

Brain Age Examination in Youth Anxiety Disorders: a Mega-Analysis of 4,312 Individuals from 92 Global Sites by the ENIGMA-Anxiety Working Group

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Introduction

Anxiety disorders are the most prevalent mental disorders among youth, with a lifetime prevalence estimate of up to 30%¹⁻³. Anxiety disorders affect millions of youths worldwide, causing enormous emotional, societal and economic burden^{4,5}, a trend that was further exacerbated by the COVID-19 pandemic and its aftermath⁶. Most anxiety disorders first develop during the critical transition from adolescence to young adulthood (10–25 years)^{1,2,5,7}, a period characterized by substantial brain development and maturation⁸. Whereas deviations from normative brain development are deemed relevant to the etiology of anxiety disorders^{1,8,9}, we still lack essential insights to inform diagnostics, prognostics, and risk-assessment.

Human brain mapping work in youth anxiety disorders points to neuroanatomical alterations in fronto-striato-limbic and temporo-parietal circuits, which may affect the perception, processing and modulation of emotionally salient information⁹⁻¹¹. However, very little is still known about delayed or accelerated neurodevelopmental processes that might be at play, or how these could be best captured at the individual-level. One promising avenue in this regard is the investigation of the neuroanatomical brain age based on MRI brain data. Here, machine learning algorithms harness the multidimensional nature of age-related brain changes at the individual-level to predict age, as a proxy for brain's biological age¹². It is posited that the brain age metric can quantify one's brain health status, where abnormally accelerated or decelerated brain aging may serve as a cumulative marker of disease and functional capacity¹³⁻¹⁵.

In a typical brain age study, a brain age model is first trained with machine learning using neuroimaging data from a large healthy population, wherein brain and chronological age relations are established across an age range to estimate normative brain aging¹³⁻¹⁵. This model is then tested in previously unseen individuals and used to quantify brain age¹³⁻¹⁵. The deviation between an individual's chronological age and age predicted from neuroimaging data – so called brain age gap (BAG) – is often the prime metric of interest. The BAG has become one of the most investigated risk markers for abnormal neuroanatomical brain aging and development across psychiatric disorders, with increased BAG ("older appearing brains") typically reported in relation to diagnostics (e.g., depression, schizo, BP) and key clinical factors (e.g., severity, medication use) patients¹⁶⁻¹⁸. However, brain age examinations of anxiety disorders, particularly amongst young anxiety patients, are extremely scarce and have yielded inconsistent effects in terms of direction, magnitude, and statistical significance¹⁹⁻²². An additional point of concern is that diagnostic boundaries between anxiety disorders tend to be blurrier in youth, with specific disorders becoming more distinguishable in adulthood^{23,24}. As such, a shift towards transdiagnostic examinations within large-scale multisite datasets is advocated, in pursuit of robust, reliable, and replicable findings on brain age patterns in youth with anxiety disorders^{1,8}.

While the brain age paradigm and its ensuing BAG metric have opened exciting new avenues for psychiatric research, its clinical application is constrained by a number of factors²⁵. To start, most prior work on the topic is limited by the use of small single-site samples for model training and validation, which can produce highly variable performances (i.e., estimation errors, explained variance) and spurious BAG estimates²⁵. Moreover, the models typically have marginal generalizability to data from sites with different demographic (i.e., age/sex), clinical (i.e., medication, symptom severity) or technical (i.e., scanner, acquisition protocols and diagnostic assessment) characteristics²⁵. The models often also lack neuroanatomical explainability: the ability to accurately pinpoint neuroanatomical features most critical to the multivariate brain age and BAG predictions²⁵. Perhaps most importantly, current brain age models typically do not account for uncertainty, and are therefore prone to spurious results, as BAG alterations might arise not only from neural changes but also erroneously from high uncertainty^{25,26}. This could be uncertainty due to noise in the observations (i.e., aleatory uncertainty) and/or uncertainty arising from the model itself (i.e., epistemic uncertainty)²⁵. Both should be ideally tackled simultaneously, which is often overlooked²⁵. Using a pioneering brain age model with uncertainty-aware deep neural network architecture, Hahn et al. (2022) recently showed that combined aleatory and epistemic uncertainty correction indeed produces more robust, reliable, and replicable BAG estimates²⁵.

We therefore leveraged this uncertainty-aware brain age model to probe neuroanatomical brain age patterns within the ENIGMA-Anxiety Working Group²⁷, which comprises the largest neuroimaging database on youth with various DSM-5 anxiety disorders (N = 4,312; age 10-25; 92 global sites). The ENIGMA-Anxiety Working Group aims for reliable and replicable inferences via multisite global collaborations, wherein data is shared and pooled, and subsequently processed and analyzed using harmonized protocols^{27,28}. Our transdiagnostic sample was aggregated from four subgroups of the ENIGMA-Anxiety Working Group, comprising the most prevalent anxiety disorders in youth: generalized anxiety disorder (GAD), social anxiety disorder (SAD), specific phobia (SPH), and panic disorder (PD) (**Table 1**)¹¹. Based on majority of brain age work on psychiatric disorders, we hypothesized youth with anxiety disorders to exhibit higher BAGs (“older appearing brains”) than their healthy control peers. We additionally explored whether BAG relates to key clinical and demographic characteristics, whilst also probing which brain regions are relevant for accurate BAG predictions across anxiety patients (neuroanatomical explainability). A transdiagnostic analytical approach was adopted to account for the substantial overlap in clinical and neural correlates of youth anxiety disorders^{9,10,29}, whilst maximizing sample size for robust and reliable inferences¹².

Methods

Study Sample

A total of 4,312 participants were included from four ENIGMA-Anxiety subgroups: GAD (23 sites): 491 patients and 674 controls; PD (36 sites): 228 patients and 534 controls; SAD (25 sites): 320 patients and 403 controls; SPH (36 sites): 738 patients and 924 controls. Sites represent independent study samples from contributing research centers. Datasets collected at the same MRI acquisition site but contributed to multiple working groups were modeled as a single site (see **Table S1**). All participants were between 10 and 25 years of age. Healthy controls (HC) were free of past and present psychopathology and psychotropic medication use at the time of scanning. Comorbid anxiety disorders (GAD, PD, SAD or SPH) were present in a subset of patients (see **Table 1**). In line with our prior work on this dataset³⁰, their assigned primary anxiety disorder diagnosis corresponds to those ascertained for in the original studies, based on clinical interviews following the criteria of the Diagnostic and Statistical Manual of Mental Disorders (Fourth or Fifth Edition). Participants' demographic and clinical characteristics are summarized in **Table 1**, with age distributions for healthy controls and patients with anxiety disorders provided in **Figure S1**. For an overview per site, see **Table S1**. Data on ethnicity and race were not collected by the majority of sites, and therefore could not be robustly analyzed, although the global nature of our dataset seems to afford ample ethnic/racial representation (see **Table S1**). The study was conducted in accordance with the Declaration of Helsinki. Individual studies were previously approved by the relevant local ethical review boards, with this study falling under the guidelines of those ethical review boards for secondary use of collected data.

Image Acquisition and Processing

Structural T1-weighted three-dimensional brain MRI scans were acquired and processed either locally at participating sites (PD, SAD, SPH data) or centrally (GAD data) using standardized protocols for harmonized analysis and quality control (available at <https://enigma.ini.usc.edu/protocols/imaging-protocols/>). Images were acquired at different field strengths (1.5 Tesla or 3.0 Tesla); sample-specific acquisition parameters are listed elsewhere³¹⁻³⁴. Regional mean cortical thickness (CT) surface area (CSA), as well as subcortical volumes (SCV) were extracted from the brain images using FreeSurfer (v.5.3 or v.6.0). Parcellations were visually inspected and statistically evaluated for outliers. For each subject, CSA and CT were calculated for 68 cortical Desikan-Killiany atlas-based regions (34 per hemisphere). In addition, gray matter SCVs were extracted for seven structures per hemisphere (nucleus accumbens, putamen, pallidum, caudate, thalamus, amygdala and hippocampus), along with lateral ventricle volumes and additional global summarized measures (i.e., total CT and CSA of the left and right hemisphere, and total intercranial volume). This yielded a total of 157 FreeSurfer features per subject. Subjects with more than 25% missing imaging features (due to quality control and segmentation errors) were excluded from analysis (N = 16) (Supplement provides details on missing values analytic). The aforementioned dataset has been included in previous ENIGMA-Anxiety publications^{32,33,35,36}.

