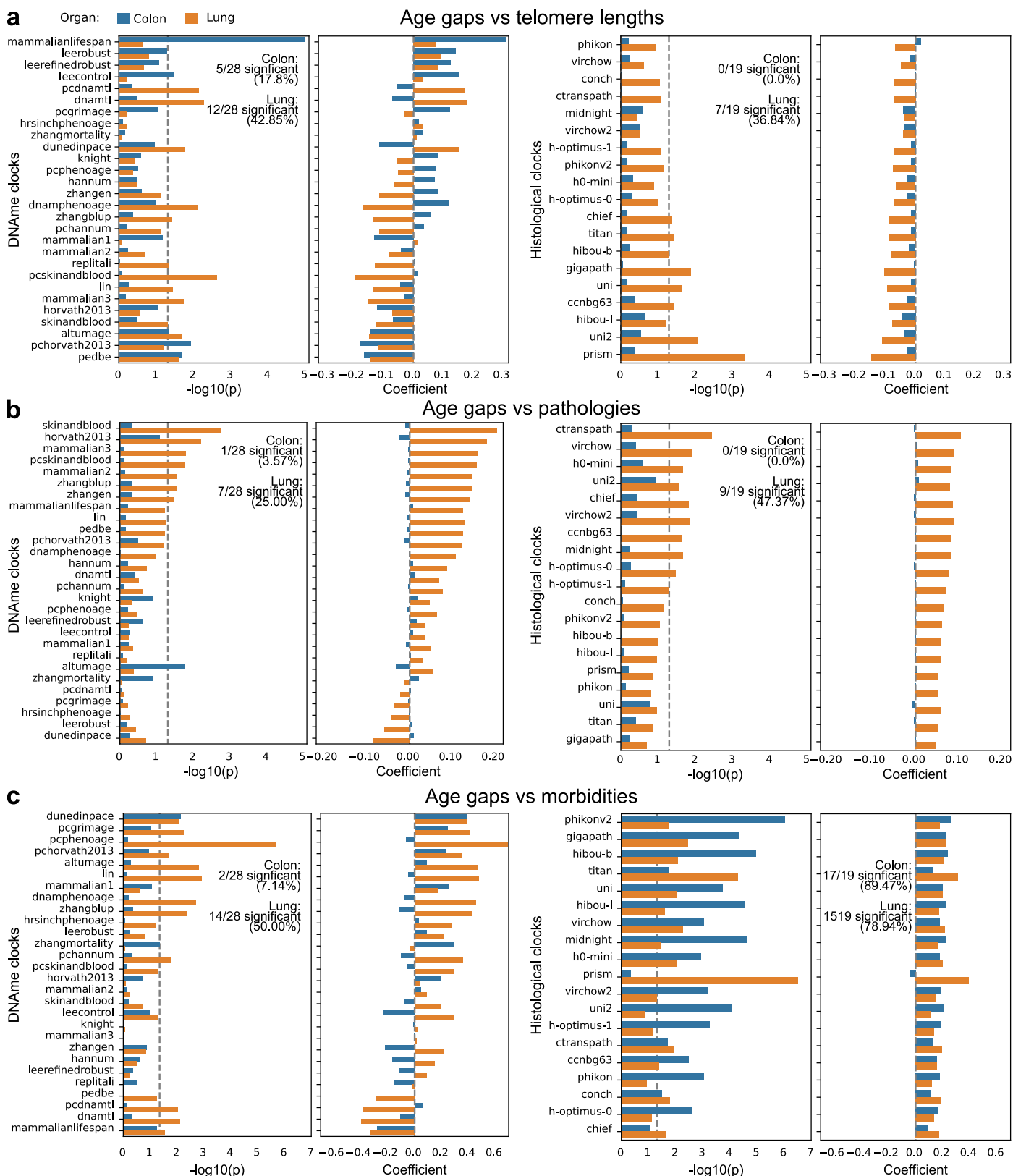


Extended Data Fig. 6 | Characterization of histological features associated with age gaps using multi-modal text-image models. a) Heatmap with the terms with highest value for each organ. b) Heatmap of changes in text terms with biological age estimates. c) Same as b) but as a volcano plot where the y-axis is the FDR-adjusted $-\log_{10}(p\text{-value})$.



