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RESEARCH ARTICLE

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Subcortical volumes across the lifespan: Data from 18,605 healthy individuals aged 3–90 years

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Abstract

Age has a major effect on brain volume. However, the normative studies available are constrained by small sample sizes, restricted age coverage and significant methodological variability. These limitations introduce inconsistencies and may obscure or distort the lifespan trajectories of brain morphometry. In response, we capitalized on the resources of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium to examine age-related trajectories inferred from cross-sectional measures of the ventricles, the basal ganglia (caudate, putamen, pallidum, and nucleus accumbens), the thalamus, hippocampus and amygdala using magnetic resonance imaging data obtained from 18,605 individuals aged 3–90 years. All subcortical structure volumes were at their maximum value early in life. The volume of the basal ganglia showed a monotonic negative association with age thereafter; there was no significant association between age and the volumes of the thalamus, amygdala and the hippocampus (with some degree of decline in thalamus) until the sixth decade of life after which they also showed a steep negative association with age. The lateral ventricles showed continuous enlargement throughout the lifespan. Age was positively associated with inter-individual variability in the hippocampus and amygdala and the lateral ventricles. These results were robust to potential confounders and could be used to examine the functional significance of deviations from typical age-related morphometric patterns.

KEYWORDS
brain morphometry, ENIGMA, longitudinal trajectories, multisite

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1 | INTRODUCTION

Over the last 20 years, studies using structural magnetic resonance imaging (MRI) have confirmed that brain morphometric measures change with age. In general, whole brain, global and regional gray matter volumes increase during development and decrease with aging (Brain Development Cooperative Group, 2012; Driscoll et al., 2009; Fotenos, Snyder, Girton, Morris, & Buckner, 2005; Good et al., 2001; Pfefferbaum et al., 2013; Pomponio et al., 2019; Raz et al., 2005; Raznahan et al., 2014; Resnick, Pham, Kraut, Zonderman, & Davatzikos, 2003; Walhovd et al., 2011). However, most published studies are constrained by small sample sizes, restricted age coverage and methodological variability. These limitations introduce inconsistencies and may obscure or distort the lifespan trajectories of brain structures. To address these limitations, we formed the Lifespan Working group of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium (Thompson et al., 2014, 2017) to perform large-scale analyses of brain morphometric data extracted from MRI images using standardized protocols and unified quality control procedures, harmonized and validated across all participating sites.

Here we focus on ventricular, striatal (caudate, putamen, nucleus accumbens), pallidal, thalamic, hippocampal and amygdala volumes. Subcortical structures are crucial for normal cognitive and emotional adaptation (Grossberg, 2009). The striatum and pallidum (together referred to as basal ganglia) are best known for their role in action selection and movement coordination (Calabresi, Picconi, Tozzi, Ghiglieri, & Di Filippo, 2014) but they are also involved in other aspects of cognition particularly memory, inhibitory control, reward and salience processing (Chudasama & Robbins, 2006; Richard, Castro, Difeliceantonio, Robinson, & Berridge, 2013; Scimeca & Badre, 2012; Tremblay, Worbe, Thobois, Sgambato-Faure, & Féger, 2015). The role of the hippocampus has been most clearly defined in connection to declarative memory (Eichenbaum, 2004; Shohamy & Turk-Browne, 2013) while the amygdala has been historically linked to affect processing (Kober et al., 2008). The thalamus is centrally located in the brain and acts as a key hub for the integration of motor and sensory information with higher-order functions (Sherman, 2005; Zhang, Snyder, Shimony, Fox, & Raichle, 2010). The role of subcortical structures extends beyond normal cognition because changes in the volume of these regions have been reliably identified in developmental (Ecker, Bookheimer, & Murphy, 2015; Krain & Castellanos, 2006), psychiatric (Hibar et al., 2016; Kempton et al., 2011; Schmaal et al., 2016; van Erp et al., 2016) and degenerative disorders (Risacher et al., 2009).

Using data from 18,605 individuals aged 3–90 years from the ENIGMA Lifespan working group we delineated the association between age and subcortical volumes from early to late life in order to (a) identify periods of volume change or stability, (b) provide normative, age-adjusted centile curves of subcortical volumes and (c) quantify inter-individual variability in subcortical volumes which is considered a major source of inter-study differences (Dickie et al., 2013; Raz, Ghisletta, Rodrigue, Kennedy, & Lindenberger, 2010).