Brain Age Model Training Testing

Data from all 2,535 HCs (80 sites) pooled across the four ENIGMA-Anxiety subgroups were used to build the normative brain age model. As shown in **Figure 1**, this model aimed to predict age using the 157 FreeSurfer-extracted neuroanatomical features. The predicted brain ages are used to calculate the “brain age gap” (BAG), the difference between an individual’s given predicted brain age and chronological age. We applied the Monte Carlo dropout composite quantile regression neural network (MCCQRNN) architecture for brain age modeling (**Figure 1**), which was recently developed within a large multi-site sample ($N = 10,691$) by Hahn et al. (2022), and is capable of estimating uncertainty-adjusted BAGs. Briefly, the MCCQRNN model takes into account confounding effects of prediction uncertainty by combining regression quantiles to estimate noise inherent to the observations ('aleatory'), and Monte Carlo dropout to estimate uncertainty that arises from the model itself ('epistemic') (see Hahn et al., 2022 for more details). The predictions of the model are computed as the median of the estimated quantiles. The model’s predicted age and estimated aleatory (σ_a^2) and epistemic (σ_e^2) uncertainty are in turn used to calculate uncertainty adjusted BAG scores using the following formula:

$$\frac{\hat{y} - y}{\sqrt{\sigma_a^2 + \sigma_e^2}}$$

\hat{y} = predicted (brain) age; y = true (chronological) age

σ_a^2 = aleatory uncertainty; σ_e^2 = epistemic uncertainty

MCCQRNN was implemented using TensorFlow 2.0, and consists of one layer of 32 rectified linear units, batch-normalization and dropout, and an output layer with 101 output units for composite quantile regression. The model was trained for 10 epochs with a learning rate of 0.01, a batch size of 64, and dropout rate of 0.2 using the Adam Optimizer with default settings. Epistemic uncertainty is estimated by sampling 1000 predictions with Monte Carlo Dropout (i.e., enabled dropout during training and inference). Model training and evaluation was performed using 10-Fold cross-validation, stratified for decile-split age bins, sex and site, so that each training and test fold had the same approximate distribution in number of males and females across different ages from each site. The model is trained using a modified pinball loss function for composite quantile prediction. No additional site/scanner harmonization step was implemented (e.g., ComBat³⁷), in line with recent large-scale data showing that it tends to increase mean absolute error for brain age prediction³⁸. Missing values were imputed using multiple imputation by chained equations (MICE) with a Bayesian ridge regression estimator that recursively estimates missing features^{39,40} (see **Supplementary Methods** for details on the imputation procedure and **Supplementary Results** for analyses of missingness). Imaging features were standardized prior to model estimation. Both imputation and standardization were performed within cross-validation

(estimated using the training set, and applied on both the training and test set). Brain age predictions for healthy controls were derived from out-of-sample test folds during 10-fold cross-validation, ensuring independence across folds.

Next, we assessed how well the trained MCCQRNN model (retrained using the entire dataset of HCs) predicted brain age in the previously unseen sample of youth with anxiety disorders ($N = 1,777$; 85 sites). Imputation and standardization for patients with anxiety disorders was performed using the imputation and standardization parameters estimated on the entire training set (HCs). We evaluated the model's performance for age prediction in the full sample, but also separately for HCs and patients, and for males and females, using mean absolute error (MAE), mean squared error (MSE), Pearson (r) correlation, and the coefficient of determination (R^2). In addition, we derived both uncertainty-adjusted and non-adjusted brain age gap (BAG) scores to investigate the effects of model uncertainty on subsequent inferences. Unadjusted BAG scores were computed as the difference between predicted brain age (median across quantiles) and chronological age, without correcting for epistemic or aleatory uncertainty.

All analyses were performed with Python 3.7.9, using the PHOTONAI toolkit (<https://www.photon-ai.com/>) for model estimation and validation ⁴¹.

Clinical Relevance Uncertainty-Adjusted BAG

BAG Scores and Anxiety Diagnosis

To test the hypothesis that youth anxiety disorders are related to higher *uncertainty-adjusted* BAGs (corrected for noise in the observations (i.e., aleatory uncertainty) and uncertainty arising from the model itself (i.e., epistemic uncertainty); all subsequent mentions of BAG refer to this adjusted measure), we first compared the BAG scores of HCs (across testing folds during cross-validation) with those of anxiety patients, derived from the optimized MCCQRNN model. We employed a mega-analytic approach using Linear Mixed Effect (LME) models, utilizing the *lme4* package in R. These models crucially accounted for data clustering within samples, incorporating sample-varying effects. Diagnosis (dichotomous: absence of diagnosis [HC] vs. presence of any anxiety disorder [transdiagnostic]) served as the fixed factor of interest, while age, age², and sex were included as covariates, with sample ID (i.e., site) incorporated as a random intercept. A supplementary exploration of potential disorder-specific effects was also carried out. To this end, an *ANOVA-like* LME tested the main effect of diagnosis across five groups (categorical: [HC, GAD, PD, SAD, SPH]), followed by post-hoc case-control testing between all HCs and specific patient groups (dichotomous: absence of diagnosis [HC] vs. presence of specific diagnosis [GAD, PD, SAD or SPH]). These analyses also statistically adjusted for age, age², sex, and site-related variance.

Clinical and Demographic Correlates of BAG

We next examined whether BAG scores also relate to key clinical and demographic characteristics. This included transdiagnostic case-control and within-case analyses of BAG, stratified based on (a) comorbid major depressive disorder (MDD), (b) psychotropic medication use at time of scanning, (c) symptom severity as measured by the State-Trait Anxiety Inventory - Trait Index (STAI-T) scores (Low: STAI-T <= 41 | High: STAI-T > 41), and (d) age of onset (AO: early <= 10 years | late > 10 years). The cutoffs for STAI-T and AO were based on the median values across cases. Finally, case-control analyses of BAG in relation to key demographics were performed, by adding multiplicative predictors as factor of interest (diagnosis-by-age, diagnosis-by-age², diagnosis-by-sex) to the main diagnostic model. Multiple comparisons correction was applied separately to each above-mentioned analysis set: transdiagnostic case-control (N=9) plus interactions (N=3) and within-cases (N=4) comparisons, along with the disorder-specific case-control comparisons (N=4), using the Benjamini-Hochberg false discovery rate (FDR) procedure. Results were considered significant if the FDR-corrected *p*-value (*q*) was < 0.05. Effect sizes (Cohen's *d*) and significance (*FDR-p*) appropriate for mixed-effects models were calculated (Nakagawa and Cuthill, 2007).

Neuroanatomical Explainability

To gain insight into brain regions crucial for accurate brain age estimations, we employed occlusion-sensitivity mapping, adapting the framework utilized by Hahn et al. (2022). This method is often used for gaining insight into which feature of an image a machine learning model leverages for accurate predictions²⁵. We employed generalized linear multilevel modeling using the *lme4* package in R to model the difference between the uncertainty-adjusted BAG based on the complete model and the uncertainty-adjusted BAG when information from a single, specific FreeSurfer feature is withheld/occluded (see **Supplementary Methods** for details). This method allows to determine whether occluding a specific region leads to a significant decrease in BAG predictive performance, hence yielding relevant feature sets for each subject²⁵. The results were mapped onto the brain and visualized using the ENIGMA TOOLBOX in Python (<https://enigmatoolbox.readthedocs.io/en/latest/>).

Results

Brain Age Prediction Performance

The performance of the model in predicting brain age for HCs (using 10-fold stratified cross-validation) is illustrated in **Figure 2A** and summarized in **Table S2**. The following metrics describing the relationship between predicted brain age and chronological age were obtained (mean; standard deviation across test folds): Pearson's *r* = 0.78 (0.02), coefficient of determination (R^2) = 0.60 (0.03), Mean Absolute Error (MAE) = 2.30 (0.10) years, Median Absolute Error (MedAE) = 1.94 (0.10) and Mean Squared Error (MSE) = 8.69 (0.90). We next then evaluated how well the optimized (retrained using all 10-folds of HC data) MCCQRNN model performed on the unseen sample of anxiety disorder patients (N = 1,777), with **Figure**

2B showing their predicted brain age against their chronological age.

