

Genetics of brain age suggest an overlap with common brain disorders

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Numerous genetic and environmental factors contribute to psychiatric disorders and other brain disorders. Common risk factors likely converge on biological pathways regulating the optimization of brain structure and function across the lifespan. Here, using structural magnetic resonance imaging and machine learning, we estimated the gap between brain age and chronological age in 36,891 individuals aged 3 to 96 years, including individuals with different brain disorders. We show that several disorders are associated with accentuated brain aging, with strongest effects in schizophrenia, multiple sclerosis and dementia, and document differential regional patterns of brain age gaps between disorders. In 16,269 healthy adult individuals, we show that brain age gap is heritable with a polygenic architecture overlapping those observed in common brain disorders. Our results identify brain age gap as a genetically modulated trait that offers a window into shared and distinct mechanisms in different brain disorders.

Psychiatric disorders and other brain disorders are among the main contributors to morbidity and disability around the world¹, often placing debilitating disadvantages on the individual². The disease mechanisms are complex, spanning a wide range of genetic and environmental contributing factors³. The inter-individual variability is large, but on a group-level, patients with common brain disorders perform worse on cognitive tests, are less likely to excel professionally, and engage in adverse health behaviours more frequently⁴.

Dynamic processes influencing the rate of maturation and change throughout the lifespan play a critical role, as reflected in the wide range of disease onset times from early childhood to old age⁵. This suggests that the age at which individual trajectories diverge from the norm is a key characteristic in the underlying pathophysiology. Whereas autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) have onset in childhood⁶, schizophrenia

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(SZ) and bipolar (BD) spectrum disorders likely evolve during adolescence, before the outbreak of severe symptoms, which is typically in early adulthood^{6,7}. Likewise, multiple sclerosis (MS) most often presents itself in early adulthood but the disease process likely starts much earlier^{8,9}. First episodes in major depressive disorder (MDD) can appear at any stage from adolescence to old age^{6,10}, whereas mild cognitive impairment (MCI) and dementia (DEM) most often evolve in old age¹¹. When attempting to decode the underlying brain dysfunction of these disorders, age-related deviations from the norm may also differ in terms of spatial location, direction, change rate and magnitude, all of which add complexity to the interpretation of observed effects.

Magnetic resonance imaging (MRI) is a powerful tool to unveil abnormal brain development^{12,13} and age-related degeneration^{14,15}. Machine learning techniques enable robust estimation of the biological age of the brain using MRI-derived features¹⁶, and initial evidence suggests that a deviation between brain and chronological age – termed the *brain age gap* – is present in several brain disorders¹⁷. These findings may render brain age gap a promising marker of brain health¹⁷, but several critical issues remain to be addressed. First, while advantageous for narrowing the complexity, reducing a rich set of brain imaging features into a single estimate of brain age inevitably compromises spatial specificity, thereby potentially removing disorder-specific patterns. Second, most studies so far have been rather small-scale, performed within a limited age range and focusing on a single disorder, which left them unable to uncover clinical specificity and lifespan dynamics. Third, the genetic underpinnings of brain age gap are not understood and it is unknown to what degree they overlap with the genetic architecture of major clinical traits. To address these critical knowledge gaps, large imaging genetics samples covering a range of prevalent brain disorders are necessary.

The availability of unprecedented sample sizes of neuroimaging and genetics data through global data sharing and population-based efforts provide new opportunities for accurate

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modelling of lifespan differences in brain anatomy and its application to brain disorders¹⁸. Here, we have gathered raw structural MRI data from a large number of individuals. We employed a centralized and harmonized processing protocol including automated surface-based morphometry and subcortical segmentation using Freesurfer¹⁹ (**Suppl. Fig. 1**). The main analysis in this study is based on data from 36,891 individuals aged 3 to 96 years that passed quality control, representing the largest brain imaging study on brain age to date.

This sample included data from healthy controls (HC; $n = 30,967$; 3-95 years), as well as from 5924 individuals with diverse brain disorders with typical onset age distributed across the lifespan^{6,11}. We included data from individuals with ASD ($n = 975$; 5-64 years) and ADHD ($n = 751$; 7-62 years), individuals with prodromal SZ or at risk mental state (SZRISK; $n = 98$; 16-42 years), individuals with SZ ($n = 1,145$; 18-66 years), a heterogeneous group with mixed diagnoses in the psychosis spectrum (PSYMIX; $n = 294$; 18-69 years), individuals with BD ($n = 445$; 18-66 years), MS ($n = 254$; 19-68 years), MDD ($n = 211$; 18-71 years), MCI ($n = 992$; 38-91 years), and DEM (including Alzheimer's disease (AD); $n = 759$; 53-96 years). **Supplementary Tables 1 and 2** provide details on the sample's characteristics.

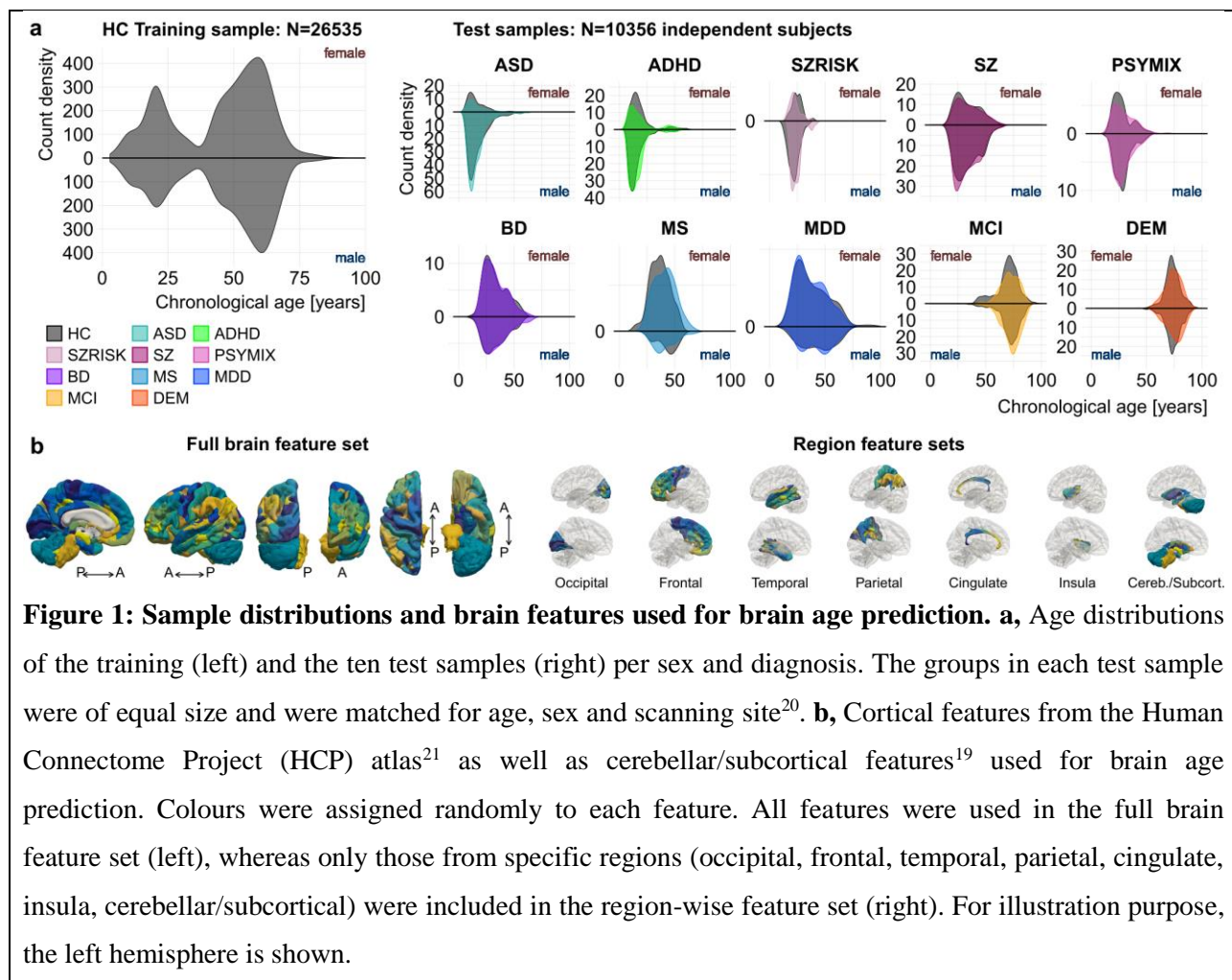
Brain age prediction across brain disorders

We used machine learning to estimate individual biological brain age based on structural brain imaging features. First, we grouped all subjects into different samples. For each of the ten clinical groups, we identified a group of healthy individuals of equal size, matched on age, sex and scanning site using propensity score matching²⁰. All remaining individuals were joined into one sample comprising healthy individuals only. The latter constituted a training sample, used to train and tune the machine learning models for age prediction ($n = 26,535$; 14,182 females and 12,353

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males, aged 3-89 years), whereas the ten clinical samples were used as independent test samples.

Figure 1a illustrates the respective age distributions per sex and diagnosis.



The large sample size and wide age-span of the training sample allowed us to model male and female brain age separately, thereby accounting for potential sexual dimorphisms in brain structural lifespan trajectories. For each sex, we built a machine learning model based on gradient tree boosting (*xgboost*)²² to predict the age of the brain from a set of thickness, area and volume features extracted using a multi-modal parcellation of the cerebral cortex²¹ as well as a set of cerebellar/subcortical volume features¹⁹ (1,118 features in total, **Fig. 1b**). Five-fold cross-validations confirmed the validity of the models, yielding high correlations between chronological age and predicted brain age ($r=.94$ and $r=.95$ for the female and male model,

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respectively; **Suppl. Fig. 2**). Next, we applied the models to predict brain age for each individual in the ten independent test samples, and tested for effects of diagnosis on the brain age gap. We used mega-analysis (across-site analysis) as the main statistical framework as it may best exploit the benefits of the big data approach, while also providing results from a meta-analysis framework in the supplement. We controlled all associations and group differences reported in this paper for age, age², sex, and scanning site. Further, to rule out confounding effects of data quality on the results²³, we repeated the main analyses using a more stringent multivariate quality control and exclusion procedure²⁴.

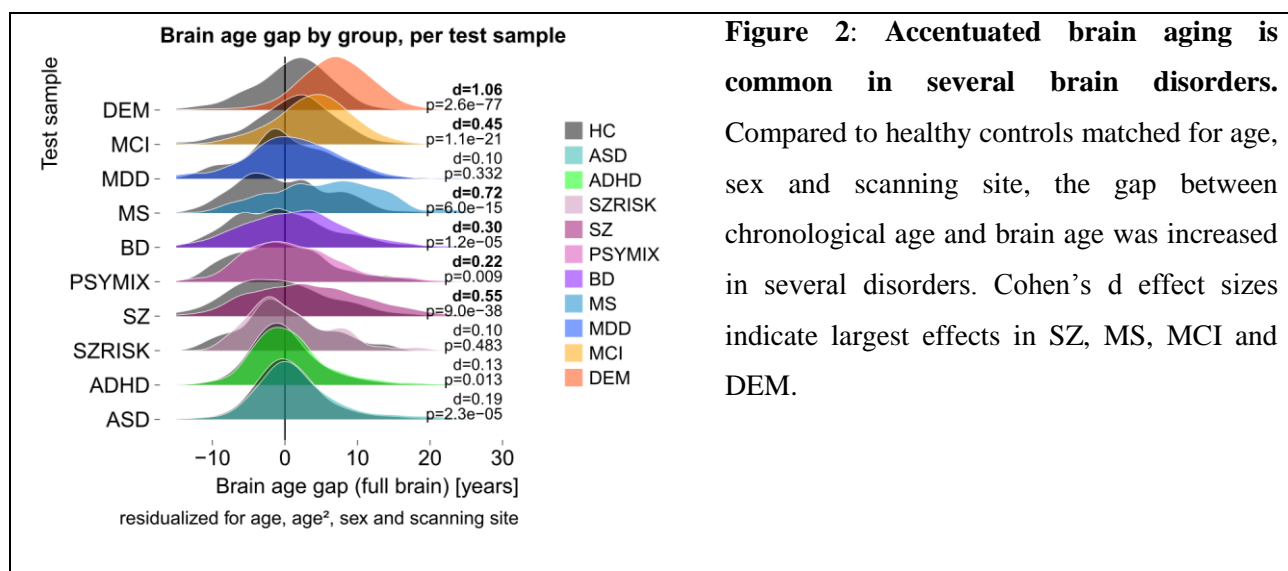


Figure 2: Accentuated brain aging is common in several brain disorders. Compared to healthy controls matched for age, sex and scanning site, the gap between chronological age and brain age was increased in several disorders. Cohen's d effect sizes indicate largest effects in SZ, MS, MCI and DEM.