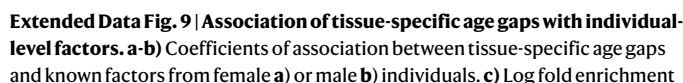
Extended Data Fig. 7 | Comparison of performance of tissue clocks to DNA methylation clocks. **a**) Mean absolute error for a variety of established DNA methylation clocks applied to the GTEx cohort (987 samples). **b**) Illustration of the 3 best performing DNA methylation clocks. **c**) Relationship between predicted age gaps using the Horvath2013 DNA methylation clock and telomere lengths of the same tissue samples. **d**) Enrichment of pathological terms

dependent on estimated DNA methylation age gap ($n = 922$ human donors). Data are represented as mean $\pm$ 95% CI. **e**) Pearson correlation values of DNA methylation and histological clocks. **f**) Illustration of the predictions of 3 most well correlated DNA methylation clocks and the predicted biological age from histological clocks. **g**) Relationship between predicted age gaps in the AltumAge DNA methylation clock and the age gap from histology.

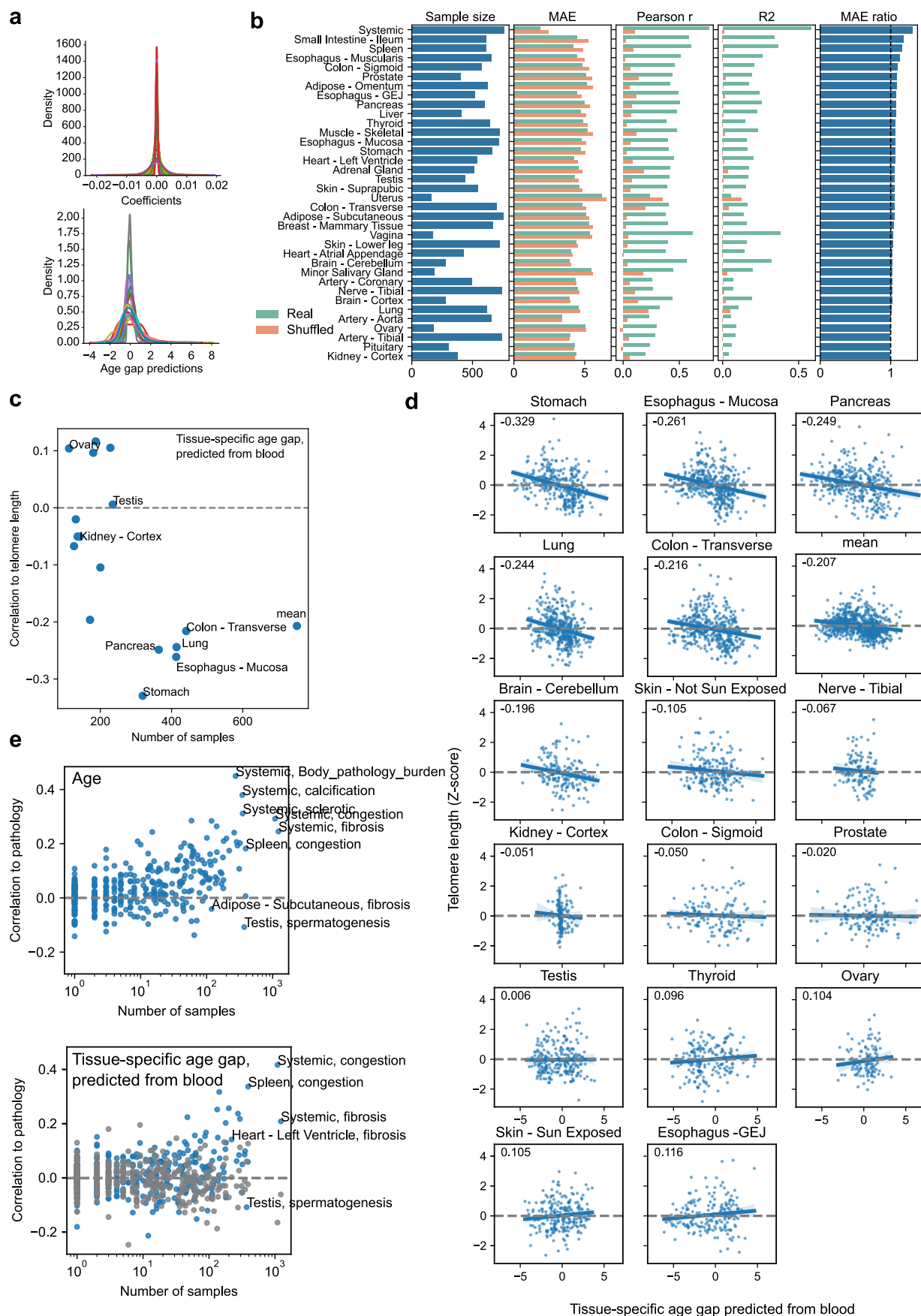


Extended Data Fig. 8 | Comparison of biological enrichment of tissue clocks to DNA methylation clocks. The effect size and significance of the association between age gaps derived by each modality and three classes of outcome are

shown for various predictors: **a)** telomere length, **b)** pathology and **c)** morbidity. The *P*-value was calculated using two-sided t-test for the regression coefficient without adjustment.



of effects between female and male individuals. **d-e)** Log fold enrichment between female and male individuals in the overall association with known factors **d)** and tissues **e)**.



Extended Data Fig. 10 | See next page for caption.

Extended Data Fig. 10 | Performance of tissue-specific age gaps predicted from blood. a) Distribution of estimated coefficients (top) or model residuals (bottom) for each organ. **b)** Performance metrics for each of the blood-based predictors. **c)** Correlation between blood-based predicted tissue-specific histological age gaps and telomere lengths for each tissue. **d)** As in **c)** but illustrating the relationship for each sample in each tissue. The Pearson