Model performance in predicting brain age for HCs was evaluated using 10-fold stratified cross-validation, with each fold trained exclusively on a subset of HCs and tested on unseen HCs (**Figure 2A; Table S2**). Across folds, the model achieved the following average performance (mean; standard deviation across test folds): Pearson's $r = 0.78$ (0.02), coefficient of determination (R^2) = 0.60 (0.03), Mean Absolute Error (MAE) = 2.30 (0.10) years, Median Absolute Error (MedAE) = 1.94 (0.10), and Mean Squared Error (MSE) = 8.69 (0.90). Afterwards, the model was retrained on the full HC dataset and then applied to the independent sample of patients with anxiety disorders ($N = 1,777$), whose predictions are shown in **Figure 2B**. The model achieved the following performance metrics: Pearson's $r = 0.74$, $R^2 = 0.55$, MAE = 2.12, MedAE = 1.78 and MSE = 7.20. Collectively, these metrics signal the model's ability to accurately cross-reference chronological age with brain age, with performance metrics comparable to or exceeding those reported for contemporary brain age models (see **Supplement** for more detailed discussion)⁴², as reflected by high correlations and coefficient of determination, along with low estimation errors. The model's performance metrics place it amongst some of the better performing brain age models in the field, with a recent comparative study further supporting this notion

Uncertainty Quantification & Bias Assessment

Non-adjustment for uncertainty as illustrated in **Figure 2C** and **2D**, resulted in larger and more variable BAGs compared to those obtained with aleatory and epistemic uncertainty correction. So, adjusting BAGs for both model uncertainty (epistemic) and noise in observations (aleatory) led to more precise estimates for both patients and controls, thereby improving the reliability of subsequent analyses on BAG²⁵. As per Hahn et al. (2022), we next performed algorithmic bias assessment by examining differences in brain age prediction performance, as a function of sex and age. Although the age range was identical across groups (10–25 years), the distribution of ages differed, with age standard deviations of 4.95 for male HCs, 4.68 for male patients, 4.33 for female HCs, and 3.69 for female patients. To account for these differences and enable comparability, MAE was standardized by dividing it by the standard deviation of age within each respective group²⁵.

Model performances as indexed by standardized MAE were highly similar in males and females (i.e., indicating no systematic sex bias), both in HCs (males=0.49 | female=0.51) and anxiety patients (males=0.50 | females=0.55), thus removing the necessity for sex-specific modeling. For age, we identified a negative correlation between the uncertainty-adjusted BAG and chronological age (Pearson's $r = -0.61$, $p < 0.001$ for HC; $r = -0.65$, $p < 0.001$ for patients), consistent with prior research^{25,43}. This phenomenon is commonly ascribed to regression dilution, model regularization or non-Gaussian age distribution⁴⁴. Here it implies that in younger participants the age is overestimated and in older

participants underestimated, underscoring the necessity to correct for chronological age in all subsequent analyses of BAG values⁴⁴. Following established recommendations of the field, we corrected for this bias by including both linear and non-linear (quadratic) age terms as covariates in all statistical models^{43,44}. This procedure effectively removed the dependence of BAG on age across diagnostic groups and individual sites, ensuring that observed case-control differences reflect true effects rather than artifacts of age (see **Supplementary Results**). Finally, Levene's tests indicated that variance in both BAG and chronological age differed between cases and controls ($F = 7.74, p < 0.01$ for BAG; $F = 42.3, p < 0.001$ for age), and these variances were strongly correlated ($r = 0.91, p = 0.03$). Including age and age² as covariates ensures that group comparisons in BAG reflect true case-control differences rather than age-related confounding, even though variance differences remain (see **Supplementary Results** and **Tables S3–4** for details).

Clinical Relevance of the Uncertainty-Adjusted BAG

Higher BAG Relates to Anxiety Diagnosis

Residualized and mean BAG estimates (adjusted for chronological age, age², sex, and scanning site) were -0.029 years ($SD = 0.67, 95\% CI = -0.055$ to -0.003) in the control and +0.042 years ($SD = 0.58, 95\% CI = 0.015$ to 0.069) across the anxiety disorders group. When all individuals with anxiety disorders were grouped together and contrasted to all HC youth (transdiagnostic examination), LMEs showed higher BAGs in the former group. This suggests that clinically anxious youth have “older appearing brains” compared to typically developing HCs (+0.09 years (1.08 months); Cohen’s $d = 0.12, 95\% CI = 0.06–0.12, FDR-p < 0.001$) (**Figure 3; Table S5**). Marginal means residualized for age, age², sex, and site within the fitted LME model revealed that the average BAG in patients was +0.09 years higher (1.08 months) than that of HC youth (patients: mean=0.24, SE=0.03 vs. HC: mean=0.15, SE=0.03). We next explored whether using BAG estimates not corrected for uncertainty (aleatory/epistemic) would affect these case-control differences. The analyses showed that while the effect size and p-value remained practically unchanged (Cohen’s $d = 0.11, 95\% CI = 0.05–0.17, FDR-p < 0.001$), the BAG case-control differences indexed in years got inflated by a factor of three (patients: residualized mean 0.13 ($SD = 1.81$) vs. HC: mean -0.09 ($SD = 2.1$); +0.26 (3.12 months)), thus further underscoring the importance of uncertainty correction.

Supplementary exploration of potential disorder-specific effects revealed evidence for differences in BAG between all HCs and specific patient groups ($F(4, 4213) = 5.15, p < 0.001$). Post-hoc testing showed higher BAGs in all disorder groups (PD: residualized mean=0.072, SD=0.42, 95% CI = 0.017 to 0.127; GAD: mean=0.018, SD=0.62, 95% CI = -0.037 to 0.073 SAD: mean=0.009, SD=0.50, 95% CI = -0.045 to 0.064; SPH: mean=0.062, SD=0.63, 95% CI = 0.016 to 0.108) compared to HCs (mean=-0.029, SD=0.67, 95% CI = -0.055 to -0.003), though only the SPH group effect proved statistically significant (average BAG +0.13 years (1.56 months), Cohen’s $d=0.15, 95\% CI = 0.08–0.22, FDR-p < 0.001$.) (**Figure 3**,

Table S5). Similar to the transdiagnostic analyses, using BAG estimates uncorrected for uncertainty (aleatory/epistemic) led to of fairly conserved effect size and p-value (Cohen's $d = 0.14$, 95% CI = 0.07–0.21, $FDR-p < 0.001$), but markedly inflated BAG differences indexed in years between SPH and HC participants (SPH: residualized mean=0.18, SD=1.93 vs. HC: mean=-0.09, SD=2.1; +0.38 years (4.56 months)). These supplementary analyses, however, should be interpreted with some reservation, given their exploratory nature and notably smaller sample sizes.

Moji, ik heb de bovenstaande resultaten hieronder opnieuw uitgeschreven, maar naar mijn mening nu duidelijker: (1) eerst de residualized means vermelden (alleen de gemiddelden, met een verwijzing naar de tabel voor details) en explicet aangeven dat dit descriptive waarden, en (2) vervolgens de case-control analyses (LME-output) waar nu ook β staat voor de geschatte +BAG verschillen bij om explicet te maken dat dit rechtstreeks uit het LME-model komt. (3) dan nog de vergelijking met uncertainty unadjusted scores. Dit doen we eerst voor main (transdiagnostic) vergelijkingen en dan voor post hoc (disorder-specific) vergelijkingen.

Higher BAG Relates to Anxiety Diagnosis

Residualized mean BAG values (adjusted for age, age², sex, and site) per group are presented for descriptive purposes (**Table S4_new**), whereas β estimates from the LME models represent the formal tests of case-control differences (**Table S5**). Residualized mean BAG values were -0.029 years (≈ -0.35 months; SD = 0.67, 95% CI = -0.055 to -0.003) in controls and +0.042 years (≈ 0.50 months; SD = 0.58, 95% CI = 0.015 to 0.069) in the anxiety group (transdiagnostic examination, in which all individuals with anxiety disorders were grouped together). LMEs confirmed higher BAG in patients relative to controls ($\beta = +0.09$ years, $\approx +1.1$ months; Cohen's $d = 0.12$, 95% CI [d]=0.06-0.12, $FDR-p < 0.001$; **Figure 3; Table S5**). This suggests that clinically anxious youth have "older appearing brains" compared to typically developing HCs. We next assessed the impact of using BAG estimates unadjusted for aleatory and epistemic uncertainty on the observed case-control differences. Analyses without uncertainty adjustment yielded very similar effect sizes (Cohen's $d = 0.11$, 95% CI [d] = 0.05-0.17, $FDR-p < 0.001$), but the estimated BAG group difference was nearly threefold ($\beta = +0.26$ years, $\approx +3.1$ months). A similar inflation was visible in the descriptive residualized means (patients: 0.13 years vs. controls: -0.09 years; **Table S4_new**), further underscoring the importance of uncertainty correction.