Figure 2 illustrates that the brain age gap was increased in several brain disorders. Strongest effects were observed in SZ (Cohen's $d = 0.55$), MS ($d = 0.72$), MCI ($d = 0.45$) and DEM ($d = 1.06$). PSYMIX ($d = 0.22$) and BD ($d = 0.30$) showed small effects of increased brain age gap, whereas other groups showed negligible effects. The meta-analysis converged on the same findings (**Suppl. Fig. 3**) and the results replicated regardless of the quality control exclusion criterion applied (**Suppl. Fig. 4**). Compared to matched healthy controls, the average brain age gap was estimated to 1.1 years for ASD, 0.7 years for ADHD, 0.6 years for SZRISK, 3.9 years for SZ, 1.4 years for PSYMIX, 2.0 years for BD, 5.6 years for MS, 0.8 years for MDD, 3.0 years

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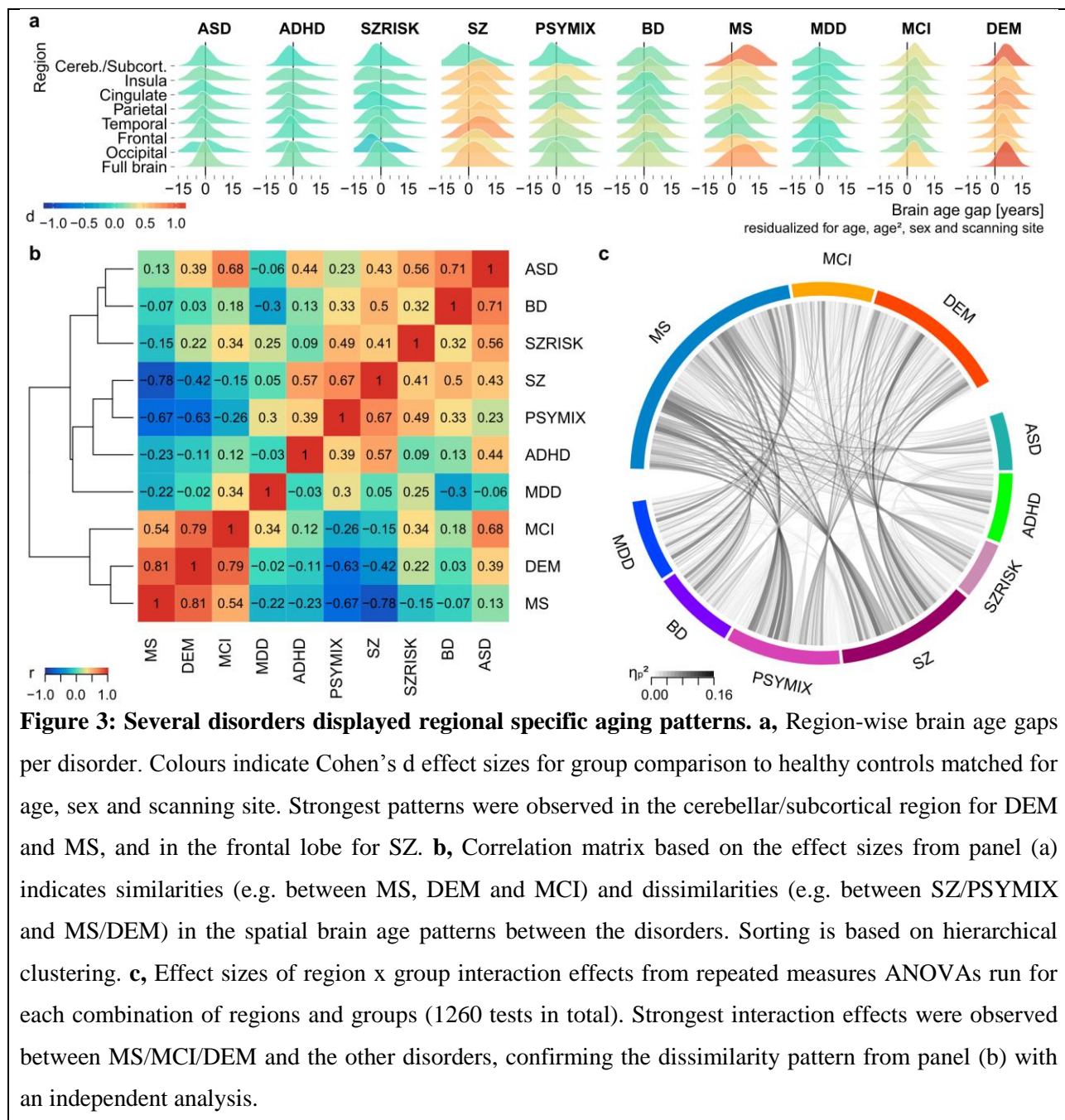
for MCI and 5.8 years for DEM. The brain age gap in all clinical groups was positive and there were no signs of a negative brain age gap (delay) in children with ASD or ADHD.

Regional specificity of brain age gap

We assessed the specificity of the spatial brain age gap patterns across clinical groups. We trained age prediction models similar to those for the full brain above, including only occipital, frontal, temporal, parietal, cingulate, insula, or cerebellar/subcortical features (**Fig. 1b**). Cross-validation confirmed the predictive performance of all regional models (**Suppl. Fig. 2**), so we used these to predict regional brain age in the ten independent test sets. Region-wise brain age gaps often corresponded to the ones observed on the full brain level, yet some notable differences in the spatial patterns of the disorders emerged (**Fig. 3a**). For example, increased cerebellar/subcortical age gap was most prominent in DEM ($d = 0.99$) and MS ($d = 0.89$) but was not present in SZ ($d = 0.08$). The largest effect in SZ was observed in the frontal lobe ($d = 0.71$). In PSYMIX, brain age gaps in the insula ($d = 0.39$) and the temporal lobe ($d = 0.34$) were larger than the brain age gap observed on the full brain level ($d = 0.22$). A brain age gap in the temporal lobe was observed in MDD ($d = 0.26$), whereas there was no evidence for a brain age gap in ASD or ADHD in any of the regions.

Figure 3b illustrates a hierarchical clustering of clinical groups based on region-wise effect sizes. One cluster of groups with similar spatial brain age gap patterns comprised MS, MCI and DEM, whereas the other groups formed a second cluster. Notably, the spatial patterns of the groups in the first cluster were negatively associated with several disorders in the second cluster, pointing toward spatial specificity of these disorders.

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To explore these differences further, we tested for group x region interactions on each pairwise combination of clinical groups and pairwise combination of region-wise brain age gaps (1260 tests). **Figure 3c** illustrates the effect sizes for all resulting group x region interactions. Confirming the results from **Figure 3b**, strongest interaction effects were observed between the groups from cluster 1 and those from cluster 2. For example, the three strongest interaction

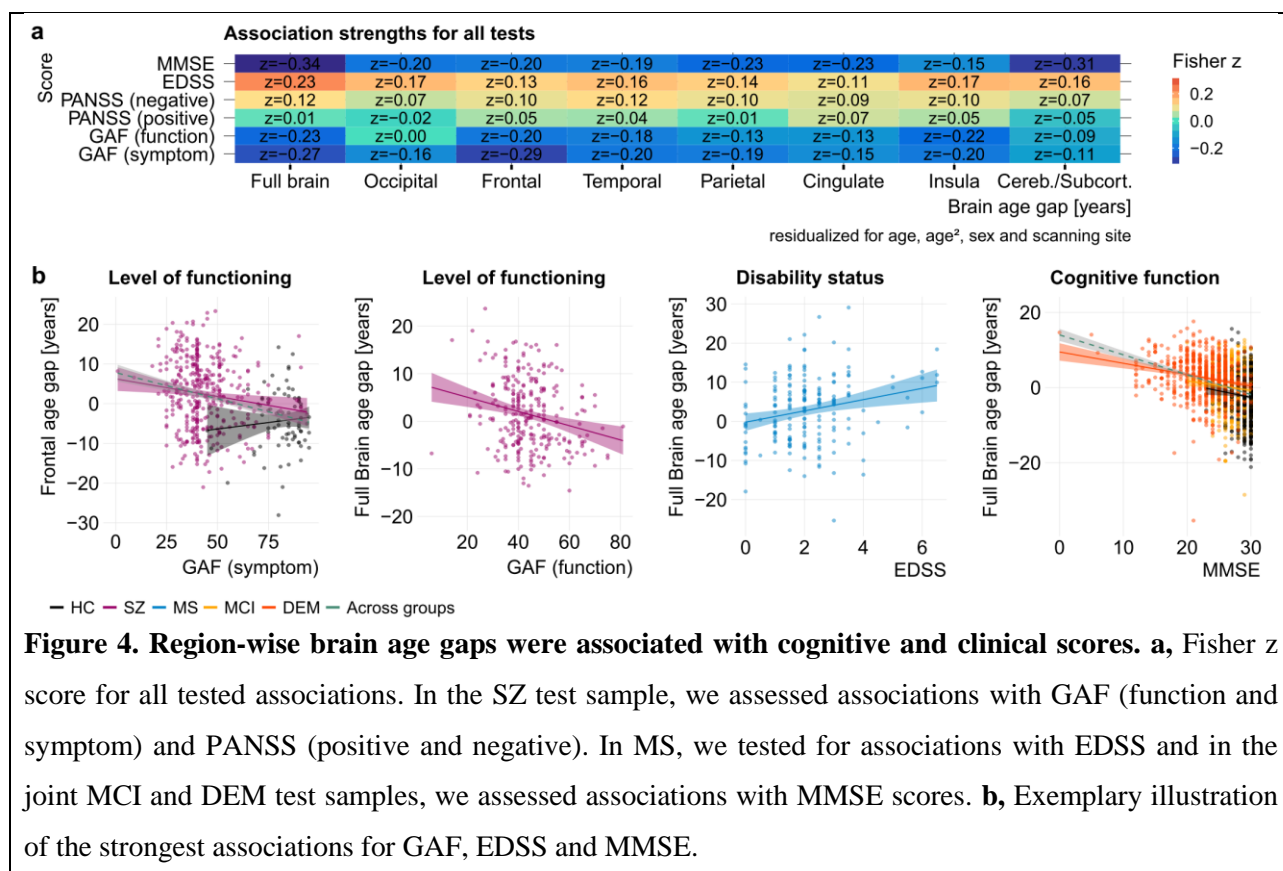
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effects indicated that brain age gaps for frontal and cerebellar/subcortical regions diverged mostly between MS and SZ (Partial Eta squared $\eta_p^2 = 0.16$), MS and PSYMIX ($\eta_p^2 = 0.15$) and between SZ and DEM ($\eta_p^2 = 0.15$; **Suppl. Fig. 5** provides effect sizes for all tests). Together, these results demonstrate that several common disorders affecting the brain show anatomically differential patterns of increased brain age gap, indicating that the rate at which different regions age in relation to each other oftentimes showed opposite patterns between disorders typically considered neurodevelopmental and neurodegenerative disorders, respectively.