2 | MATERIALS AND METHODS

2.1 | Study samples

The study data derive from 88 samples comprising 18,605 healthy participants, aged 3–90 years, with near equal representation of men and women (48% and 52%) (Table 1, Figure 1). At the time of scanning, participating individuals were screened to exclude the presence of mental disorders, cognitive impairment or significant medical morbidity. Details of the screening process and eligibility criteria for each research group are shown in Table S1).

2.2 | Neuroimaging

Detailed information on scanner vendor, magnet strength and acquisition parameters for each sample are presented in Table S1. For each sample, the intracranial volume (ICV) and the volume of the basal ganglia (caudate, putamen, pallidum, nucleus accumbens), thalamus, hippocampus, amygdala and lateral ventricles were extracted using FreeSurfer (http://surfer.nmr.mgh.harvard.edu) from high-resolution T_1-weighted MRI brain scans (Fischl, 2012; Fischl et al., 2002). Prior to data pooling, images were visually inspected at each site to exclude participants whose scans were improperly segmented. After merging the samples, only individuals with complete data were included outliers were identified and excluded using Mahalanobis distances. All analyses described below were repeated for ICV-unadjusted volumetric measures which yielded identical results and are only presented as a separate supplement.

Approximately 20% of the samples had a multi-scanner design. During data harmonization the scanner was modeled as a site. In each

TABLE 1 Characteristics of the included samples

Sample	Age, mean, years	Age, *SD*, years	Age range		Sample size *N*	Number of males	Number of females
ABIDE	17	7.8	6	56	534	439	95
ADHD NF	13	1	12	15	13	7	6
ADNI	76	5.1	60	90	150	70	80
ADNI2GO	73	6.1	56	89	133	55	78
AMC	23	3.4	17	32	92	60	32
Barcelona 1.5T	15	1.8	11	17	30	14	16
Barcelona 3T	15	2.1	11	17	44	24	20
Betula	61	12.9	25	81	234	104	130
BIG 1.5T	28	13.3	13	77	1,288	628	660
BIG 3T	24	7.9	18	69	1,276	540	736
BIL&GIN	27	7.8	18	57	444	217	227
Bonn	39	6.5	29	50	174	174	0
BRAINSCALE	10	1.4	9	15	270	125	145
BRCATLAS	38	15.8	18	80	153	77	76
CAMH	41	17.6	18	86	128	65	63
Cardiff	25	7.4	18	58	316	87	229
CEG	16	1.7	13	19	32	32	0
CIAM	27	5	19	40	30	16	14
CLING	25	5.3	18	58	320	131	189
CODE	40	13.3	20	64	74	31	43
COMPULS/TS Eurotrain	11	1	9	13	53	36	17
Dublin (1)	37	13	17	65	52	23	29
Dublin (2)	30	8.3	19	52	92	51	41
Edinburgh	24	2.9	19	31	55	35	20
ENIGMA-HIV	25	4.4	19	33	31	16	15
ENIGMA-OCD (AMC/Huyser)	14	2.6	9	17	23	9	14
ENIGMA-OCD (IDIBELL)	33	10.1	18	61	65	29	36
ENIGMA-OCD (Kyushu/Nakao)	39	12.5	22	63	40	15	25
ENIGMA-OCD (London Cohort/Mataix-Cols)	37	11.2	21	63	32	11	21
ENIGMA-OCD (van den Heuvel 1.5T)	31	7.6	21	53	48	18	30
ENIGMA-OCD (van den Heuvel 3T)	39	11.2	22	64	35	16	19
ENIGMA-OCD-3T-CONTROLS	31	10.6	19	56	27	10	17
FBIRN	37	11.2	19	60	173	123	50
FIDMAG	38	10.2	19	64	122	53	69
GSP	26	14.9	18	89	1962	860	1,102
HMS	40	12.2	19	64	55	21	34
HUBIN	42	8.9	19	56	99	66	33
IDIVAL (1)	65	10.2	49	87	31	10	21
IDIVAL (3)	30	7.7	19	50	114	69	45
IDIVAL(2)	28	7.6	15	52	79	49	30
IMAGEN	14	0.4	13	16	1744	864	880
IMH	32	10	20	59	79	50	29
IMpACT-NL	37	12	19	63	134	52	82
Indiana 1.5T	60	11	37	79	41	7	34
Indiana 3T	27	18.8	6	73	197	95	102

(Continues)

TABLE 1 (Continued)