Supplementary analyses exploring disorder-specific effects revealed significant differences in BAG across diagnoses ($F(4, 4213) = 5.15, p < 0.001$). Residualized mean BAGs were higher in each anxiety disorder compared with controls (GAD: 0.018 years ≈ 0.2 months; PD: 0.072 years ≈ 0.9 months; SAD: 0.010 years ≈ 0.1 months; SPH: 0.062 years ≈ 0.7 months; vs. HC: -0.029 years ≈ -0.3 months). Full descriptive statistics, including SDs and 95% CIs, are provided in **Table S4_new**. Notably, inferential LME

models indicated that only SPH differed significantly from controls ($\beta = +0.13$ years, $\approx +1.6$ months; Cohen's $d = 0.15$, 95% CI [d] = 0.08–0.22, FDR- $p < 0.001$; **Figure 3; Table S5**). Similar to transdiagnostic analyses, uncertainty unadjusted BAG values produced similar effect sizes (Cohen's $d = 0.14$, 95% CI [d] = 0.07–0.21, FDR- $p < 0.001$) but exaggerated the estimated case-control difference ($\beta = +0.38$ years, $\approx +4.6$ months). These supplementary analyses, however, should be interpreted with some reservation, given their exploratory nature and notably smaller sample sizes.

<dit staat ook in Supplement, heb het voor gemak ook tijdelijk hier gezet>

Supplementary Table S4-NEW. Descriptive residualized uncertainty-corrected BAG values across groups.

Uncertainty-adjusted BAG scores are adjusted for age, age², sex, and site.

Group	Mean (years)	SD	95% CI (years)	Mean (months)
HC	-0,029	0,67	-0,055 to -0,003	-0,35
Transdiagnostic	0,042	0,58	0,015 to 0,069	0,50
GAD	0,018	0,62	-0,037 to 0,073	0,22
PD	0,072	0,42	0,017 to 0,127	0,86
SAD	0,010	0,50	-0,045 to 0,064	0,12
SPH	0,062	0,63	0,016 to 0,108	0,74

Clinical and Demographic Correlates of BAG

We next examined whether uncertainty-adjusted BAG scores also relate to key clinical and demographic characteristics. In line with our rationale, all analyses were transdiagnostic, while bearing in mind that the small subgroups that would have emerged render any disorder-specific analyses fairly infeasible. Results for stratified case-control analyses of BAG based on clinical subgroups were very similar to those identified in the main diagnostic examinations. That is, anxiety disorder patients had significantly higher BAGs (“older appearing brains”) than their HC peers, regardless of symptom severity, psychotropic medication use and comorbid MDD (β 's = +0.08 to +0.13 years, Cohen's d = 0.10–0.16, FDR - p 's < 0.03;) (**Figure 4; Table S6**). No effects were found though for early or late age of onset patients versus HCs (FDR - p 's > 0.05). Moreover, no significant differences were found for within-cases BAG comparisons (e.g., patients with vs. without comorbid MDD; patients with vs. without current use of psychotropic medication; early vs. late onset patients; and low vs. high severity patients) (FDR - p 's > 0.05) (**Table S7**). Case-control interaction analyses of BAG in relation to key demographics also revealed no interaction effects (i.e., diagnosis-by-age, diagnosis-by-age² or diagnosis-by-sex) (FDR - p 's > 0.05) (**Table S8**). This indicates that both linear and non-linear relationships between chronological age and BAG manifest similarly in youth with anxiety disorders and HCs, and that both male and female anxiety patients exhibit comparably higher BAGs than their HC peers.

Sensitivity Analysis

While age, age², and sex were corrected for in all analyses, we additionally repeated our main BAG case-control comparison with the same LME models, but now in an age- and sex-matched subset of participants (patient = 1777, HC = 1767), obtained through propensity score matching (see **Supplementary Results**). The results proved nearly identical to the original analysis, suggesting that age and sex do not significantly affect the outcomes. Specifically, uncertainty-corrected BAG scores were significantly higher across young anxiety patients versus HCs (β = +0.08 years, \approx +1 month, Cohen's d = 0.12, 95% CI [d] = 0.07-0.21, FDR - p < 0.001), with significant disorder-specific effects observed only for SPH (β = +0.12 years, \approx +1.4 months, Cohen's d = 0.14, 95% CI [d] = 0.07-0.21, FDR - p < 0.001).

Neuroanatomical Explainability

Combining occlusion-sensitivity mapping and generalized linear multilevel modeling, we investigated which brain regions are relevant for accurate BAG predictions. This revealed a widely distributed multivariate signature of structural BAG across anxiety patients (**Figure 5**), which was highly similar to that of HCs (r = 0.99, p < 0.001) **Figures S2-3**). Further examination showed that occlusion of 126 out of 157 FreeSurfer features significantly affected BAG predictive performance across anxiety patients (see

Table S9). Herein, the occlusion of 60 features increased the BAG, while occlusion of 66 features decreased the BAG. The top 20 most relevant features in BAG prediction across anxiety patients consisted of fronto-striato-limbic and temporo-parietal regions (**Figure 5**).

Further exploratory decomposition of this neuroanatomical feature set across patients revealed highly similar patterns throughout the “extended adolescence period”⁴⁵, encompassing early adolescence (10-15 years), middle adolescence (15-20 years), and late adolescence-young adulthood (20-25 years) ($r = 0.96\text{--}0.99$, $p < 0.001$; **Figures S4-9**). Analyses revealed near-identical neuroanatomical feature sets across male and female anxiety patients ($r = 0.99$, $p < 0.001$; **Figures S10-13**). Likewise, the neuroanatomical feature set identified across all patients (transdiagnostic) was almost identical to those observed in each anxiety disorder separately (disorder-specific) ($r = 0.93 - 0.99$, $p < 0.001$; **Figures S14-21**), further reaffirming our transdiagnostic approach.

Discussion

This ENIGMA-Anxiety Working Group study represents the largest transdiagnostic case-control examination of brain age in youth with various anxiety disorders (N = 4,312; age = 10-25 years, global sites = 92). Uncertainty-aware, deep neural network brain age modeling of neuroanatomical MRI data revealed robust evidence for subtle increases in BAG (“older appearing brains”), across youth with anxiety disorders. These effects were seen across the entire age range and in both sexes, indicating the absence of age- or sex-specific effects. Patient stratifications produced similar case-control effects, with higher BAGs emerging across youth with anxiety disorders, regardless of their symptom severity, medication use, and comorbid MDD status. Occlusion sensitivity mapping moreover revealed a highly multivariate and distributed signature of structural brain age across anxiety disorders, with fronto-striato-limbic and temporo-parietal regions contributing the most to individual-level variations in BAG. Given the paucity of data on the topic, this large-scale study represents an important milestone towards identifying abnormal patterns of brain development and aging in youth with anxiety disorders.

Older Appearing Brains in Youth with Anxiety Disorders

To our knowledge, this is the largest and most comprehensive brain age study in youth with anxiety disorders to date. Clinically anxious youth, grouped here together across the most prevalent anxiety disorders –GAD/PD/SAD/SPH– exhibited “older appearing brains” compared to their typically developing HC peers (average BAG +0.09 years [1.08 months] higher than HC, Cohen’s $d = 0.12$). This is in line with prior reports of older appearing brains in mood and anxiety disorders, both in youth and adult populations^{17,18,20-22,46}. Of note, the results seem to corroborate a recent and similar transdiagnostic case-control examination of brain aging in adult GAD, PD, and SAD patients, wherein “older appearing brains” also emerged across patients⁴⁷. The findings also dovetail a recent brain age study by the

ENIGMA Anxiety Working Group, which specifically focused on adult SPH patients and found “older appearing brains” specifically within their youngest age group (22-35 years)⁴⁸.

The effect sizes reported here are comparable to those of prior large-scale multisite examinations of brain age in depression (highest Cohen’s d= ~0.15)^{16,17} and anxiety disorders (highest Cohen’s d= ~0.14)⁴⁸, but smaller than those reported in schizophrenia (highest Cohen’s d= ~0.48)⁴⁹ and bipolar disorder (highest Cohen’s d ~0.28)⁵⁰. This aligns with previous ENIGMA work that showed largest effect sizes of cortical and subcortical gray matter anomalies in schizophrenia (highest Cohen’s d effect size= 0.53)^{51,52}, followed by bipolar disorder (highest Cohen’s d= ~0.32)^{53,54}, depression (highest Cohen’s d= ~0.17)^{40,41}, and anxiety disorders (highest Cohen’s ~0.14)^{33,55}. This may also partly explain the relatively lower BAG reported here (+0.09 years) in comparison to prior large-scale work in depression (+1.0 years)¹⁷, bipolar disorder (+1.93 years)⁵⁰, and schizophrenia (+3.55 years)⁴⁹, suggesting that abnormalities in brain aging and development might be more subtle in anxiety disorders.