With converging findings suggesting largest brain age gaps in SZ, MS, MCI and DEM, we explored the functional relevance of the region-wise brain age gaps for these groups, testing for associations with clinical and cognitive data. Clinical data available in the SZ test sample included symptom ($n = 81$ HC, $n = 391$ SZ) and function ($n = 271$ SZ) scores of the Global Assessment of Functioning scale²⁵ (GAF) as well as positive ($n = 57$ HC, $n = 653$ SZ) and negative ($n = 57$ HC, $n = 655$ SZ) scores of the Positive and Negative Syndrome Scale²⁶ (PANSS). In the MS test sample, we assessed associations with scores from the Expanded Disability Status Scale²⁷ (EDSS, $n = 188$ MS) and in the joint MCI and DEM test samples, we assessed associations with Mini Mental State Examination scores²⁸ (MMSE, $n = 901$ HC, $n = 921$ MCI, $n = 707$ DEM). **Figure 4a** depicts association strengths for all tests and **Figure 4b** illustrates the strongest association for each test, except for the PANSS scores where only weak associations were found. In SZ, larger brain age gaps were associated with lower functioning, in particular for full brain, frontal, temporal and insula brain age gaps (GAF function all $z < -0.18$, all $P < 0.003$; GAF symptom all $z < -0.20$, all $P < 2 \times 10^{-5}$). In MS, larger brain age gap was associated with higher disability, in particular for the full brain age gap ($z = 0.23$, $P = .001$). Finally, lower cognitive functioning was associated with larger brain age gaps in the joint

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MCI/DEM samples, with strongest effects for full brain ($z = -0.34$, $P = 4 \times 10^{-65}$) and cerebellar/subcortical ($z = -0.31$, $P = 2 \times 10^{-53}$) brain age gaps.



The genetic architecture of brain age gap

Given the known genetic contributions to brain disorders, our results pose the question to what degree brain age patterns are genetically constrained and if the implied genes overlap with the polygenic architectures of the disorders. In our cohorts, single nucleotide polymorphism (SNP) data were available for 16,269 adult healthy controls with European ancestry, after disregarding subsets with data from clinical groups, children and individuals with non-European ancestry, all of which were too small to warrant an analysis. We estimated full and region-wise brain age for these individuals using 5-fold cross-validation in a model trained on all healthy controls ($n = 30,967$) and regressed age, age², sex, and scanning site effects from the resulting brain age gaps.

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First, we ran genome-wide complex trait analysis (GCTA²⁹) across all 16,269 individuals, including the first four population components from multidimensional scaling as covariates to further control for population stratification. The results revealed significant heritability (**Fig. 5a**), with common SNPs explaining 18.3% of the variance in brain age gap across all individuals (full brain, $h^2_{\text{SNP}} = 0.1828$, $\text{SE} = 0.02$, $P < 1 \times 10^{-16}$) and 11.1-18.4% of the variance in region-wise brain age gaps (all $P < 2 \times 10^{-9}$).

Next, we assessed the overlap between the genetic underpinnings of brain age gap and common brain disorders. Focusing on those disorders that showed a significant brain age gap in the main analysis, we gathered genome-wide association analysis (GWAS) summary statistics for SZ and BD from the Psychiatric Genomics Consortium^{30,31}, MS from the International Multiple Sclerosis Genetics Consortium³², and AD from the International Genomics of Alzheimer's Project³³. In addition, we performed GWAS on the full brain and region-wise brain age gaps in the above-described set of 16,269 healthy controls. We used conditional Q-Q plots³⁴ to assess polygenic overlap between two complex traits, conditioning GWAS summary statistics from each of the brain age gaps on GWAS summary statistics from each of the disorders. Notably, our results indicate genetic overlap between brain age gap and brain disorders. **Figure 5b** provides exemplary illustrations of conditional Q-Q plots for the frontal brain age gap stratified by SZ, the cingulate brain age gap stratified by BD and the full brain age gap stratified by MS. When selecting subsets of SNPs based on their associations with the disorders, the nominal $-\log_{10}$ transformed P-values of the brain age gaps deviated from the trajectories expected under the global null hypothesis, indicating that the brain age gaps are enriched for SNP associations with the relevant disorder. SZ and MS also showed patterns of enrichment with subcortical brain age gap and BD with frontal brain age gap, whereas no clear patterns were observed for AD (**Suppl. Fig. 6**).

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Next, we combined GWAS summary statistics of brain age gaps and the disorders in conjunctive FDR analyses^{35,36}, to identify SNPs that are associated with both phenotypes. We found 15 independent, significant loci showing pleiotropy between brain age gaps and SZ (2 occipital, 4 frontal, 3 temporal, 1 parietal, 2 cingulate, 1 insula, 2 cerebellar/subcortical; 116 SNPs in total), 6 loci for BD (3 frontal, 2 cingulate, 1 insula; 40 SNPs in total), 7 loci for MS (2 full brain, 2 frontal, 1 temporal, 2 subcortical; 7 SNPs in total) and 1 locus for AD (temporal, 1 SNP), respectively (**Suppl. Table 3**). An intronic variant (rs940904) in protein coding gene PITPNM2 at chromosome 12q24.31 underlying the frontal brain age gap significantly overlapped both with SZ and MS.

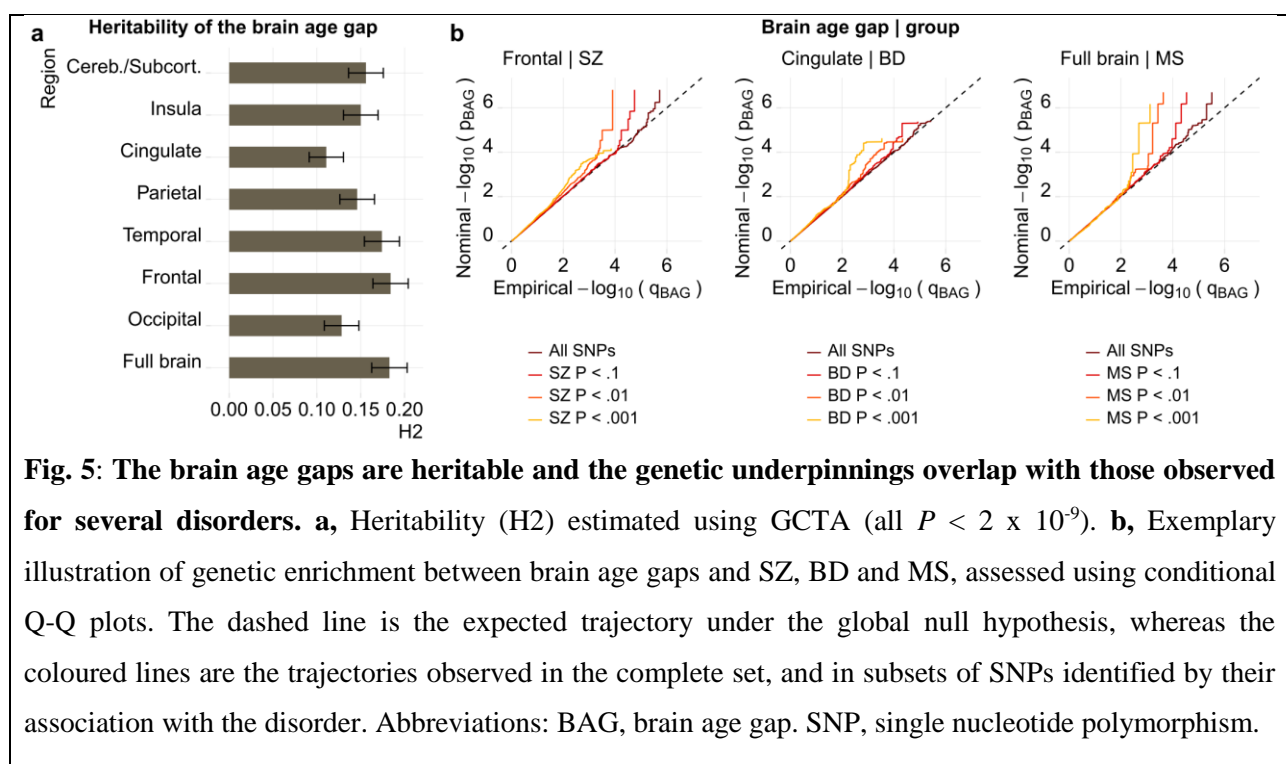


Fig. 5: The brain age gaps are heritable and the genetic underpinnings overlap with those observed for several disorders. **a**, Heritability (H^2) estimated using GCTA (all $P < 2 \times 10^{-9}$). **b**, Exemplary illustration of genetic enrichment between brain age gaps and SZ, BD and MS, assessed using conditional Q-Q plots. The dashed line is the expected trajectory under the global null hypothesis, whereas the coloured lines are the trajectories observed in the complete set, and in subsets of SNPs identified by their association with the disorder. Abbreviations: BAG, brain age gap. SNP, single nucleotide polymorphism.

Discussion

Taken together, our results provide strong evidence that several common brain disorders are associated with accentuated aging of the brain compared to chronological age, with effects observed in SZ, PSYMI, BD, MS, MDD, MCI and DEM; but not in ASD, ADHD or SZRISK.

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Importantly, we revealed a distinct neuroanatomical distribution of brain age gaps in several disorders. Associations with clinical and cognitive data underlined the functional relevance of the brain age gaps and genetic analyses in healthy controls provided evidence that the brain age gaps are heritable, with overlapping genes implicated in the genetic underpinnings of brain age gaps and common brain disorders.

Our approach of estimating brain age at the level of brain regions was useful to reveal differential spatial patterns between disorders. Whereas the implicated regions in the spatial brain age profiles of the disorders matched previously reported structural and functional abnormalities (e.g. frontal in SZ³⁷⁻³⁹, or the widespread volume loss in AD with large effects in subcortical structures⁴⁰), our region-wise brain age approach preserved the well-established benefit of down-sampling a large number of brain imaging features into a highly condensed and interpretable score without a total loss of spatial sensitivity. As such, the analysis revealed substantial differences in spatial aging profiles between disorders typically regarded neurodegenerative disorders (MS, MCI, DEM) and disorders with established neurodevelopmental sources, especially SZ and PSY MIX. Whereas these disorders were all associated with an increased brain age gap on the full brain level, the region-wise analysis uncovered an interaction between the frontal brain age patterns observed in SZ and PSY MIX and the cerebellar/subcortical patterns observed in MS and DEM. Moreover, brain age gaps covered functional relevance beyond the group differences. We identified significant associations with clinical and cognitive data, in particular with scores of the Global Assessment of Functioning scale²⁵ in SZ, with the Expanded Disability Status Scale²⁷ in MS and with Mini Mental State Examination scores²⁸ in the dementia spectrum. These results may warrant further research in which the link between the rate of changes in brain age gaps and the clinical and cognitive outcome can be studied in a longitudinal setting. Depending on the sensitivity of such associations to dynamic changes in clinical and

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cognitive function, such studies may also explore the biological mechanisms underlying these associations as a potential anchor point for treatment options.