correlation value is indicated in the upper left corner of each plot. The shaded area represents 95% CI of the regression line. **e)** Correlation between chronological age (top) or blood-based tissue-specific histological age gaps (bottom) with incidence of tissue specific pathology. Each point is a tissue-pathology pair.

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Data collection	No software was used for data collection.
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GTEX whole slide images, RNA expression and DNA methylation data are available from its portal (<https://gtexportal.org>). The phenotypic data for the individuals are available from the dbGaP platform under accession phs000424.v9.p2. We make available the balanced datasets used to fine tune vision models at the following publicly available repository: <https://doi.org/10.5281/zenodo.13330659>. Processed data for the GTEX cohort is available at <https://10.5281/zenodo.20709093>. Restrictions apply to the availability of the datasets derived from post-mortem brain, skin, and lung samples that were used retrospectively for this project with institutional permission and are, thus, not publicly available. Data from the validation cohorts are available from GEO with accessions GSE66573, GSE72420, GSE72509, GSE84891, GSE89403, GSE102114, GSE109313, GSE110685, GSE111459, GSE112087, GSE113386, GSE120691, GSE123658, GSE123786/7, GSE124548, GSE125512, GSE129752, GSE131475, GSE134080, GSE136053, GSE136371, GSE143507, GSE147931/33, GSE151282, GSE159121, GSE160268, GSE161196, GSE161731, GSE162828, GSE169687, GSE171770, GSE174056, GSE184050, GSE184876/7, GSE185263, GSE186593, GSE187429, GSE199819, GSE206250, GSE206648, GSE208405, GSE212610, GSE222408.