It should be noted though, that these studies typically examined adult patients within a broad age range (18-70 years), while we focused on youth within a much narrower age range (10-25 years), rendering any BAG case-control differences inevitably subtle. The focus on youth may have also limited the accumulating neural impact of chronic psychopathology, and everything that comes with it (e.g., medication use, unfavorable lifestyle and health factors), as typically seen in adult populations⁵⁰. Finally, methodological differences may equally well explain the variability in BAGs, including the algorithm used for brain age estimations, size of training-test samples, correction for uncertainty/noise, and differences in patient characteristics^{12,25,50}. While it was impossible to probe all these factors, our data did show that not correcting for uncertainty/noise (aleatory and epistemic) inflated the BAG case-control differences by a factor of three (with correction: +0.09 vs. without correction: +0.27 years). That said, the BAG increase of +0.09 years in patients versus controls . . . Overall, these findings point to subtle increases in brain age among youth with anxiety disorders, and underscore the need for further research into age-, disorder-, and symptom-specific mechanisms of brain aging across developmental stages.

Mechanisms Underlying Older Appearing Brains

The underlying mechanisms linking clinical anxiety in youth to higher BAGs, and thus older appearing brains, remain poorly understood, though several plausible pathways have been suggested. Chronic stress associated with anxiety disorders has emerged as a particularly relevant factor, for it could set in motion processes that may disrupt typical brain development⁵⁶. Chronically elevated stress can dysregulate the hypothalamic-pituitary-adrenal axis, increase cortisol levels, and promote neuroinflammation, which may collectively affect neurotoxicity, neurogenesis and neuroplasticity⁵⁶⁻⁶⁰. These processes are believed to disproportionately expedite neural development and maturation⁴⁷⁻⁵¹, which might be partly reflected in older appearing brains. According to the Stress Acceleration

Hypothesis⁵⁶, such rapid biological development in youth may serve as a compensatory mechanism to deal with chronic stress.

Previous work shows that youth exposed to chronic stress or trauma not only exhibit older appearing brains (higher BAGs)⁶¹, but also earlier pubertal maturation and older DNA methylation age⁶²⁻⁶⁵. Negative lifestyle and health factors such as alcohol/tobacco consumption, unhealthy diet, physical inactivity, and inadequate sleep also seem to predict increased BAGs, by means of elevating oxidative stress⁶⁶⁻⁶⁹. These negative lifestyle and health factors are also commonly reported in anxiety patients^{9,70,71}, and may as such play a contributing role in the increased BAG patterns revealed here. Finally, genetics seem to play an important role as well, with data from the UK Biobank (N~28.000) convincingly linking BAG variations to specific genetic loci implicated in neurological, metabolic, and immunological pathways⁷². Of note, genetic variants associated with BAG seem to partly overlap with those of major psychiatric disorders, suggestive of shared genetic mechanisms between BAG and psychopathology⁷³. Research in this area is still developing, however, and pathways connecting psychopathology or clinical anxiety to older appearing brains are not yet fully elucidated.

Clinical and Demographic Correlates of BAG

Patient stratifications produced similar case-control effects as the main diagnostic analyses, with higher BAGs emerging across youth with anxiety disorders, regardless of their symptom severity, psychotropic medication use, and comorbid MDD status (Cohen's d = 0.10–0.16). A similar pattern also emerged in prior ENIGMA work on brain aging in major depression¹⁷, suggesting that older appearing brains reported here are probably not driven by specific clinical features. Our supplementary disorder-specific analyses also revealed increased BAGs in GAD, PD, SAD, and SPH patients versus HCs, though only the SPH effect proved statistically significant (average BAG +0.13 years and +83.9% higher than HC, Cohen's d = 0.15). This finding aligns with a recent study by the ENIGMA Anxiety Working Group, which focused solely on adult SPH patients and reported older appearing brains in their youngest age group (22–35 years; BAG +1.20 years, Cohen's d = 0.15)⁴⁸.

The lack of significant findings for the other anxiety disorders could perhaps reflect the smaller sample sizes (see **Table 1**) and thus reduced statistical power. However, high genetic correlation between anxiety disorders, shared environmental risks, and overlapping personality traits of anxiety patients^{9,29,47}, may equally well underlie the lack of disorder-specific effects. It is moreover postulated that SPH may involve distinct and possibly stronger biological foundations compared to other anxiety disorders^{9,74,75}. Some even theorize that fear of specific threats (e.g., spiders, snakes, heights, darkness) may have had evolutionary benefits, rendering them more biologically ingrained^{9,75}. Our results might be detecting this more deeply embedded biological predisposition of SPH compared to other anxiety disorders, though this tentative notion warrants further examination. Overall, the BAG metric thus seems not particularly

sensitive to specific clinical features or diagnostic classes of anxiety disorders, but rather reflects a transdiagnostic marker of brain health and development across young anxiety patients.

Finally, we found that both linear and non-linear relationships between chronological age and BAG manifest similarly in individuals with anxiety disorders and HCs, and that both male and female anxiety patients exhibit comparably higher BAGs than their HC peers. A sensitivity analysis within an age- and sex-matched subsample moreover showed near-identical results for BAG differences, suggesting that case-control differences in BAG were not driven by group differences in age or sex. These findings indicate the absence of age- or sex-specific effects, suggesting that transdiagnostic BAG increases reported here are conserved across the entire age range and in both sexes, in line with prior brain age work in affective disorders^{16,17}.

Neuroanatomical Explainability

The BAG metric addresses a major challenge in neuroimaging research: processing of high dimensional data for individual-level prediction, by means of an intuitive single number^{21,25}. However, reducing high dimensional brain imaging data into a person-specific single estimate of BAG inevitably compromises spatial specificity, thereby overlooking subtleties in underlying mechanisms^{21,25}. To this end, we adopted occlusion-sensitivity mapping²⁵, which revealed a highly multivariate and distributed signature of structural brain age across anxiety disorder patients (**Figure 5**). The top 20 most relevant features consisted of fronto-striato-limbic and temporo-parietal regions (**Figure 5**), which partly overlap with previously reported structural anomalies in cortical and subcortical territories amongst anxiety patients⁹⁻¹¹. Abnormalities in these regions are believed to collectively affect the perception, processing and modulation of emotionally salient information, rendering an individual potentially susceptible to clinical anxiety⁹⁻¹¹. Further exploratory decomposition of this neuroanatomical feature set across patients importantly revealed highly similar patterns during early adolescence (10-15 years), middle adolescence (15-20 years), and late adolescence-young adulthood (20-25 years) (**Figures S4-9**), as well as in males and females (**Figures S10-13**). Moreover, the feature set across anxiety disorders and in each disorder separately were highly overlapping (**Figures S14-21**). Collectively, these findings point to transdiagnostic neuroanatomical signatures of brain age in young anxiety patients, which seem conserved across sexes, developmental periods, and disorder classes.

Strengths & Limitations

The key advantages of this study include the large and diverse international sample (N = 4,312; global sites = 92), access to harmonized individual-level brain morphometry data, and the conservative nature of the analytical pipeline. This massive dataset overcomes hurdles faced by prior work on the topic carried out in significantly smaller and clinically more homogeneous samples, as it greatly boosts sample diversity (e.g., clinical heterogeneity, sociodemographics, data acquisition, geographical location),

statistical power and generalizability of output^{77,78}. Moreover, the use of an uncertainty-aware deep neural network brain age model that uniquely controls for both aleatory and epistemic noise²⁵, along with replication of our main results in an age- and sex-matched subset of participants, increase the precision of findings. In fact, in line with prior work²⁵, our analyses convincingly showed that not adjusting for aleatory/epistemic uncertainty leads to larger and more variable BAG estimates.