Genetic analysis offers one way of exploring the constraining factors underlying phenotypic variation. Here, we provided evidence that full and region-wise brain age gaps represent genetically influenced traits, and illustrated that the genetic variants associated with brain age gaps are also associated with SZ, BD, MS and AD. In line with the accumulating evidence that common disorders of the brain are highly polygenic and partly overlapping^{30-34,36,41}, these results suggest shared molecular genetic mechanisms between brain age gaps and brain disorders. Statistical associations do not necessarily signify causation, and functional interpretations of the identified genes should be made with caution. Larger imaging genetics samples, in particular those including individuals with common brain disorders, may in the future allow the investigation of specificity of the implicated genes. Considering the observed interaction effects in spatial brain age profiles between some disorders, we speculate that such analyses may offer novel insight into specific molecular mechanisms and will allow us to delineate the processes that affect the pace and profile of global and regional brain aging for each of these disorders.

In conclusion, in this largest brain age study to date, we established that the brain age gap is genetically constrained, increased in several common brain disorders, and linked to clinical and cognitive phenotypes. Our results establish the potential of advanced lifespan modelling in the clinical neurosciences, highlighting the benefit of big data resources that cover a wide span of ages and disease conditions. Delineating dynamic lifespan trajectories within and across individuals will be essential to disentangle the pathophysiological complexity of brain disorders.

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Author contributions

T.K. and L.T.W. conceived the study; T.K., N.T.D. and L.T.W. pre-processed all data in Freesurfer; N.T.D., M.J.L., C.L.B, L.B.N., L.T.W. and T.K. performed quality control of the data; T.K. performed the analysis with contributions from L.T.W. and D.v.d.M.; T.K., L.T.W., N.T.D., D.v.d.M. and O.A.A. contributed to interpretation of the results. All remaining authors were involved in data collection at various sites as well as cohort-specific tasks. T.K. and L.T.W. wrote the first draft of the paper and all authors contributed to and approved the final manuscript.

Competing financial interests

Some authors received educational speaker's honorarium from Lundbeck (O.A. Andreassen, A. Bertolino, T. Elvsåshagen, M. Zink, N. I. Landrø), Sunovion (O.A. Andreassen), Shire (B. Franke), Medice (B. Franke), Otsuka (A. Bertolino, M. Zink) and Janssen (A. Bertolino), Roche (M. Zink), Ferrer (M. Zink), Trommsdorff (M. Zink), Servier (M. Zink), all of these unrelated to this work. A. Bertolino is a stockholder of Hoffmann-La Roche Ltd and has received consultant fees from Biogen Idec. E. G. Celius and H. F. Harbo have received travel support, honoraria for advice and lecturing from Almirall (Celius), Biogen Idec (both), Genzyme (both), Merck (both), Novartis(both), Roche (both), Sanofi-Aventis (both) and Teva (both). They have received

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Materials & Correspondence

The data incorporated in this work were gathered from various resources (see acknowledgements). Material requests will need to be placed with individual PIs. Corresponding authors Tobias Kaufmann (tobias.kaufmann@medisin.uio.no) and Lars T. Westlye (l.t.westlye@psykologi.uio.no) will provide additional detail upon correspondence.

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Online methods

Samples

We have included data collected through collaborations, data sharing platforms, consortia as well as available in-house cohorts. **Supplementary Table 1** and **2** provide detailed information on the individual cohorts. All included cohorts have been published on, and we refer to a list of publications that can be consulted for a more detailed overview of cohort characteristics. Data collection in each cohort was performed with participants' written informed consent and with approval by the respective local Institutional Review Boards.

Image pre-processing and quality control

Raw T1 data for all study participants were stored and analysed locally at University of Oslo, following a harmonized analysis protocol applied to each individual subject data (**Suppl. Fig. 1**). We performed automated surface-based morphometry and subcortical segmentation using Freesurfer 5.3¹⁹. We deployed an automated quality control protocol executed within each of the contributing cohorts (**Suppl. Tables 1-2**), that excluded potential outliers based on global data quality measures. In brief, we regressed age, age², sex and (in case of multiple scanners) scanning site from mean cortical thickness, cortex volume, subcortical grey matter volume and from estimated total intracranial volume. Next, we z-standardized the resulting absolute of the residuals and excluded those subjects that exceeded a pre-defined standard deviation (SD) threshold of 4 SD. On top of this, a random set of data was carefully screened by trained research personnel to identify segmentation errors, assess the quality of each subject's brain images manually, edit segmentation where possible and to exclude data of insufficient quality ($n = 3957$ manually controlled, $n = 166$ excluded, $n = 219$ edited). Taken together, the main analysis excluded cases identified by manual QC as well as cases exceeding a threshold of 4 SD in the

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automated quality control on either of the four brain imaging measures, yielding 36,891 subjects. In addition, we performed supplementary analyses using a subset of data, where a more stringent quality control and exclusion procedure was applied. Using multivariate outlier detection based on robust methods as implemented in the R package *mvoutlier*²⁴, we identified an additional 5513 data sets with potentially less sufficient data quality. Thus, supplemental analysis provides a sanity check with those subjects excluded (sample size: $n = 31,378$).

Brain age prediction

We utilized the most recent cortical parcellation scheme²¹ to extract cortical thickness, area and volume for 180 regions of interest (ROI) per hemisphere. In addition, we extracted the classic set of cerebellar/subcortical and cortical summary statistics¹⁹. This yielded a total set of 1118 structural brain imaging features (360/360/360/38 for cortical thickness/area/volume as well as cerebellar/subcortical and cortical summary statistics, respectively).

We used machine learning on this feature set to predict the age of each individual's brain. First, we split the available data into a training sample and ten independent test samples, as described in the main text (**Fig. 1a**). Next, for each sex, we trained machine learning models utilizing the *xgboost* package in R⁴², chosen due to its resource efficiency and demonstrated superior performance in previous machine learning competitions, to predict the age of the brain using data available in the training set. First, model parameters were tuned using a 5-fold cross-validation of the training data. This step identified the optimal number of model training iterations by assessing the prediction error for 1500 rounds and implementing an early stopping if the performance did not improve for 20 rounds. Based on previous experience, the learning rate was pre-set to $\eta=0.01$ and all other parameters were set to default⁴² for linear *xgboost* tree models. After determining the optimal number of training iterations, the full set of training data

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was used to train the final models with the adjusted *nrounds* parameter. In addition, to assess overall model performance, prediction models were cross-validated within the training set using a 5-fold cross validation, each fold implementing the above described training procedure and testing on the hold-out part of the training set. Brain age predictions on the level of individual brain regions followed the same procedures as those described for the full brain level, except that the feature set was reduced to cover only those features that overlapped more than 50% with a given lobe. Regions were defined following the Freesurfer *lobesStrict* segmentation as *occipital*, *frontal*, *temporal*, *parietal*, *cingulate* and *insula*. In addition, given the limited number of cerebellar features available in the Freesurfer summary statistics, cerebellar and subcortical features were grouped into a *cerebellar/subcortical* region (**Fig. 1b**).

For the genetic analyses, a different approach had to be taken to ensure maximum exploitation of the limited availability of genetic data. Rather than splitting into training and test sets, we selected all healthy subjects and estimated their brain age using a 5-fold cross-validation approach like the one performed when validating performance of the training set. The resulting unbiased estimates of brain age gaps for all individuals with genetic data available went into the genome-wide complex trait analysis and conjunctive FDR.

Main statistical analysis framework

We performed both mega- (across cohorts) and meta- (within cohort) analyses. To estimate group effects on a given measure in a mega-analysis framework, we computed the effect of diagnosis in relation to the healthy controls for each of the ten test samples in a linear model accounting for age, age², sex and scanning site. Cohen's d effect sizes were estimated based on contrast t-statistics⁴³ following **Formula 1**:

$$d = \frac{t(n_1 + n_2)}{\sqrt{n_1 n_2} \sqrt{df}} \quad (1)$$

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For the meta-analysis, similar models were computed within cohorts. In addition to estimating Cohen's d (**Formula 1**), we estimated the variance of d following **Formula 2**.

$$v = \left(\frac{n_1 + n_2}{n_1 n_2} + \frac{d^2}{2(n_1 + n_2 - 2)} \right) \left(\frac{n_1 + n_2}{n_1 + n_2 - 2} \right) \quad (2)$$

Cumulative effects across cohorts were then estimated using a variance-weighted random-effects model as implemented in the *metafor* package in R⁴⁴.

Assessment of regional specificity

The clustering in **Figure 3b** was performed using heatmap.2 from the *gplots* package⁴⁵ in R. A correlation matrix was computed based on the case-control effect sizes obtained from each test sample and region and hierarchical clustering was performed using the default settings. To further explore regional specificity, we performed another analysis that involved only the clinical groups. We regressed age, age², sex and scanning site from the brain age gaps in each test sample. Next, we joined data from each pair of clinical groups and each pair of regions for repeated measures analysis of variance and estimated the effect sizes of region x group interactions (1260 ANOVAs in total). The interaction effects were visualized in **Figure 3c** using the *circlize* package⁴⁶ in R.

Genetic analyses

We restricted all genetic analyses to individuals with European ancestry, as determined through multidimensional scaling (MDS), and included the first four population components as covariates to further control for population stratification. Single Nucleotide Polymorphism (SNP) data were available for 16,269 adult healthy individuals with European ancestry. We used genome-wide complex trait analysis²⁹ (GCTA) to estimate the proportion of variance in brain age explained by SNPs. Before the analysis, we removed high LD regions from the genetic data and pruned it, using a sliding window approach with a window size of 50 base pair (bp), a step size of 5 bp and

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an r^2 of 0.2, leaving 133,147 SNPs. All GCTA analyses accounted for age, age², sex, scanning site and genetic batch.

Furthermore, we used conditional Q-Q plots³⁴ and conjunctural FDR analyses^{35,36} to assess polygenic overlap between two complex traits. We gathered genome-wide association analysis (GWAS) summary statistics for SZ and BD from the Psychiatric Genomics Consortium^{30,31}, MS from the International Multiple Sclerosis Genetics Consortium³², and AD from the International Genomics of Alzheimer's Project³³; and performed GWAS on the full brain and region-wise brain age gaps in the above-described sample of 16,269 healthy adults. The MHC region was excluded from the analysis. The SNPs were pruned using a pairwise correlation coefficient approximation to LD (r^2), where SNPs were disregarded at $r^2 < 0.2$ and pruning performed with 20 iterations, as described elsewhere³⁴. Conjunctural FDR was run for each pair of full brain / region-wise brain age gap and group, using conjunctural FDR threshold of 0.05. SNPs were annotated using the Ensembl Variant Effect Predictor⁴⁷.

Cognitive and clinical associations

Cognitive and clinical associations were tested in subsets based on data availability as described in the main text. First, we regressed age, age², sex and scanning site from the brain age gaps. Next, we correlated the resulting residuals with scores of the Global Assessment of Functioning scale²⁵ (GAF), the Positive and Negative Syndrome Scale²⁶ (PANSS), the Expanded Disability Status Scale²⁷ (EDSS) and Mini Mental State Examination scores²⁸ (MMSE). We transformed the resulting correlations using Fisher's z transform. Therefore, the reported associations essentially reflect a partial correlation between full brain / region-wise brain age gaps and clinical/cognitive scores, controlling for confounding effects of age, sex and site.

Code availability.

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The main analysis was performed using R statistics⁴⁸. The code needed to reproduce the results is available from the authors upon request.