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Reporting on sex and gender	We used the "Sex" variable available from the GTEX project. To maximize the sample size, models were trained across all donors using sex as a covariate, but we performed an associative analysis of demographic, lifestyle, and clinical factors in relation to age for each sex separately and report those metrics. Individual-level data will not be shared to comply with the policies from the GTEX project and dbGaP.
Reporting on race, ethnicity, or other socially relevant groupings	Race or ethnicity were not used in this study focusing on biological age estimation, as the GTEX dataset has known imbalances in racial and ethnic representation, limiting statistical power for subgroup analysis.
Population characteristics	983 individuals who experienced incidental death (no terminal disease) and whose tissues were collected under a rapid autopsy protocol. Ages ranged from 20 to 70 years old, with 33% female, 85% White, 13 % Black or African American, 1% Asian, 0.3% American Indian or Alaskan native.
Recruitment	The individuals were recruited by the GTEX project.
Ethics oversight	This study used publicly available data from the GTEX consortium, which was collected under protocols approved by the institutional review boards at participating institutions. Analysis of data from deceased donors is not classified as human subject research. The research adhered to all relevant guidelines for human data usage, as outlined by the GTEX consortium and relevant authorities.

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Sample size	No statistical methods were used to predetermine sample size due to the predetermined sample availability of the GTEX Project.
Data exclusions	3 samples were excluded from the study as they were annotated with the wrong tissue label: GTEX-1GMR2-0426', 'GTEX-1S82U-0426', 'GTEX-11ZTS-0426'.
Replication	We employed 5 fold cross validation to train tissue-based predictors and validated the blood based predictors in independent cohorts.
Randomization	The main target variable was chronological age which is provided by the GTEX dataset as an integer in years for each donor. We added covariates for ischemic time in minutes, sex, and mode of death. For the blood-based cohort the group allocation was predetermined by sample availability.

Blinding

Blinding was not feasible due to the inherent nature of model development and our goal of achieving biological interpretation for the observations. The main target variable - biological age estimation - was derived computationally, minimizing subjective bias in result interpretation. Additionally potential sources of bias were mitigated through objective quantitative metrics (cross validation, shuffled age controls, independent validation cohorts).

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State the research sample (e.g. Harvard university undergraduates, villagers in rural India) and provide relevant demographic information (e.g. age, sex) and indicate whether the sample is representative. Provide a rationale for the study sample chosen. For studies involving existing datasets, please describe the dataset and source.

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Describe the sampling procedure (e.g. random, snowball, stratified, convenience). Describe the statistical methods that were used to predetermine sample size OR if no sample-size calculation was performed, describe how sample sizes were chosen and provide a rationale for why these sample sizes are sufficient. For qualitative data, please indicate whether data saturation was considered, and what criteria were used to decide that no further sampling was needed.

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Provide details about the data collection procedure, including the instruments or devices used to record the data (e.g. pen and paper, computer, eye tracker, video or audio equipment) whether anyone was present besides the participant(s) and the researcher, and whether the researcher was blind to experimental condition and/or the study hypothesis during data collection.

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If no data were excluded from the analyses, state so OR if data were excluded, provide the exact number of exclusions and the rationale behind them, indicating whether exclusion criteria were pre-established.

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Describe the measures taken to verify the reproducibility of experimental findings. For each experiment, note whether any attempts to repeat the experiment failed OR state that all attempts to repeat the experiment were successful.

Randomization

Describe how samples/organisms/participants were allocated into groups. If allocation was not random, describe how covariates were controlled. If this is not relevant to your study, explain why.

Blinding

Describe the extent of blinding used during data acquisition and analysis. If blinding was not possible, describe why OR explain why blinding was not relevant to your study.