Notwithstanding these strengths, there are several limitations to consider. The cross-sectional nature of this study precludes thorough investigation of developmental trajectories and causal pathways potentially relevant to BAG increases we documented in young anxiety patients. As these BAG increases were fairly subtle, future work should aim to unravel potential sources of inter-individual variability in BAG, such as key biological (e.g., oxidative stress/genetics/puberty), clinical (e.g., severity/medication), and lifestyle factors (e.g., diet/sleep). While we had some clinical data in a subset of patients, harmonized and processed biological and lifestyle data were practically unavailable. We also had access to regional brain measures only (FreeSurfer metrics), with voxel-wise MRI data or other brain-imaging modalities (e.g., function or connectivity) not readily available. While incorporation of such additional data forms might allow for even more accurate brain age estimations, it is still unclear whether higher precision (i.e., MAE close to zero) would always translate to higher validity of outcomes or better tracking of psychopathology^{12,79}. Finally, no brain age model to date provides single-subject risk assessment capability, as is the case with our MCCQRNN model. There is ongoing work, however, to extend this model with conformal prediction theory, which would offer statistical guarantees for personalized risk scores of abnormal brain aging, across different samples and age ranges⁸⁰.

Conclusions

In sum, we find robust evidence for subtle increases in BAG (“older appearing brains”) across young anxiety patients, within the largest neuroimaging dataset on youth anxiety disorders worldwide. The effects were seen across the entire age range and in both sexes, and were not driven by specific clinical features. The direction and magnitude of effects were moreover on par with recent brain age examinations in mood and anxiety disorders amongst adults, conducted within ENIGMA and other multisite consortia. The BAG increases documented here thus seem to reflect a transdiagnostic marker of brain health and development across youth with anxiety disorders. Longitudinal brain age work should integrate key clinical, biological, and lifestyle-health factors, so as to assess the potential utility of BAG in informing diagnostics, prognostics, and risk assessment in youth anxiety disorders.

Table 1. Demographic and clinical characteristics for included patients and controls of the four ENIGMA-Anxiety Working Groups.

Characteristic	ENIGMA-Anxiety Working Group												Transdiagnostic ^a (92 sites)		
	PD (36 sites)			GAD (23 sites)			SAD (25 sites)			SPH (36 sites)					
	Patients (N=228)	Controls (N=534)	p	Patients (N=491)	Controls (N=674)	p	Patients (N=320)	Controls (N=403)	p	Patients (N=738)	Controls (N=924)	p	Patients (N=1,777)	Controls (N=2,535)	p
Age, Years	22.09 ± 2.38	21.87 ± 3.00	0.33	18.86 ± 4.21	16.63 ± 4.63	<0.001	21.55 ± 2.21	22.10 ± 2.32	0.001	18.47 ± 4.23	18.32 ± 4.70	0.49	19.60 ± 4.01	19.22 ± 4.62	0.005
Sex (N, Male/Female)	72/156	192/342	0.28	153/338	297/377	<0.001	98/222	118/285	0.76	157/571	341/583	<0.001	490/1287	948/1587	<0.001
STAI-T ^b	49.81 ± 11.67	-		46.84 ± 11.54	-		51.72 ± 11.20	-		36.16 ± 10.31	-		42.74 ± 12.71	-	
Age of onset ^c	17.08 ± 5.58	-		10.59 ± 5.06	-		12.67 ± 4.77	-		7.28 ± 4.45	-		11.10 ± 6.04	-	
Medication, (N, %) ^d	67 (30.18)	-		97 (20.06)	-		39 (12.38)	-		87 (12.87)	-		290 (17.28)	-	
- Antidepressants	52 (24.64)	-		64 (13.76)	-		33 (10.82)	-		21 (3.33)	-		170 (10.55)	-	
- Benzodiazepines	14 (8.00)	-		33 (7.27)	-		0 (0)	-		3 (0.48)	-		50 (3.26)	-	
- Antipsychotics	11 (5.91)	-		28 (6.17)	-		3 (1.08)	-		12 (1.94)	-		54 (3.51)	-	
Comorbid Anxiety (N, %) ^e	-	-		-	-		-	-		-	-		-	-	
- PD	-	-		40 (9.32)	-		12 (3.82)	-		18 (2.59)	-		70 (4.87)	-	
- GAD	51 (23.18)	-		-	-		16 (5.11)	-		36 (5.26)	-		103 (8.46)	-	
- SAD	43 (19.91)	-		233 (46.65)	-		-	-		165 (23.84)	-		431 (31.1)	-	
- SPH	29 (14.36)	-		53 (13.02)	-		18 (6.29)	-		-	-		100 (11.17)	-	
- Mixed ^f	27 (11.84)	-		55 (11.2)	-		5 (1.56)	-		31 (4.2)	-		118 (6.64)	-	
Comorbid Depression (N, %) ^g	105 (48.17)	-		189 (40.65)	-		106 (33.23)	-		101 (14.64)	-		501 (29.61)	-	

PD = Panic Disorder, GAD = Generalized Anxiety Disorder, SAD = Social Anxiety Disorder; SPH = Specific Phobia; STAI_T = The State-Trait Anxiety Inventory – Trait Index scores.

^a All anxiety disorder patients (PD+GAD+SAD+SPH) combined.

^b Available data on STAI-T: PD = 112/GAD = 342/SAD = 186/SPH = 566.

^c Available data age of onset: PD = 92/GAD = 97/SAD = 117/SPH = 179.

^d Available data on psychotropic medication use at the time of scan: PD = 222/GAD = 465/SAD = 315/SPH = 676.

^e Available data on comorbid anxiety disorders: PD = 202/GAD = 407/SAD = 286/SPH = 685. Assigned primary anxiety disorder diagnoses correspond to respective working groups.

^f Patients diagnosed with all four anxiety disorders.

^g Available data on comorbid major depressive disorder: PD = 218/GAD = 465/SAD = 319/SPH = 690.

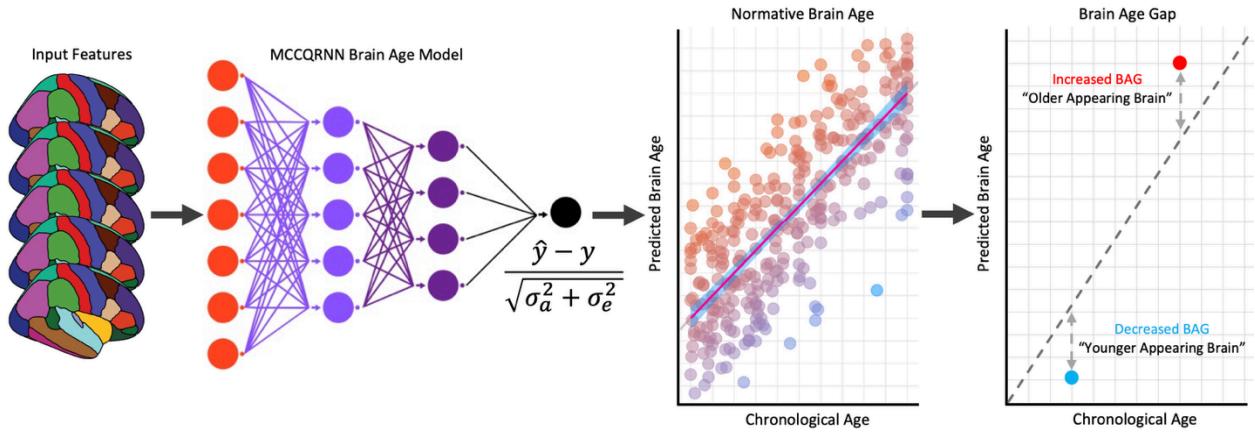


Figure 1. Simplistic visualization of the brain age modeling pipeline. In brief, 157 FreeSurfer-extracted neuroanatomical features are utilized by the MCCQRNN model to estimate normative brain age. The model's predicted brain age and estimated aleatory and epistemic uncertainty are in turn used to calculate the uncertainty-adjusted "brain age gap" (BAG): the difference between an individual's given chronological and predicted brain age. MCCQRNN = Monte Carlo Dropout Composite Quantile Regression Neural Network.