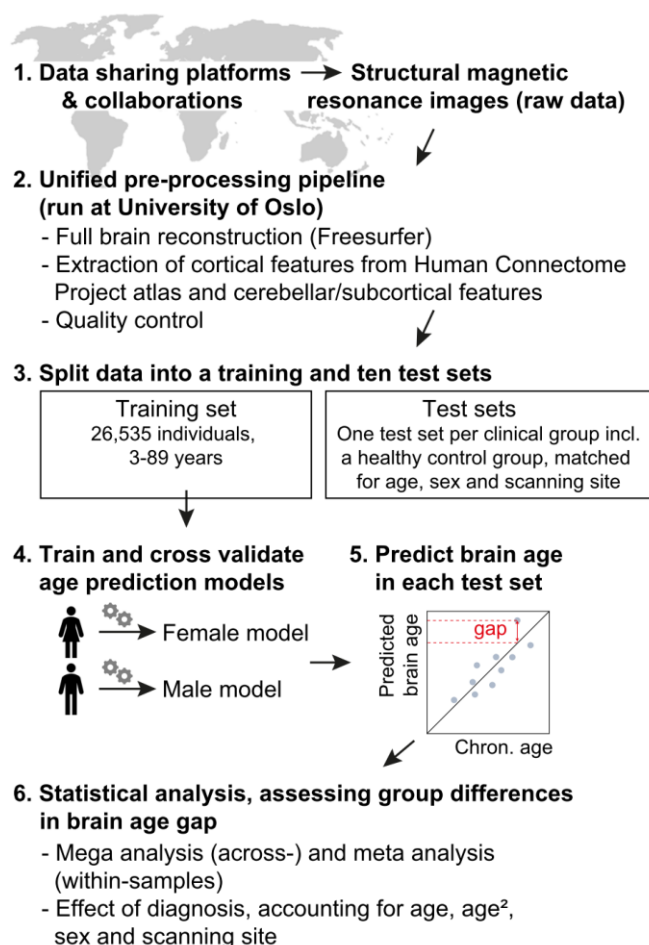
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111. Pergola, G., *et al. Schizophrenia research* **180**, 13-20 (2017).

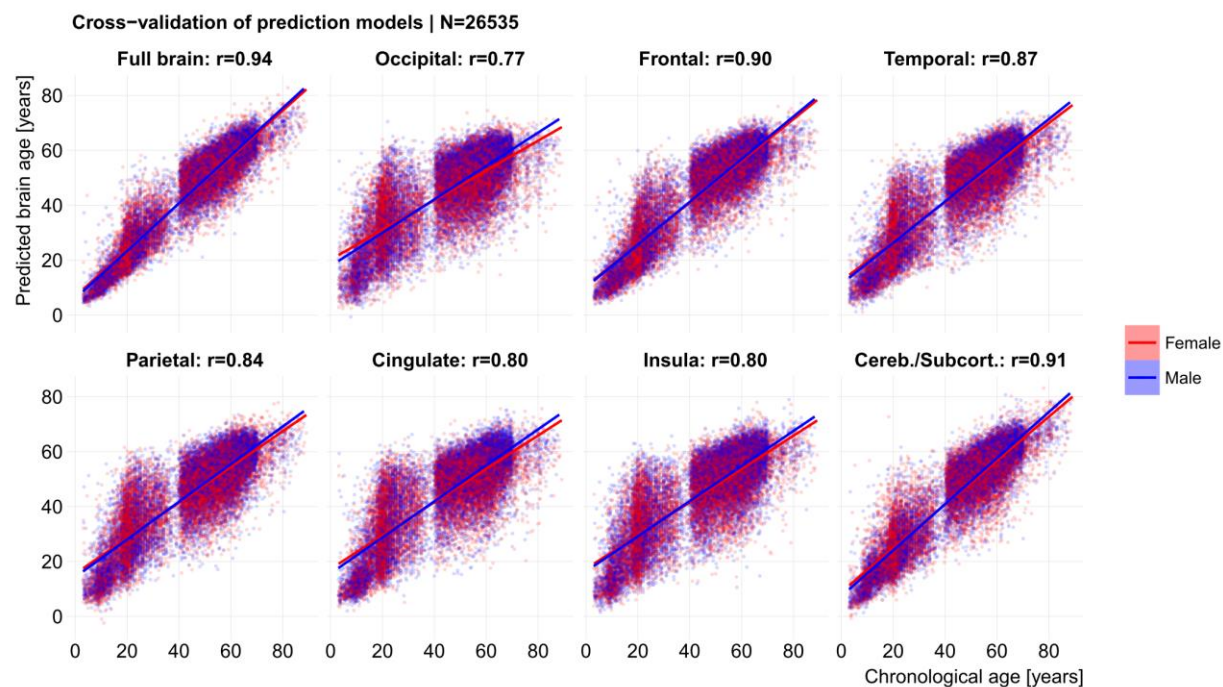
679 **Supplementary Figures**



Suppl. Figure 1: Outline of the main analysis pipeline.

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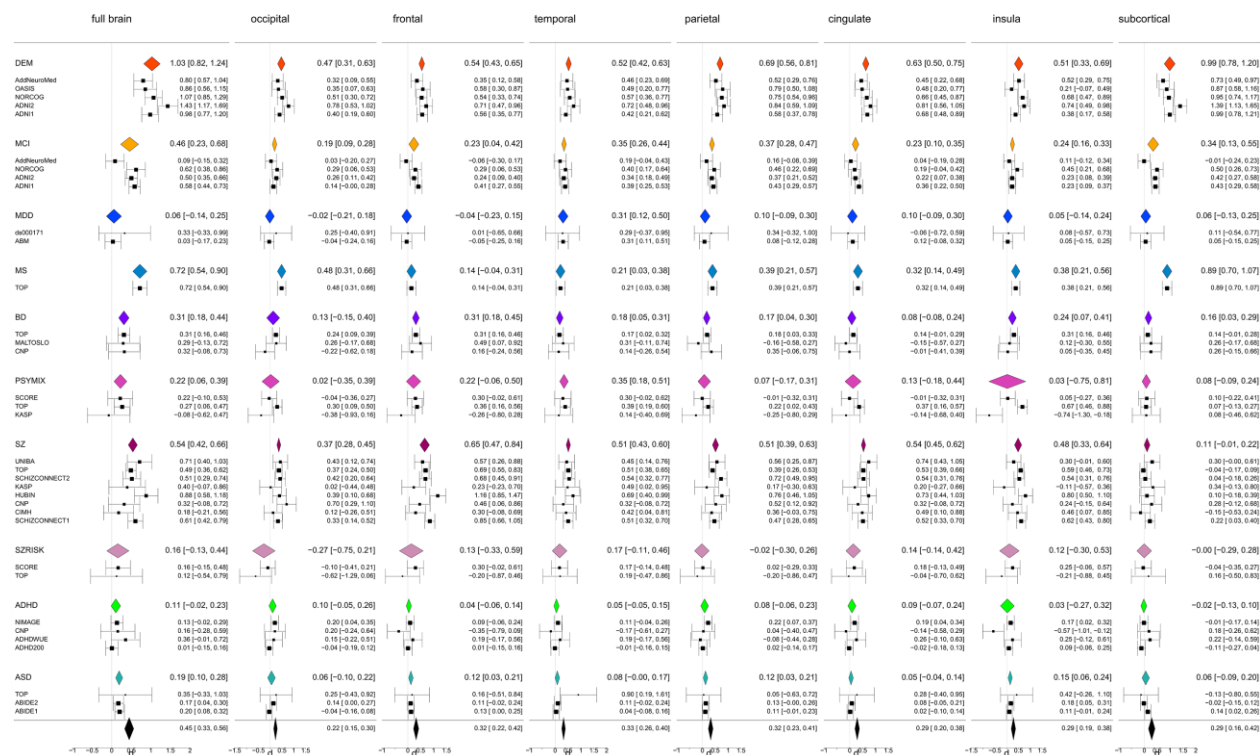
Suppl. Figure 2: Cross-validation of the prediction models confirmed validity of the models. The correlation between chronological age and predicted brain age estimated using 5-fold cross-validation within the training set is shown for each feature set.

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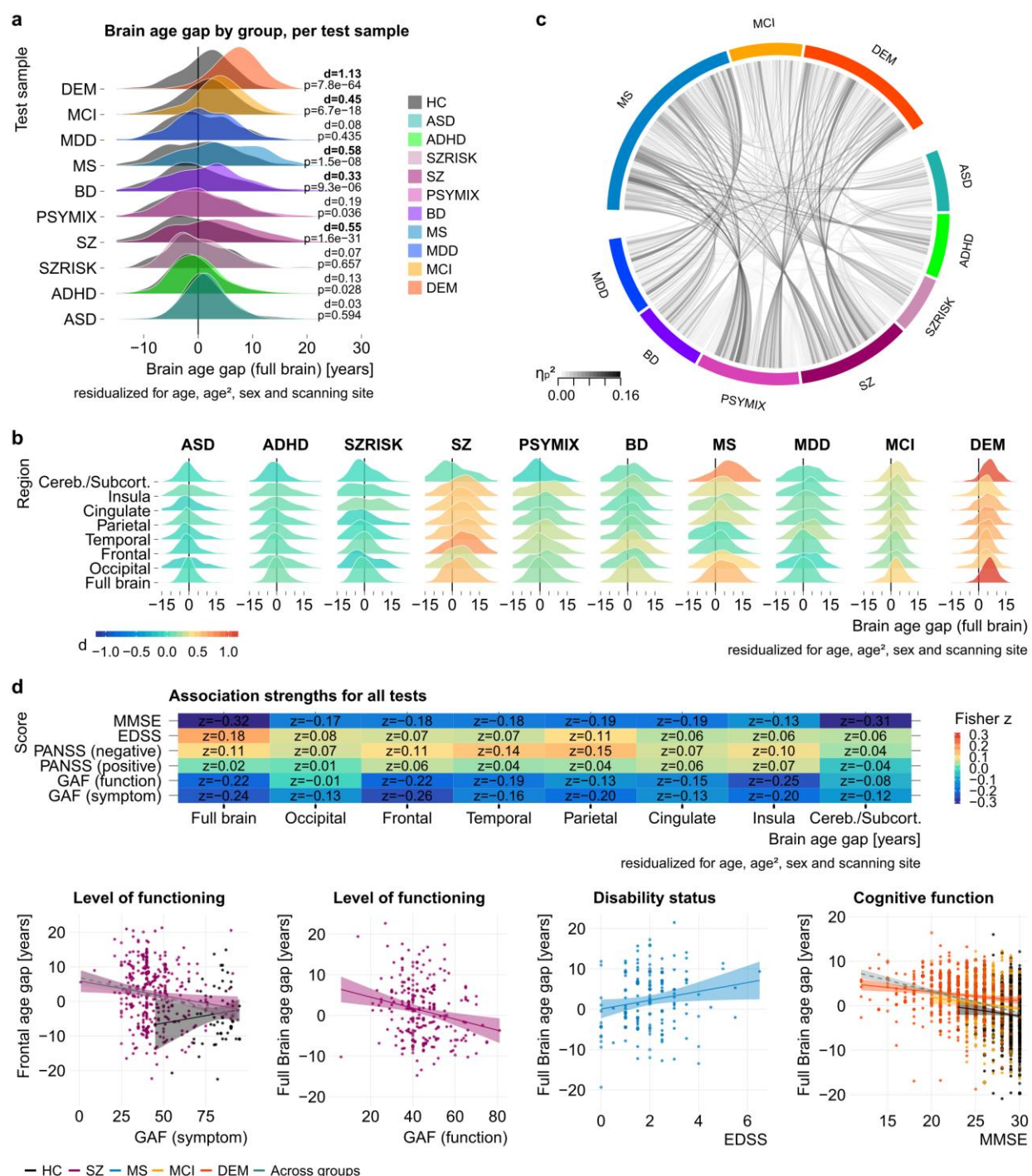
682