Sample	Age, mean, years	Age, *SD*, years	Age range		Sample size *N*	Number of males	Number of females
Johns Hopkins	44	12.5	20	65	87	41	46
KaSP	27	5.7	20	43	32	15	17
Leiden	17	4.8	8	29	565	274	291
MAS	78	4.5	70	89	361	137	224
MCIC	33	12	18	60	93	63	30
Melbourne	20	3	15	26	102	54	48
METHCT	27	7.3	18	53	62	48	14
MHRC	22	2.9	16	28	52	52	0
Moods	33	9.8	18	51	310	146	164
NCNG	50	16.7	19	79	311	92	219
NESDA	40	9.8	21	56	65	22	43
NeuroIMAGE	17	3.7	8	29	376	172	204
Neuroventure	14	0.6	12	15	137	62	75
NTR (1)	15	1.4	11	18	34	11	23
NTR (2)	34	10.3	19	57	105	39	66
NTR (3)	30	5.9	20	42	29	11	18
NU	41	18.8	17	68	15	1	14
NUIG	37	11.5	18	58	89	50	39
NYU	31	8.7	19	52	51	31	20
OATS (1)	71	5.3	65	84	94	27	67
OATS (2)	68	4.4	65	81	33	13	20
OATS (3)	69	4.3	65	81	128	44	84
OATS (4)	70	4.6	65	89	95	23	72
OLIN	36	12.8	21	87	594	236	358
Oxford	16	1.4	14	19	38	18	20
PING	12	4.9	3	21	518	271	247
QTIM	23	3.4	16	30	342	112	230
Sao Paolo 1	27	5.8	17	43	69	45	24
Sao Paolo 3	30	8.1	18	50	83	44	39
SCORE	25	4.3	19	39	44	17	27
SHIP 2	55	12.3	31	84	368	206	162
SHIP TREND	50	13.9	21	81	788	439	349
StagedDep	47	8	27	59	84	20	64
Stanford	37	10.7	19	61	54	20	34
STROKEMRI	42	21.3	18	77	47	17	30
Sydney	37	21.1	12	79	147	58	89
TOP	35	9.8	18	73	296	155	141
Tuebingen	40	12.1	24	61	53	24	29
UMC Utrecht 1.5T	32	12.1	17	66	289	171	118
UMCU 3T	45	15.2	19	81	109	52	57
UNIBA	27	8.7	18	63	130	66	64
UPENN	36	13.6	16	85	185	85	100
Yale	14	2.2	10	18	23	12	11
Total	31	18.4	3	90	18,605	8,980	9,625

Abbreviations: ABIDE = Autism Brain Imaging Data Exchange; ADNI = Alzheimer's Disease Neuroimaging Initiative; ADNI2GO = ADNI-GO and ADNI-2; ADHD-NF = Attention Deficit Hyperactivity Disorder-Neurofeedback Study; AMC = Amsterdam Medisch Centrum; Basel = University of Basel; Barcelona = University of Barcelona; Betula = Swedish longitudinal study on aging, memory, and dementia; BIG = Brain Imaging Genetics; BIL&GIN = a multimodal multidimensional database for investigating hemispheric specialization; Bonn = University of Bonn; BrainSCALE = Brain Structure and Cognition: an Adolescence Longitudinal twin study; CAMH = Centre for Addiction and Mental Health; Cardiff = Cardiff University; CEG = Cognitive-experimental and Genetic study of ADHD and Control Sibling Pairs; CIAM = Cortical Inhibition and Attentional Modulation study; CLiNG = Clinical Neuroscience Göttingen; CODE = formerly Cognitive Behavioral Analysis System of Psychotherapy (CBASP) study; Dublin = Trinity College Dublin; Edinburgh = The University of Edinburgh; ENIGMA-HIV = Enhancing NeuroImaging Genetics through Meta-Analysis-Human Immunodeficiency Virus Working Group; ENIGMA-OCD = Enhancing NeuroImaging Genetics through Meta-Analysis- Obsessive Compulsive Disorder Working Group; FBIRN = Function Biomedical Informatics Research Network; FIDMAG = Fundación para la Investigación y Docencia Maria Angustias Giménez; GSP = Brain Genomics Superstruct Project; HMS = Homburg Multidiagnosis Study; HUBIN = Human Brain Informatics; IDIVAL = Valdecilla Biomedical Research Institute; IMAGEN = the IMAGEN Consortium; IMH=Institute of Mental Health, Singapore; IMpACT = The International Multicentre persistent ADHD Genetics Collaboration; Indiana = Indiana University School of Medicine; Johns Hopkins = Johns Hopkins University; KaSP = The Karolinska Schizophrenia Project; Leiden = Leiden University; MAS = Memory and Ageing Study; MCIC = MIND Clinical Imaging Consortium formed by the Mental Illness and Neuroscience Discovery (MIND) Institute now the Mind Research Network; Melbourne = University of Melbourne; Meth-CT = study of methamphetamine users, University of Cape Town; MHRC = Mental Health Research Center; Muenster = Muenster University; N = number; NESDA = The Netherlands Study of Depression and Anxiety; NeuroIMAGE = Dutch part of the International Multicenter ADHD Genetics (IMAGE) study; Neuroventure: the imaging part of the Co-Venture Trial funded by the Canadian Institutes of Health Research (CIHR); NCNG = Norwegian Cognitive NeuroGenetics sample; NTR = Netherlands Twin Register; NU = Northwestern University; NUIG = National University of Ireland Galway; NYU = New York University; OATS = Older Australian Twins Study; Olin = Olin Neuropsychiatric Research Center; Oxford = Oxford University; QTIM = Queensland Twin Imaging; Sao Paulo = University of Sao Paulo; SCORE = University of Basel Study; SHIP-2 and SHIP TREND = Study of Health in Pomerania; Staged-Dep = Stages of Depression Study; Stanford = Stanford University; StrokeMRI = Stroke Magnetic Resonance Imaging; Sydney = University of Sydney; TOP = Tematisk Område Psykoser (Thematically Organized Psychosis Research); TS-EUROTRAIN = European-Wide Investigation and Training Network on the Etiology and Pathophysiology of Gilles de la Tourette Syndrome; Tuebingen = University of Tuebingen; UMCU = Universitair Medisch Centrum Utrecht; UNIBA = University of Bari Aldo Moro; UPENN = University of Pennsylvania; Yale = Yale University.