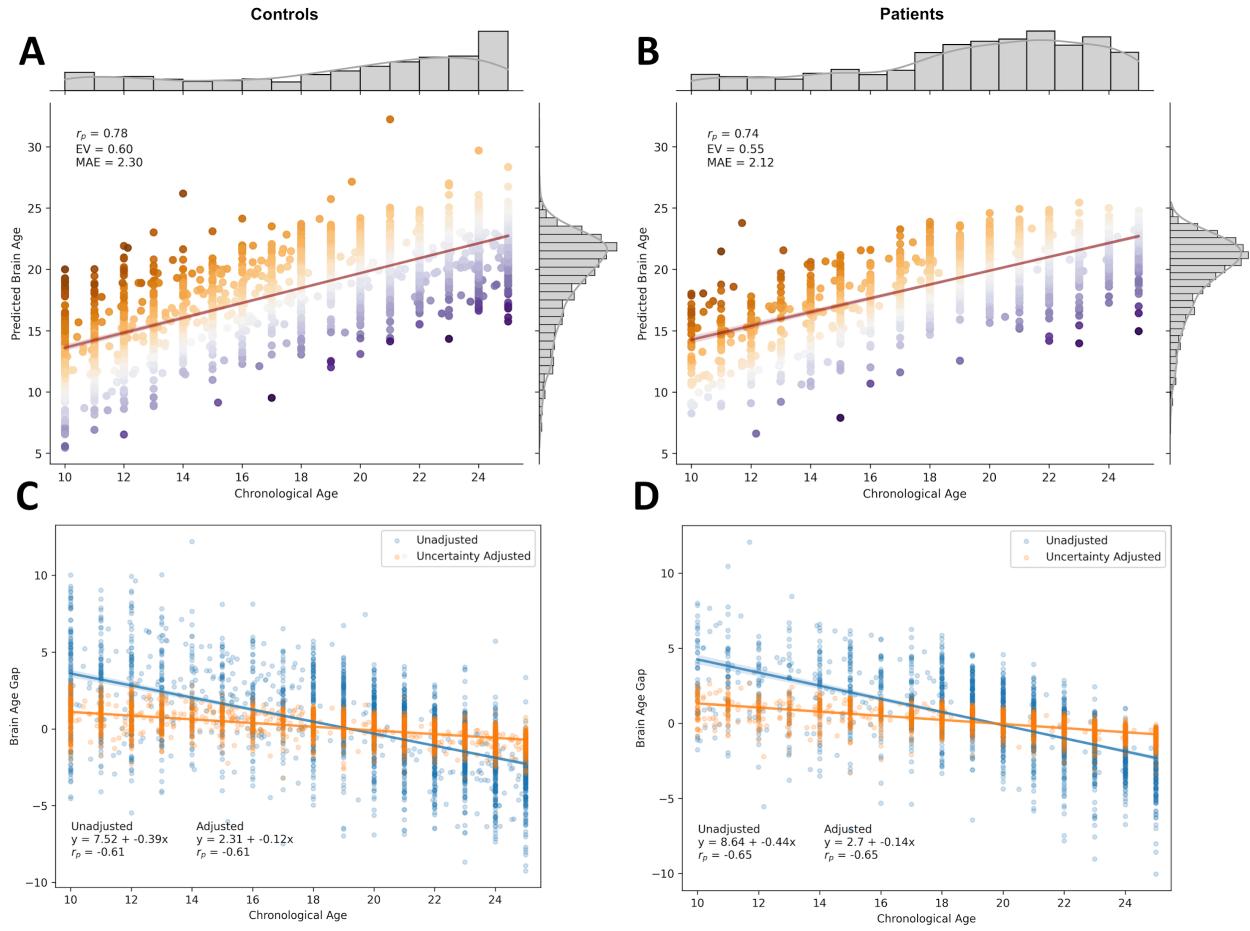


Figure 2. Brain age model predictions and performance. A) Predictions in healthy controls using 10-fold stratified cross-validation. Provided metrics are averaged across folds. B) Brain age predictions and performance in anxiety disorder patients. In panel A and B, warmer colors indicate predicted brain age estimates that are higher than chronological age, while cooler colors indicate the opposite. C) Comparison between uncertainty adjusted and unadjusted brain-age gap (BAG) scores obtained for healthy controls. D) Comparison between uncertainty adjusted and unadjusted BAG scores obtained for patients. r_p = Pearson correlation, R^2 = coefficient of determination, MAE = Mean Absolute Error. Histograms depict distributions of the chronological age (x-axis) and predicted age (y-axis).

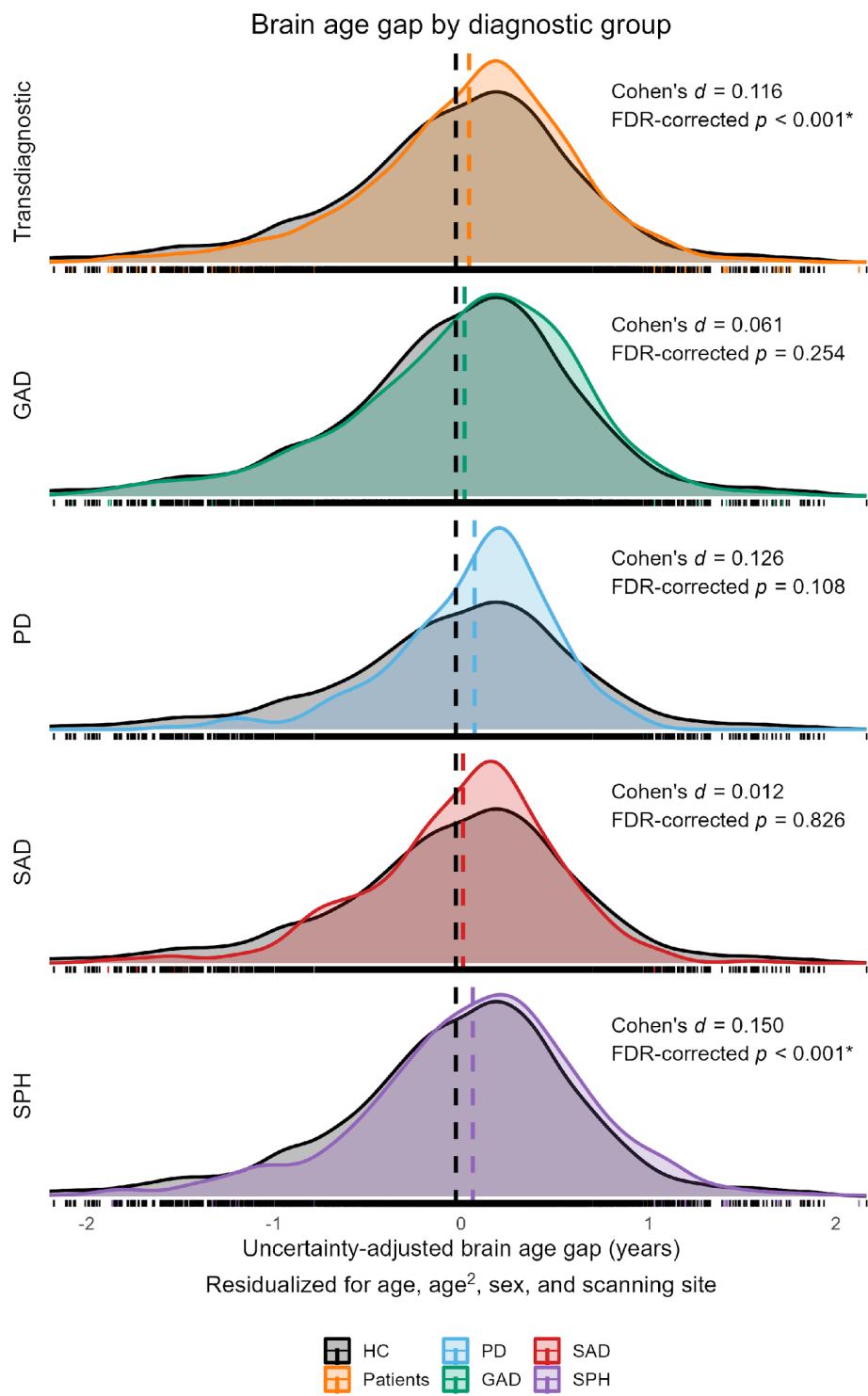


Figure 3. Distribution plots depicting the case-control differences in uncertainty-adjusted BAG scores. Uncertainty-adjusted BAG scores are adjusted for age, age², sex, and site varying effects. Vertical dashed lines indicate the mean residualized BAG in cases (colored) and controls (black). The gray shading behind each clinical group reflects the controls. HC = Healthy Controls, GAD = Generalized Anxiety Disorder, PD = Panic Disorder, SAD = Social Anxiety Disorder; SPH = Specific Phobia.