Did the study involve field work? ☐ Yes ☐ No

Field work, collection and transport

Field conditions	<i>Describe the study conditions for field work, providing relevant parameters (e.g. temperature, rainfall).</i>
Location	<i>State the location of the sampling or experiment, providing relevant parameters (e.g. latitude and longitude, elevation, water depth).</i>
Access & import/export	<i>Describe the efforts you have made to access habitats and to collect and import/export your samples in a responsible manner and in compliance with local, national and international laws, noting any permits that were obtained (give the name of the issuing authority, the date of issue, and any identifying information).</i>
Disturbance	<i>Describe any disturbance caused by the study and how it was minimized.</i>

Reporting for specific materials, systems and methods

We require information from authors about some types of materials, experimental systems and methods used in many studies. Here, indicate whether each material, system or method listed is relevant to your study. If you are not sure if a list item applies to your research, read the appropriate section before selecting a response.

Materials & experimental systems

Methods

n/a	Involved in the study	n/a	Involved in the study
☒	☐ Antibodies	☒	☐ ChIP-seq
☒	☐ Eukaryotic cell lines	☒	☐ Flow cytometry
☒	☐ Palaeontology and archaeology	☒	☐ MRI-based neuroimaging
☒	☐ Animals and other organisms		
☒	☐ Clinical data		
☒	☐ Dual use research of concern		
☒	☐ Plants		

Antibodies

Antibodies used	<i>Describe all antibodies used in the study; as applicable, provide supplier name, catalog number, clone name, and lot number.</i>
Validation	<i>Describe the validation of each primary antibody for the species and application, noting any validation statements on the manufacturer's website, relevant citations, antibody profiles in online databases, or data provided in the manuscript.</i>

Eukaryotic cell lines

Policy information about [cell lines and Sex and Gender in Research](#)

Cell line source(s)	<i>State the source of each cell line used and the sex of all primary cell lines and cells derived from human participants or vertebrate models.</i>
Authentication	<i>Describe the authentication procedures for each cell line used OR declare that none of the cell lines used were authenticated.</i>
Mycoplasma contamination	<i>Confirm that all cell lines tested negative for mycoplasma contamination OR describe the results of the testing for mycoplasma contamination OR declare that the cell lines were not tested for mycoplasma contamination.</i>
Commonly misidentified lines (See ICLAC register)	<i>Name any commonly misidentified cell lines used in the study and provide a rationale for their use.</i>

Palaeontology and Archaeology

Specimen provenance	<i>Provide provenance information for specimens and describe permits that were obtained for the work (including the name of the issuing authority, the date of issue, and any identifying information). Permits should encompass collection and, where applicable, export.</i>
Specimen deposition	<i>Indicate where the specimens have been deposited to permit free access by other researchers.</i>
Dating methods	<i>If new dates are provided, describe how they were obtained (e.g. collection, storage, sample pretreatment and measurement), where</i>

Dating methods

they were obtained (i.e. lab name), the calibration program and the protocol for quality assurance OR state that no new dates are provided.

☐ Tick this box to confirm that the raw and calibrated dates are available in the paper or in Supplementary Information.

Ethics oversight

Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Animals and other research organisms

Policy information about [studies involving animals](#); [ARRIVE guidelines](#) recommended for reporting animal research, and [Sex and Gender in Research](#)

Laboratory animals

For laboratory animals, report species, strain and age OR state that the study did not involve laboratory animals.

Wild animals

Provide details on animals observed in or captured in the field; report species and age where possible. Describe how animals were caught and transported and what happened to captive animals after the study (if killed, explain why and describe method; if released, say where and when) OR state that the study did not involve wild animals.

Reporting on sex

Indicate if findings apply to only one sex; describe whether sex was considered in study design, methods used for assigning sex. Provide data disaggregated for sex where this information has been collected in the source data as appropriate; provide overall numbers in this Reporting Summary. Please state if this information has not been collected. Report sex-based analyses where performed, justify reasons for lack of sex-based analysis.

Field-collected samples

For laboratory work with field-collected samples, describe all relevant parameters such as housing, maintenance, temperature, photoperiod and end-of-experiment protocol OR state that the study did not involve samples collected from the field.

Ethics oversight

Identify the organization(s) that approved or provided guidance on the study protocol, OR state that no ethical approval or guidance was required and explain why not.