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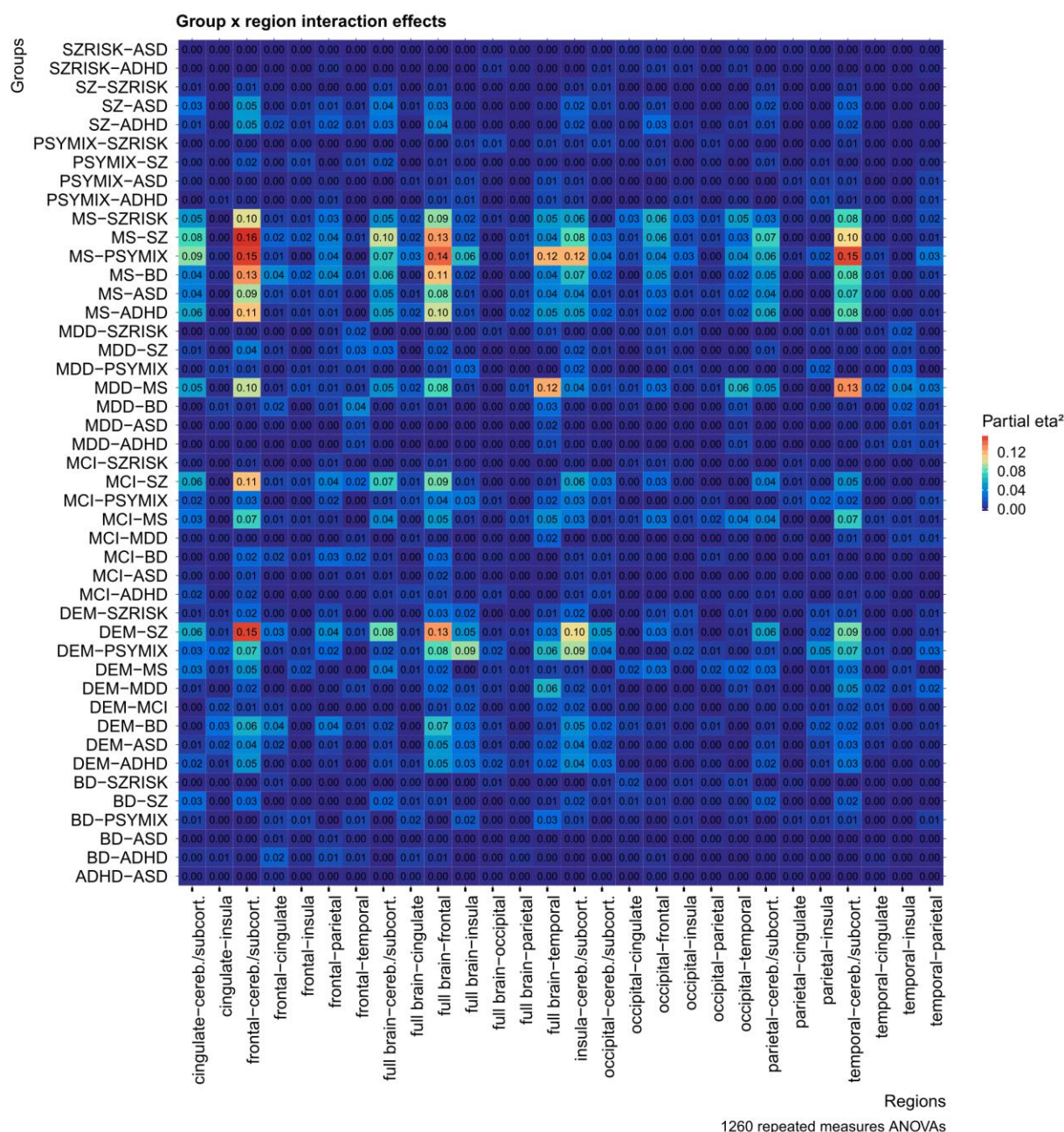


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Suppl. Figure 4: Replication of results in a subset of 31,378 individuals following more stringent, multivariate exclusion criteria. a, Replication of group effects (for comparison, see Fig. 2) **b,** Replication of spatial brain age gap patterns (for comparison, see Fig. 3a) **c,** Replication of interaction effect pattern (for comparison, see Fig. 3c). **d,** Replication of associations with clinical and cognitive scores (for comparison, see Fig. 4).

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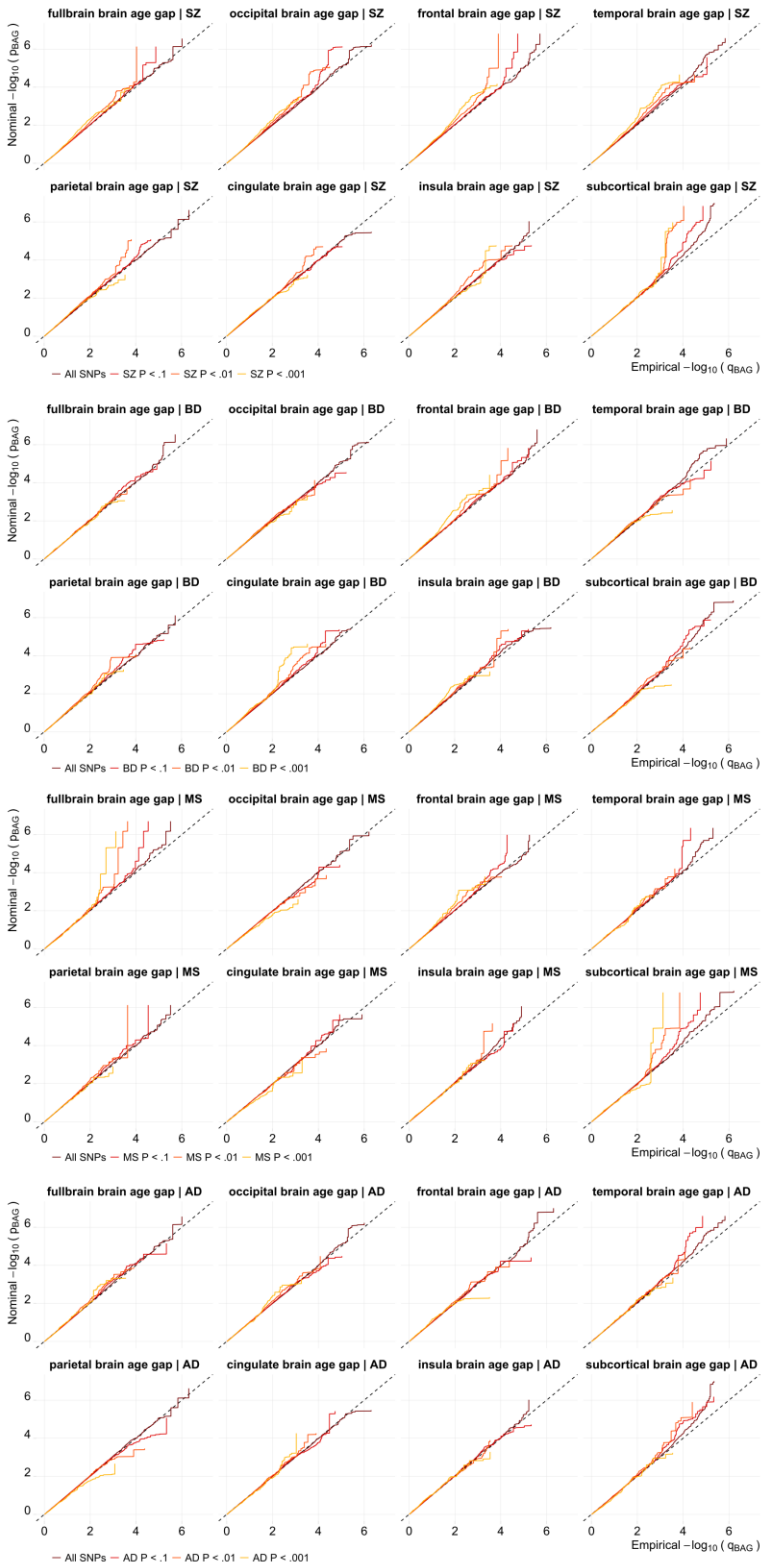


Suppl. Figure 5: Results from 1260 repeated measures ANOVAs confirm group x region interaction effects in brain age patterns. Strongest effects were observed between MS and SZ, MS and PSYMIX as well as DEM and SZ, suggesting divergent aging patterns in these disorders.

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Suppl. Figure 6: Conditional Q-Q plots for all brain age gaps conditioned for SZ, BD, MS or AD suggests enrichment for several brain age gaps.

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Supplementary Tables

Suppl. Table 1: Summary of the included cohorts. Several of the cohorts are under ongoing data collection, thus the subject numbers provided in the reference publications may not match those in this article.

Cohort	Source	Comment	Reference
ABIDE1	http://fcon_1000.projects.nitrc.org/	Primary support for the work by Adriana Di Martino was provided by the NIMH (K23MH087770) and the Leon Levy Foundation. Primary support for the work by Michael P. Milham and the INDI team was provided by gifts from Joseph P. Healy and the Stavros Niarchos Foundation to the Child Mind Institute, as well as by an NIMH award to MPM (R03MH096321).	49
ABIDE2	http://fcon_1000.projects.nitrc.org/	Primary support for the work by Adriana Di Martino and her team was provided by the National Institute of Mental Health (NIMH 5R21MH107045). Primary support for the work by Michael P. Milham and his team provided by the National Institute of Mental Health (NIMH 5R21MH107045); Nathan S. Kline Institute of Psychiatric Research). Additional Support was provided by gifts from Joseph P. Healey, Phyllis Green and Randolph Cowen to the Child Mind Institute.	50
ABM	Authors	ABM was supported by the Research Council of Norway (grant number 229135) and Health South East Research Funding Agency (grant number 2015052)	https://www.biorxiv.org/content/early/2018/02/19/267591
ADDNEUROMED	Authors	AddNeuroMed consortium was led by Simon Lovestone, Bruno Vellas, Patrizia Mecocci, Magda Tsolaki, Iwona Kloszewska, Hilka Soininen. Their work was supported by InnoMed (Innovative Medicines in Europe), an integrated project funded by the European Union of the Sixth Framework program priority (FP6-2004- LIFESCIHEALTH-5)	51,52
ADHD200	http://fcon_1000.projects.nitrc.org/	F. Xavier Castellanos, David Kennedy, Michael Milham, and Stewart Mostofsky are responsible for the initial conception of the ADHD-200 Consortium. Consortium steering committee includes Jan Buitelaar, F. Xavier Castellanos, Dan Dickstein, Damien Fair, David Kennedy, Beatriz Luna, Michael Milham (Project Coordinator), Stewart Mostofsky, and Julie Schweitzer. Data aggregation and organization was coordinated by the INDI team, which included Saroja Bangaru, David Gutman, Maarten Mennes, and Michael Milham. Web infrastructure and data storage were coordinated by Robert Buccigrossi, Albert Crowley, Christian Hasselgrove, David Kennedy, Kimberly Pohland, and Nina Preuss. The ADHD-200 Global Competition Coordinators were Damien Fair (Chair of Selection Committee, Editor in Chief for Global Competition Special issue) and Michael Milham	53,54
ADHDWUE	Authors	Primary support for the study was provided by the German Research Foundation, grant number DFG KFO 125 1/2 and Pa566/7-3. KPL and his team are supported by the Deutsche Forschungsgemeinschaft (DFG: CRU 125, CRC TRR 58 A1/A5), European Community (EC: AGGRESSOTYPE FP7/No. 602805; Fritz Thyssen Foundation (No. 10.13.1185), ERA-Net NEURON/RESPOND, No. 01EW1602B, and 5-100 Russian Academic Excellence Project.	55,56
ADNI1	http://adni.loni.usc.edu/	Data used in the preparation of this article were obtained from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (adni.loni.usc.edu). The ADNI was launched in 2003 as a public-private partnership, led by Principal Investigator Michael W. Weiner, MD. The primary goal of ADNI has been to test whether serial magnetic resonance imaging (MRI), positron emission tomography (PET), other biological markers, and clinical and neuropsychological assessment can be combined to measure the progression of mild cognitive impairment (MCI) and early Alzheimer's disease (AD). For up-to-date information, see www.adni-info.org .	57,58
ADNI2	http://adni.loni.usc.edu/	Data collection and sharing for this project was funded by the Alzheimer's Disease Neuroimaging Initiative (ADNI) (National Institutes of Health Grant U01 AG024904) and DOD ADNI (Department of Defense award number W81XWH-12-2-0012). ADNI is funded by the National Institute on Aging, the National Institute of Biomedical Imaging and Bioengineering, and through generous contributions from the following: AbbVie, Alzheimer's Association; Alzheimer's Drug Discovery Foundation; Araclon Biotech; BioClinica, Inc.; Biogen; Bristol-Myers Squibb Company; CereSpir, Inc.; Cogstate; Eisai Inc.; Elan Pharmaceuticals, Inc.; Eli Lilly and Company; EuroImmun; F. Hoffmann-La Roche Ltd and its affiliated company Genentech, Inc.; Fujirebio; GE Healthcare; IXICO Ltd.; Janssen Alzheimer Immunotherapy Research & Development, LLC.; Johnson & Johnson Pharmaceutical Research & Development LLC.; Lumosity; Lundbeck; Merck & Co., Inc.;	