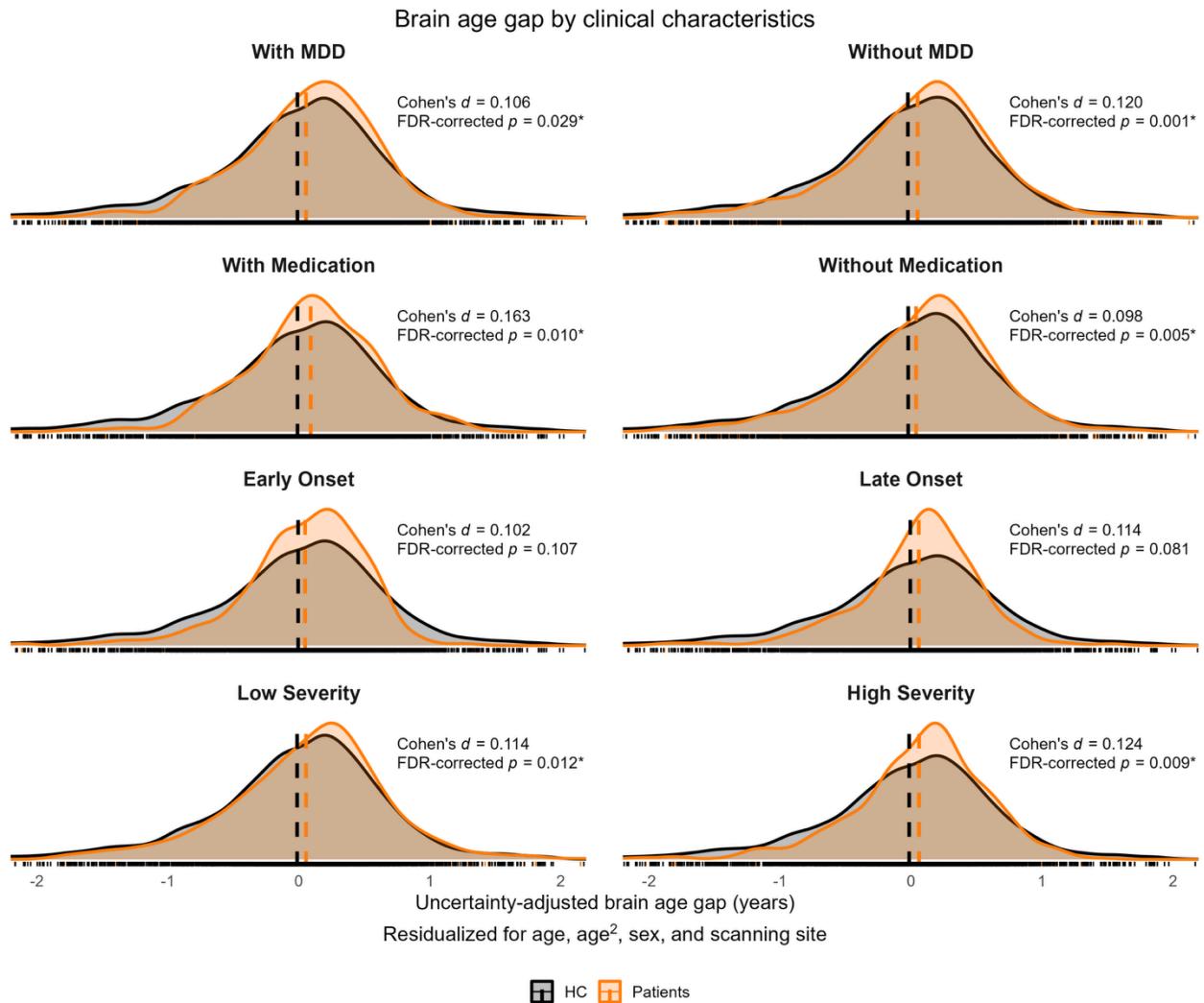
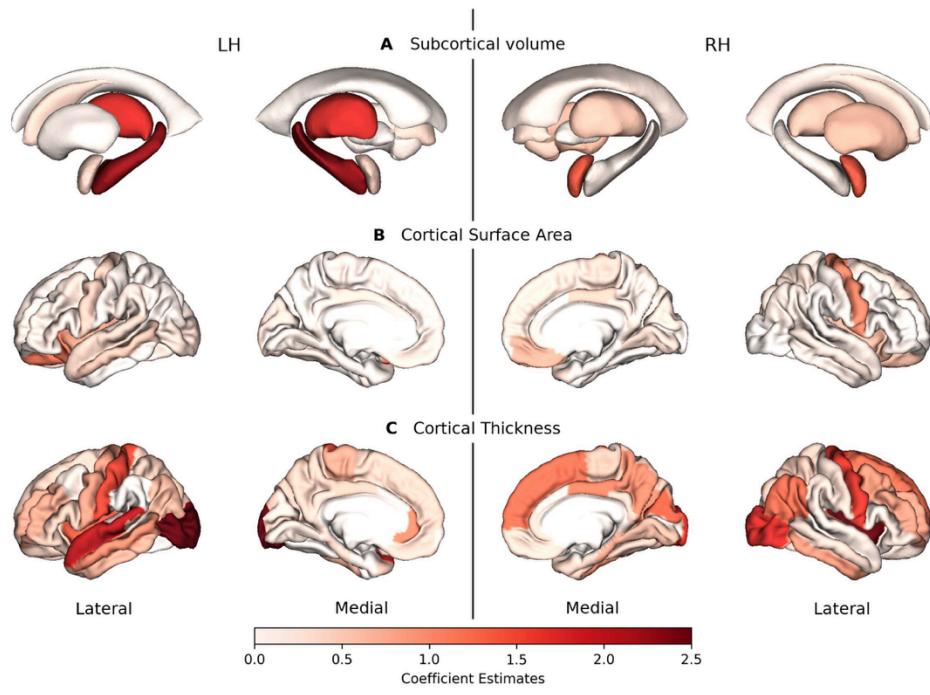
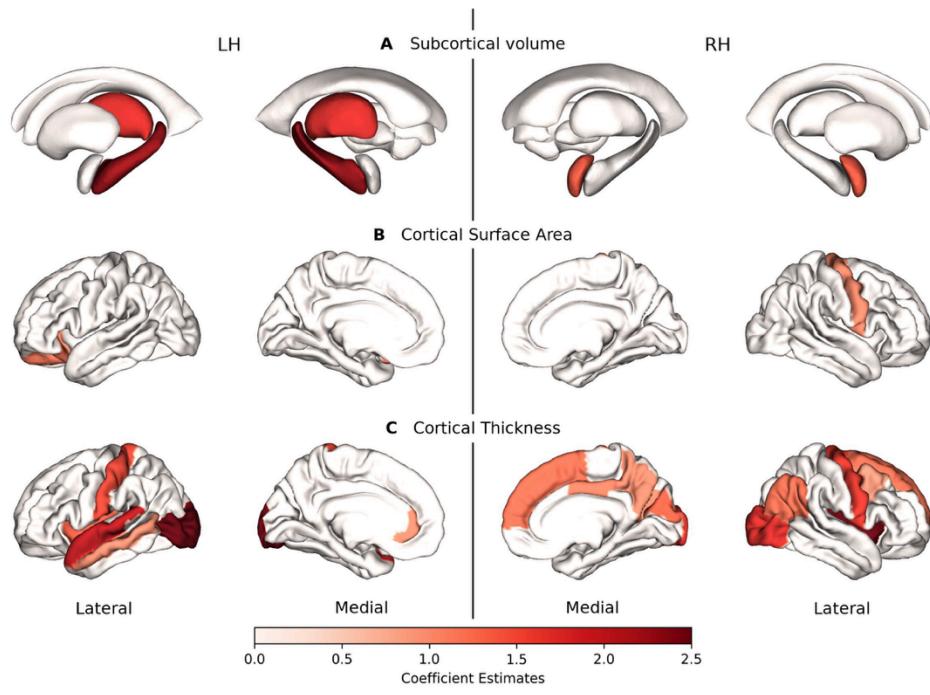


Figure 4. Distribution plots depicting stratified case-control differences in uncertainty-adjusted BAG scores based on clinical subgroups (transdiagnostic). Obtained from a linear mixed effect model residualized for age, age², sex, and site varying effects. Vertical dashed lines indicate the mean residualized BAG in cases (orange) and controls (black). The gray shading behind each clinical group reflects the controls. MDD = Major Depressive Disorder, HC = Healthy Controls.



1



2

Figure 5. Relevant brain regions for accurate brain age prediction in individuals with anxiety disorders (transdiagnostic). The colors represent absolute beta coefficients derived from generalized linear multilevel modeling using an occlusion-sensitivity mapping approach. Darker shades indicate greater impact from occluding specific regions on the accuracy of brain age prediction. Only brain regions that significantly (FDR corrected, $q=0.05$) affected brain age prediction are shown here. Panel 1 depicts all regions that significantly contributed to accurate brain age prediction, while panel 2 depicts regions with top 20 highest absolute beta coefficients. LH = Left Hemisphere; RH = Right Hemisphere.

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