Note that full information on the approval of the study protocol must also be provided in the manuscript.

Clinical data

Policy information about [clinical studies](#)

All manuscripts should comply with the ICMJE [guidelines for publication of clinical research](#) and a completed [CONSORT checklist](#) must be included with all submissions.

Clinical trial registration

Provide the trial registration number from ClinicalTrials.gov or an equivalent agency.

Study protocol

Note where the full trial protocol can be accessed OR if not available, explain why.

Data collection

Describe the settings and locales of data collection, noting the time periods of recruitment and data collection.

Outcomes

Describe how you pre-defined primary and secondary outcome measures and how you assessed these measures.

Dual use research of concern

Policy information about [dual use research of concern](#)

Hazards

Could the accidental, deliberate or reckless misuse of agents or technologies generated in the work, or the application of information presented in the manuscript, pose a threat to:

No Yes

☐ ☐ Public health

☐ ☐ National security

☐ ☐ Crops and/or livestock

☐ ☐ Ecosystems

☐ ☐ Any other significant area

Experiments of concern

Does the work involve any of these experiments of concern:

No Yes

- | | | |
|--------------------------|--------------------------|---|
| ☐ | ☐ | Demonstrate how to render a vaccine ineffective |
| ☐ | ☐ | Confer resistance to therapeutically useful antibiotics or antiviral agents |
| ☐ | ☐ | Enhance the virulence of a pathogen or render a nonpathogen virulent |
| ☐ | ☐ | Increase transmissibility of a pathogen |
| ☐ | ☐ | Alter the host range of a pathogen |
| ☐ | ☐ | Enable evasion of diagnostic/detection modalities |
| ☐ | ☐ | Enable the weaponization of a biological agent or toxin |
| ☐ | ☐ | Any other potentially harmful combination of experiments and agents |

Plants

Seed stocks

N/A

Novel plant genotypes

N/A

Authentication

N/A

ChIP-seq

Data deposition

- ☐ Confirm that both raw and final processed data have been deposited in a public database such as [GEO](#).
- ☐ Confirm that you have deposited or provided access to graph files (e.g. BED files) for the called peaks.

Data access links

May remain private before publication.

For "Initial submission" or "Revised version" documents, provide reviewer access links. For your "Final submission" document, provide a link to the deposited data.

Files in database submission

Provide a list of all files available in the database submission.

Genome browser session

(e.g. [UCSC](#))

Provide a link to an anonymized genome browser session for "Initial submission" and "Revised version" documents only, to enable peer review. Write "no longer applicable" for "Final submission" documents.

Methodology

Replicates

Describe the experimental replicates, specifying number, type and replicate agreement.

Sequencing depth

Describe the sequencing depth for each experiment, providing the total number of reads, uniquely mapped reads, length of reads and whether they were paired- or single-end.

Antibodies

Describe the antibodies used for the ChIP-seq experiments; as applicable, provide supplier name, catalog number, clone name, and lot number.

Peak calling parameters

Specify the command line program and parameters used for read mapping and peak calling, including the ChIP, control and index files used.

Data quality

Describe the methods used to ensure data quality in full detail, including how many peaks are at FDR 5% and above 5-fold enrichment.

Software

Describe the software used to collect and analyze the ChIP-seq data. For custom code that has been deposited into a community repository, provide accession details.

Flow Cytometry

Plots

Confirm that:

- ☐ The axis labels state the marker and fluorochrome used (e.g. CD4-FITC).
- ☐ The axis scales are clearly visible. Include numbers along axes only for bottom left plot of group (a 'group' is an analysis of identical markers).
- ☐ All plots are contour plots with outliers or pseudocolor plots.
- ☐ A numerical value for number of cells or percentage (with statistics) is provided.