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		Meso Scale Diagnostics, LLC.; NeuroRx Research; Neurotrack Technologies; Novartis Pharmaceuticals Corporation; Pfizer Inc.; Piramal Imaging; Servier; Takeda Pharmaceutical Company; and Transition Therapeutics. The Canadian Institutes of Health Research is providing funds to support ADNI clinical sites in Canada. Private sector contributions are facilitated by the Foundation for the National Institutes of Health (www.fnih.org). The grantee organization is the Northern California Institute for Research and Education, and the study is coordinated by the Alzheimer's Therapeutic Research Institute at the University of Southern California. ADNI data are disseminated by the Laboratory for Neuro Imaging at the University of Southern California. Betula was supported by a Wallenberg Scholar Grant (KAW).	59
BETULA	Authors		
CAMCAN	https://camcan-archive.mrc-cbu.cam.ac.uk/dataaccess/	Data collection and sharing for this project was provided by the Cambridge Centre for Ageing and Neuroscience (CamCAN). CamCAN funding was provided by the UK Biotechnology and Biological Sciences Research Council (grant number BB/H008217/1), together with support from the UK Medical Research Council and University of Cambridge, UK.	60,61
CIMH	Authors	CIMH was supported by the Deutsche Forschungsgesellschaft (DFG, projects ZI1253/3-1, ZI1253/3-2, KI 576/14-2, ME 1591/6-2) and the European Community's Seventh Framework Programme (FP7/2007–2013) grant agreement #602450 (IMAGEMEND)	62,63
CORR	http://fcon_1000.projects.nitrc.org/		64
DLBS	http://fcon_1000.projects.nitrc.org/		65
DS000030 (CNP)	https://openfmri.org/	DS* data sets were obtained from the OpenfMRI database.	66,67
DS000115 (CCNMD)	https://openfmri.org/	<i>DS000030</i> work was supported by the Consortium for Neuropsychiatric Phenomics (NIH Roadmap for Medical Research grants UL1-DE019580, RL1MH083268, RL1MH083269, RL1DA024853, RL1MH083270, RL1LM009833, PL1MH083271, and PL1NS062410). <i>DS000115</i> was supported through NIH Grants P50 MH071616 and R01 MH56584. <i>DS000119</i> was supported by the National Institutes of Mental Health (NIMH R01 MH067924).	68,69
DS000119	https://openfmri.org/		70
DS000171	https://openfmri.org/	Enami Yasui provided assistance with data collection. <i>DS000171</i> : Trisha Patrician and Natalie Stroupe assisted with screening of participants. Allan Schmitt and Franklin Hunsinger collected the MR data.	71
DS000202	https://openfmri.org/		72,73
DS000222	https://openfmri.org/		74
HCP	https://www.humanconnectome.org/	Data were provided [in part] by the Human Connectome Project, MGH-USC Consortium (Principal Investigators: Bruce R. Rosen, Arthur W. Toga and Van Wedeen; U01MH093765) funded by the NIH Blueprint Initiative for Neuroscience Research grant; the National Institutes of Health grant P41EB015896; and the Instrumentation Grants S10RR023043, S10RR023401, S10RR019307.	75
HUBIN	Authors	This study was supported by the Swedish Research Council (2006-2992, 2006-986, K2007-62X-15077-04-1, 2008-2167, K2008-62P-20597-01-3, K2010-62X-15078-07-2, K2012-61X-15078-09-3, 2017-00949), the regional agreement on medical training and clinical research between Stockholm County Council and the Karolinska Institutet, the Knut and Alice Wallenberg Foundation, and the HUBIN project.	76
HUNT	https://www.ntnu.edu/hunt	The HUNT Study is a collaboration between HUNT Research Centre, Faculty of Medicine and Health Sciences, Norwegian University of Science and Technology (NTNU), Nord-Trøndelag County Council, Central Norway Regional Health Authority, and the Norwegian Institute of Public Health. HUNT-MRI and the genetic analysis were funded by grants from the Liaison Committee between the Central Norway Regional Health Authority and NTNU to principal investigator Asta Häberg, and the Norwegian National Advisory Unit for functional MRI. We thank the HUNT MRI participants, MRI technicians and the Department of Diagnostic Imaging at Levanger Hospital, Professor Lars Jacob Stovner (NTNU) and the administrative staff at HUNT.	77,78
IXI	http://brain-development.org/ixi-dataset/		79
KASP	Authors	KaSP was supported by grants from the Swedish Medical Research Council (SE: 2009-7053; 2013-2838; SC: 523-2014-3467), the Swedish Brain Foundation, Åhlén-siftelsen, Svenska Läkaresällskapet, Petrus och Augusta Hedlunds Stiftelse, Torsten Söderbergs Stiftelse, the AstraZeneca-Karolinska Institutet Joint Research Program in Translational Science, Söderbergs Königska Stiftelse, Professor Bror Gadelius Minne, Knut och Alice Wallenbergs stiftelse, Stockholm County Council (ALF and PPG), Centre for Psychiatry Research, KID-funding from the Karolinska Institutet.	80,81
MALTOSLO	Authors	The study was funded by the South-Eastern Norway Regional Health Authority (2015-2015078), Oslo University Hospital, a research grant from Mrs. Throne-Holst, and the Ebbe Frøland	82,83

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		foundation.	
NCNG	Authors	The sample collection was supported by grants from the Bergen Research Foundation and the University of Bergen, the Dr Einar Martens Fund, the K.G. Jebsen Foundation, the Research Council of Norway, to SLH, VMS, AJL, and TE. The authors thank Dr. Eike Wehling for recruiting participants in Bergen, and Professor Jonn-Terje Geitung and Haraldplass Deaconess Hospital for access to the MRI facility. Additional support by RCN grants 177458/V50 and 231286/F20.	84
NIMAGE	Authors	This project was supported by grants from National Institutes of Health (grant R01MH62873 to SV Faraone) for initial sample recruitment, and from NWO Large Investment (grant 1750102007010 to JK Buitelaar), NWO Brain & Cognition (grant 433-09-242 to JK Buitelaar), ZonMW Grant 60-60600-97-193, and grants from Radboud University Medical Center, University Medical Center Groningen, Accare, and VU University Amsterdam for subsequent assessment waves. NeuroIMAGE also receives funding from the European Community's Seventh Framework Programme (FP7/2007 – 2013) under grant agreements n° 602805 (Aggressotype), n° 278948 (TACTICS), and n° 602450 (IMAGEMEND), and from the European Community's Horizon 2020 Programme (H2020/2014 – 2020) under grant agreements n° 643051 (MiND) and n° 667302 (CoCA).	85
NORCOG	Authors	The Norwegian register of persons assessed for cognitive symptoms (NorCog) includes clinical, imaging and biological data from memory clinics in Norway (https://www.aldringoghelse.no/norkog/). The register is owned by Oslo University Hospital and administered by Norwegian National Advisory Unit on Ageing and Health.	86
OASIS	http://www.oasis-brains.org/	The study was supported by grants P50 AG05681, P01 AG03991, R01 AG021910, P50 MH071616, U24 RR021382, R01 MH56584.	87,88
PING	http://pingstudy.ucsd.edu/	Data used in the preparation of this article were obtained from the Pediatric Imaging, Neurocognition and Genetics (PING) Study database (http://ping.chd.ucsd.edu/). PING was launched in 2009 by the National Institute on Drug Abuse (NIDA) and the Eunice Kennedy Shriver National Institute Of Child Health & Human Development (NICHD) as a 2-year project of the American Recovery and Reinvestment Act. The primary goal of PING has been to create a data resource of highly standardized and carefully curated magnetic resonance imaging (MRI) data, comprehensive genotyping data, and developmental and neuropsychological assessments for a large cohort of developing children aged 3 to 20 years. The scientific aim of the project is, by openly sharing these data, to amplify the power and productivity of investigations of healthy and disordered development in children, and to increase understanding of the origins of variation in neurobehavioral phenotypes. For up-to-date information, see http://ping.chd.ucsd.edu/ . Data collection and sharing for this project was funded by the Pediatric Imaging, Neurocognition and Genetics Study (PING) (National Institutes of Health Grant RC2DA029475). PING is funded by the National Institute on Drug Abuse and the Eunice Kennedy Shriver National Institute of Child Health & Human Development. PING data are disseminated by the PING Coordinating Center at the Center for Human Development, University of California, San Diego.	89
PNC	https://www.med.upenn.edu	Support for the collection of the data sets was provided by grant RC2MH089983 awarded to R. Gur and RC2MH089924 awarded to H. Hakonarson	90,91
RSI-MS	Authors	Data collection in this MS cohort was supported by the South-Eastern Norway Regional Health Authority project 39569, Research Council of Norway grant 240102 and 240102, Oslo MS Society, Odd Fellow's Society for MS research.	92
SALD	http://fcon_1000.projects.nitrc.org/	Healthy controls were sampled from the TOP study (same scanner).	93
SCHIZCONNECT1	http://schizconnect.org/	Data used in preparation of this article were obtained from the SchizConnect (http://schizconnect.org) database. As such, the investigators within SchizConnect contributed to the design and implementation of SchizConnect and/or provided data but did not participate in analysis or writing of this report. Data collection and sharing for this project was funded by NIMH cooperative agreement 1U01 MH097435	94-99
SCHIZCONNECT2	http://schizconnect.org/	<i>SCHIZCONNECT1</i> comprised BrainGluSchi, COBRE and MCIC samples (COINS). <i>SCHIZCONNECT2</i> comprised NUSDAST and NUNDA samples. Duplicate subjects in different sources were excluded. The respective samples were supported by the following grants: <i>BrainGluSchi</i> : NIMH R01MH084898-01A1. <i>COBRE</i> : 5P20RR021938 /P20GM103472 from the NIH to Dr. Vince	

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SCORE	Authors	Calhoun, <i>MCIC</i> : Department of Energy under Award Number DE-FG02-08ER64581. <i>NUSDA</i> : NIMH Grant 1R01 MH084803. <i>NUNDA</i> : MH056584.	100,101
SLIM	http://fcon_1000.projects.nitrc.org/	This work was supported by the Swiss National Science Foundation (grant No. 119382)	102,103
STROKEMRI/ MOT	Authors	Support was provided by grant numbers 31271087; 31470981; 31571137, 31500885, SWU1509383, SWU1509451, cstc2015jcyjA10106, 151023, 2015M572423, 2015M580767, Xm2015037, 14JJD880009	104
TOP	Authors	Supported by the Research Council of Norway (249795, 248238), the South-Eastern Norway Regional Health Authority (2014097, 2015044, 2015073, 2016083), and the Norwegian ExtraFoundation for Health and Rehabilitation (2015/FO5146).	105-108
UBA	Authors	The work was funded by the Research Council of Norway (213837, 223273, 204966/F20, 213694, 229129, 249795/F20, 248778), the South-Eastern Norway Regional Health Authority (2013-123, 2014-097, 2015-073, #2017-112) and Stiftelsen Kristian Gerhard Jebsen.	109
UKBB	https://www.ukbiobank.ac.uk/	European Community's Seventh Framework Programme (FP7/2007–2013) grant agreement #602450 (IMAGEMEND)	110
UNIBA	Authors	This research has been conducted using the UK Biobank Resource (access code 27412). All subjects with a primary or secondary ICD-10 diagnosis with a mental or neurological disorder were excluded prior to analysis and the remaining subjects included as healthy controls.	111
		This work was supported by a “Capitale Umano ad Alta Qualificazione” grant by Fondazione Con Il Sud awarded to Alessandro Bertolino and by a Hoffmann-La Roche Collaboration Grant awarded to Giulio Pergola. This project has received funding from the European Union Seventh Framework Programme for research, technological development and demonstration under grant agreement no. 602450 (IMAGEMEND). This paper reflects only the author's views and the European Union is not liable for any use that may be made of the information contained therein.	