Methodology

Sample preparation	<i>Describe the sample preparation, detailing the biological source of the cells and any tissue processing steps used.</i>
Instrument	<i>Identify the instrument used for data collection, specifying make and model number.</i>
Software	<i>Describe the software used to collect and analyze the flow cytometry data. For custom code that has been deposited into a community repository, provide accession details.</i>
Cell population abundance	<i>Describe the abundance of the relevant cell populations within post-sort fractions, providing details on the purity of the samples and how it was determined.</i>
Gating strategy	<i>Describe the gating strategy used for all relevant experiments, specifying the preliminary FSC/SSC gates of the starting cell population, indicating where boundaries between "positive" and "negative" staining cell populations are defined.</i>

- ☐ Tick this box to confirm that a figure exemplifying the gating strategy is provided in the Supplementary Information.

Magnetic resonance imaging

Experimental design

Design type	<i>Indicate task or resting state; event-related or block design.</i>
Design specifications	<i>Specify the number of blocks, trials or experimental units per session and/or subject, and specify the length of each trial or block (if trials are blocked) and interval between trials.</i>
Behavioral performance measures	<i>State number and/or type of variables recorded (e.g. correct button press, response time) and what statistics were used to establish that the subjects were performing the task as expected (e.g. mean, range, and/or standard deviation across subjects).</i>

Acquisition

Imaging type(s)	<i>Specify: functional, structural, diffusion, perfusion.</i>
Field strength	<i>Specify in Tesla</i>
Sequence & imaging parameters	<i>Specify the pulse sequence type (gradient echo, spin echo, etc.), imaging type (EPI, spiral, etc.), field of view, matrix size, slice thickness, orientation and TE/TR/flip angle.</i>
Area of acquisition	<i>State whether a whole brain scan was used OR define the area of acquisition, describing how the region was determined.</i>
Diffusion MRI	☐ Used ☐ Not used

Preprocessing

Preprocessing software	<i>Provide detail on software version and revision number and on specific parameters (model/functions, brain extraction, segmentation, smoothing kernel size, etc.).</i>
Normalization	<i>If data were normalized/standardized, describe the approach(es): specify linear or non-linear and define image types used for transformation OR indicate that data were not normalized and explain rationale for lack of normalization.</i>
Normalization template	<i>Describe the template used for normalization/transformation, specifying subject space or group standardized space (e.g. original Talairach, MNI305, ICBM152) OR indicate that the data were not normalized.</i>
Noise and artifact removal	<i>Describe your procedure(s) for artifact and structured noise removal, specifying motion parameters, tissue signals and physiological signals (heart rate, respiration).</i>

Volume censoring

Define your software and/or method and criteria for volume censoring, and state the extent of such censoring.

Statistical modeling & inference

Model type and settings

Specify type (mass univariate, multivariate, RSA, predictive, etc.) and describe essential details of the model at the first and second levels (e.g. fixed, random or mixed effects; drift or auto-correlation).

Effect(s) tested

Define precise effect in terms of the task or stimulus conditions instead of psychological concepts and indicate whether ANOVA or factorial designs were used.

Specify type of analysis: ☐ Whole brain ☐ ROI-based ☐ Both

Statistic type for inference

Specify voxel-wise or cluster-wise and report all relevant parameters for cluster-wise methods.

(See [Eklund et al. 2016](#))

Correction

Describe the type of correction and how it is obtained for multiple comparisons (e.g. FWE, FDR, permutation or Monte Carlo).

Models & analysis

n/a | Involved in the study

☐ ☐ Functional and/or effective connectivity

☐ ☐ Graph analysis

☐ ☐ Multivariate modeling or predictive analysis

Functional and/or effective connectivity

Report the measures of dependence used and the model details (e.g. Pearson correlation, partial correlation, mutual information).

Graph analysis

Report the dependent variable and connectivity measure, specifying weighted graph or binarized graph, subject- or group-level, and the global and/or node summaries used (e.g. clustering coefficient, efficiency, etc.).

Multivariate modeling and predictive analysis

Specify independent variables, features extraction and dimension reduction, model, training and evaluation metrics.