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Suppl. Table 2: Summary of group size, age and sex for each cohort.

Cohort	Number of subjects per group	Age in years: mean \pm sd range (group)	Sex: f/m
ABIDE1	561 (HC) 517 (ASD)	17.1 \pm 7.8 6.5-56.2 (HC) 17.2 \pm 8.5 7.0-64.0 (ASD)	161/917
ABIDE2	498 (HC) 440 (ASD)	15.8 \pm 9.9 5.9-64.0 (HC) 15.4 \pm 9.6 5.1-62.0 (ASD)	212/726
ABM	73 (HC) 192 (MDD)	42.2 \pm 13.3 19.0-64.0 (HC) 39.3 \pm 13.4 18.0-71.0 (MDD)	179/86
AddNeuroMed	126 (HC) 141 (MCI) 148 (DEM)	73.3 \pm 6.5 53.0-87.8 (HC) 74.8 \pm 5.9 56.8-90.1 (MCI) 76.0 \pm 6.5 58.2-88.6 (DEM)	237/178
ADHD200	542 (HC) 320 (ADHD)	11.3 \pm 3.0 7.0-21.0 (HC) 10.6 \pm 2.5 7.0-17.0 (ADHD)	322/540
ADHDWUE	55 (HC) 59 (ADHD)	40.0 \pm 12.1 24.0-61.0 (HC) 40.1 \pm 10.7 18.0-62.0 (ADHD)	56/58
ADNI1	218 (HC) 386 (MCI) 187 (DEM)	75.9 \pm 5.1 59.9-89.6 (HC) 74.7 \pm 7.4 54.4-89.3 (MCI) 75.2 \pm 7.5 55.1-90.9 (DEM)	334/457
ADNI2	268 (HC) 323 (MCI) 139 (DEM)	72.9 \pm 6.0 56.2-90.1 (HC) 71.7 \pm 7.3 55.0-91.4 (MCI) 74.5 \pm 7.9 55.6-90.3 (DEM)	347/383
BETULA	347 (HC)	63.0 \pm 13.2 25.0-81.3 (HC)	181/166
CAMCAN	648 (HC)	54.2 \pm 18.6 18.0-88.0 (HC)	329/319
CIMH	43 (HC) 53 (SZ)	30.6 \pm 11.5 18.0-60.0 (HC) 31.2 \pm 8.6 18.0-48.0 (SZ)	31/65
CNP	125 (HC) 41 (ADHD) 50 (SZ) 49 (BD)	31.5 \pm 8.8 21.0-50.0 (HC) 32.3 \pm 10.4 21.0-50.0 (ADHD) 36.5 \pm 8.9 22.0-49.0 (SZ) 35.3 \pm 9.0 21.0-50.0 (BD)	112/153

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CoRR	1360 (HC)	26.1±15.9 6.0-88.0 (HC)	694/666
DLBS	311 (HC)	54.3±20.0 20.6-89.1 (HC)	194/117
ds000119	73 (HC)	16.2±4.7 8.1-26.8 (HC)	43/30
ds000171	20 (HC) 19 (MDD)	29.4±11.3 18.0-59.0 (HC) 33.5±13.7 18.0-56.0 (MDD)	22/17
ds000202	94 (HC)	22.1±2.7 18.0-30.0 (HC)	94/0
ds000222	79 (HC)	44.4±20.1 21.0-73.0 (HC)	41/38
HCP	1113 (HC)	28.8±3.7 22.0-37.0 (HC)	606/507
HUBIN	102 (HC) 94 (SZ)	42.0±8.8 19.4-56.2 (HC) 41.7±7.6 24.9-56.3 (SZ)	57/139
HUNT	909 (HC)	58.8±4.2 50.5-66.8 (HC)	477/432
IXI	562 (HC)	48.6±16.5 20.0-86.3 (HC)	312/250
KASP	45 (HC) 37 (SZ) 27 (PSYMIX)	25.7±5.2 19.0-43.0 (HC) 28.5±7.5 18.0-50.0 (SZ) 29.1±8.3 18.0-48.0 (PSYMIX)	43/66
MALTOSLO	44 (HC) 44 (BD)	31.2±9.1 20.0-50.0 (HC) 34.4±7.3 18.0-48.0 (BD)	58/30
MOT	57 (HC)	25.3±3.9 21.0-36.0 (HC)	33/24
NCNG	465 (HC)	53.3±16.5 19.4-82.3 (HC)	310/155
NIMAGE	372 (HC) 331 (ADHD)	16.9±3.8 7.7-28.6 (HC) 16.8±3.6 7.4-27.5 (ADHD)	310/393
NORCOG	312 (HC) 142 (MCI) 186 (DEM)	63.3±10.9 40.0-95.0 (HC) 65.0±10.2 38.1-85.2 (MCI) 71.5±8.1 52.9-90.7 (DEM)	351/289
OASIS	315 (HC) 99 (DEM)	45.0±23.9 18.0-94.0 (HC) 76.9±7.1 62.0-96.0 (DEM)	254/160
PING	1162 (HC)	12.0±5.1 3.0-21.0 (HC)	556/606
PNC	1466 (HC)	15.1±3.6 8.2-23.2 (HC)	775/691
RSI-MS	254 (MS), HC were sampled from TOP (same scanner)	41.0±10.0 19.0-68.3 (MS)	196/58
SALD	493 (HC)	45.2±17.4 19.0-80.0 (HC)	307/186
SCHIZCONNECT1	230 (HC) 225 (SZ)	35.2±12.2 18.0-65.0 (HC) 36.3±13.0 18.0-66.0 (SZ)	117/338
SCHIZCONNECT2	145 (HC) 158 (SZ)	32.3±13.1 14.0-68.1 (HC) 34.4±11.7 19.0-62.4 (SZ)	120/183
SCORE	44 (HC) 80 (SZRISK) 78 (PSYMIX)	25.5±4.3 19.0-39.0 (HC) 24.3±5.2 18.0-42.0 (SZRISK) 26.9±6.7 18.0-42.0 (PSYMIX)	69/133
SLIM	556 (HC)	20.1±1.2 17.0-27.0 (HC)	316/240
STROKEMRI	61 (HC)	27.7±5.6 18.0-40.0 (HC)	36/25
TOP	958 (HC) 18 (ASD) 18 (SZRISK) 444 (SZ) 189 (PSYMIX) 352 (BD)	33.0±10.2 12.0-59.0 (HC) 27.7±9.3 18.6-48.2 (ASD) 21.8±4.4 15.6-29.1 (SZRISK) 31.2±9.3 18.0-62.0 (SZ) 30.5±9.6 18.0-69.0 (PSYMIX) 33.6±11.3 18.0-65.9 (BD)	913/1066
UBA	1099 (HC)	22.5±3.4 18.0-35.0 (HC)	714/385
UKBB	14581 (HC)	55.7±7.5 40.2-70.2 (HC)	7573/7008
UNIBA	435 (HC) 84 (SZ)	26.7±7.7 18.0-63.0 (HC) 34.3±7.7 19.0-58.0 (SZ)	246/273

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Suppl. Table 3: Significant loci from conjunctive FDR analysis reflecting overlap between brain age gaps and the respective disorders. The gene column reflects the gene closest to the significant SNP as identified via the Ensembl Variable Effect Predictor⁴⁷, unless the closest gene is more than 5000 bp away in which case no annotation is provided.

Brain region, group	Lead SNP	Chr. region	Chr. position	Conj. FDR	Consequence	Gene
occipital, SZ	rs354232	2p16.2	54916910	0.042	Intergenic variant	-
occipital, SZ	rs994261	2q33.1	199908378	0.033	Intron variant, non-coding transcript variant	AC018717.1
frontal, SZ	rs10803691	2p25.2	5449582	0.047	Downstream gene variant	AC073143.1
frontal, SZ	rs12820906	12q24.31	123493123	0.014	Intron variant	PITPNM2
frontal, SZ	rs4981695	14q12	29700996	0.028	Intergenic variant	-
frontal, SZ	rs221923	14q24.2	71584473	0.035	Downstream gene variant	PCNX
temporal, SZ	rs11892879	2q24.1	156114425	0.048	Intergenic variant	-
temporal, SZ	rs4689287	4p16.2	5990110	0.049	Missense variant	C4orf50
temporal, SZ	rs2764264	6q21	108934461	0.0065	Intron variant	FOXO3
parietal, SZ	rs9379851	6p22.2	26354780	0.0061	Upstream gene variant	RNU6-1259P
cingulate, SZ	rs6704641	2q33.1	200164252	0.031	Intron variant	SATB2
cingulate, SZ	rs7729320	5p13.1	38725149	0.04	Upstream gene variant	RP11-122C5.1
insula, SZ	rs10460398	2q33.1	200214742	0.0061	Intron variant	SATB2
subcortical, SZ	rs673253	1p34.2	44062154	0.045	Intron variant	PTPRF
subcortical, SZ	rs13107325	4q24	103188709	0.00026	Missense variant	SLC39A8
frontal, BD	rs9489193	6q22.1	117769728	0.039	Downstream gene variant	RP1-92C8.3
frontal, BD	rs10160070	10q21.1	54201572	0.046	Intergenic variant	-
frontal, BD	rs1884431	20q11.22	33338585	0.05	Intron variant	NCOA6
cingulate, BD	rs174583	11q12.2	61609750	0.016	Intron variant	FADS2
cingulate, BD	rs1034589	22q12.2	31579233	0.013	Intron variant	RNF185
insula, BD	rs2273684	20q11.22	33529766	0.035	Intron variant	GSS
full brain, MS	rs4465231	1p36.22	9347278	0.018	Intergenic variant	-
full brain, MS	rs12146713	12q23.3	106476805	0.02	Intron variant	NUAK1
frontal, MS	rs11164855	1p22.1	93466960	0.032	Intergenic variant	-
frontal, MS	rs940904	12q24.31	123491572	0.032	Intron variant	PITPNM2
temporal, MS	rs10484566	6p21.32	32835258	0.045	Regulatory region variant	-
subcortical, MS	rs6482190	10p12.31	22037809	0.049	Intergenic variant	-
subcortical, MS	rs12146713	12q23.3	106476805	0.026	Intron variant	NUAK1
temporal, AD	rs6485758	11p11.2	47530024	0.046	Intron variant	CELF1