site, the intracranial volume (Figure S1) was used to adjust the subcortical volumes via a formula based on the analysis of the covariance approach: "adjusted volume = raw volume − $b \times$ (ICV − mean ICV)", where b is the slope of regression of a region of interest volume on ICV (Raz et al., 2005). The values of the subcortical volumes were then harmonized between sites using the ComBat method in R (Fortin et al., 2017, 2018; Radua et al., 2020). Originally developed to adjust for batch effect in genetic studies, ComBat uses an empirical Bayes to adjust for inter-site variability in the data, while preserving variability related to the variables of interest.

2.3 | Fractional polynomial regression analyses

The effect of age on each ICV- and site-adjusted subcortical volume was modeled using high order fractional polynomial regression (Royston & Altman, 1994; Sauerbrei, Meier-Hirmer, Benner, & Royston, 2006) in each hemisphere. Because the effect of site (scanner and Freesurfer version) was adjusted using ComBat, we only included sex as a covariate in the regression models. Fractional polynomial regression is currently considered the most advantageous modeling strategy for continuous variables (Moore, Hanley, Turgeon, & Lavoie, 2011) as it allows testing for a wider range of trajectory shapes than conventional lower-order polynomials (e.g., linear or quadratic) and for multiple turning points (Royston & Altman, 1994; Royston, Ambler, & Sauerbrei, 1999). For each subcortical structure, the best model was obtained by comparing competing models of up to three power combinations. The powers used to identify the best fitting model were −2, −1, −0.5, 0.5, 1, 2, 3 and the natural logarithm (ln) function. The optimal model describing the association between age and each of the volumes was selected as the lowest degree model based on the partial F-test (if linear) or the likelihood-ratio test. To avoid overfitting at ages with more data points, we used the stricter .01 level of significance as the cut-off for each respective likelihood-ratio tests, rather than adding powers, until the .05 level was reached. For ease of interpretation we centered the volume of each structure so that the intercept of a fractional polynomial was represented as the effect at zero for sex. Fractional polynomial regression models were fitted using Stata/IC software v.13.1 (Stata Corp., College Station, TX). Standard errors were also adjusted for the effect of site in the FP regression.

We conducted two supplemental analyses: (a) we specified additional FP models separately for males and females and, (b) we calculated Pearson's correlation coefficient between subcortical volumes and age in the early (6–29 years), middle (30–59 years), and late-life (60–90 years) age-group. The results of these analyses have been included in the supplemental material.

2.4 | Inter-individual variability

Inter-individual variability was assessed using two complimentary approaches. First, for each subcortical structure we compared the early (6–29 years), middle (30–59 years) and late-life (60–90 years) age-groups in terms of their mean inter-individual variability; these groups were defined following conventional notions regarding periods of development, midlife and aging. The variance of each structure in each age-group was calculated as

$$\ln\left(\frac{\sum\sqrt{e_i^2}}{n_t}\right)$$

where e represents the residual variance of each individual (i) around the nonlinear best fitting regression line, and n the number of

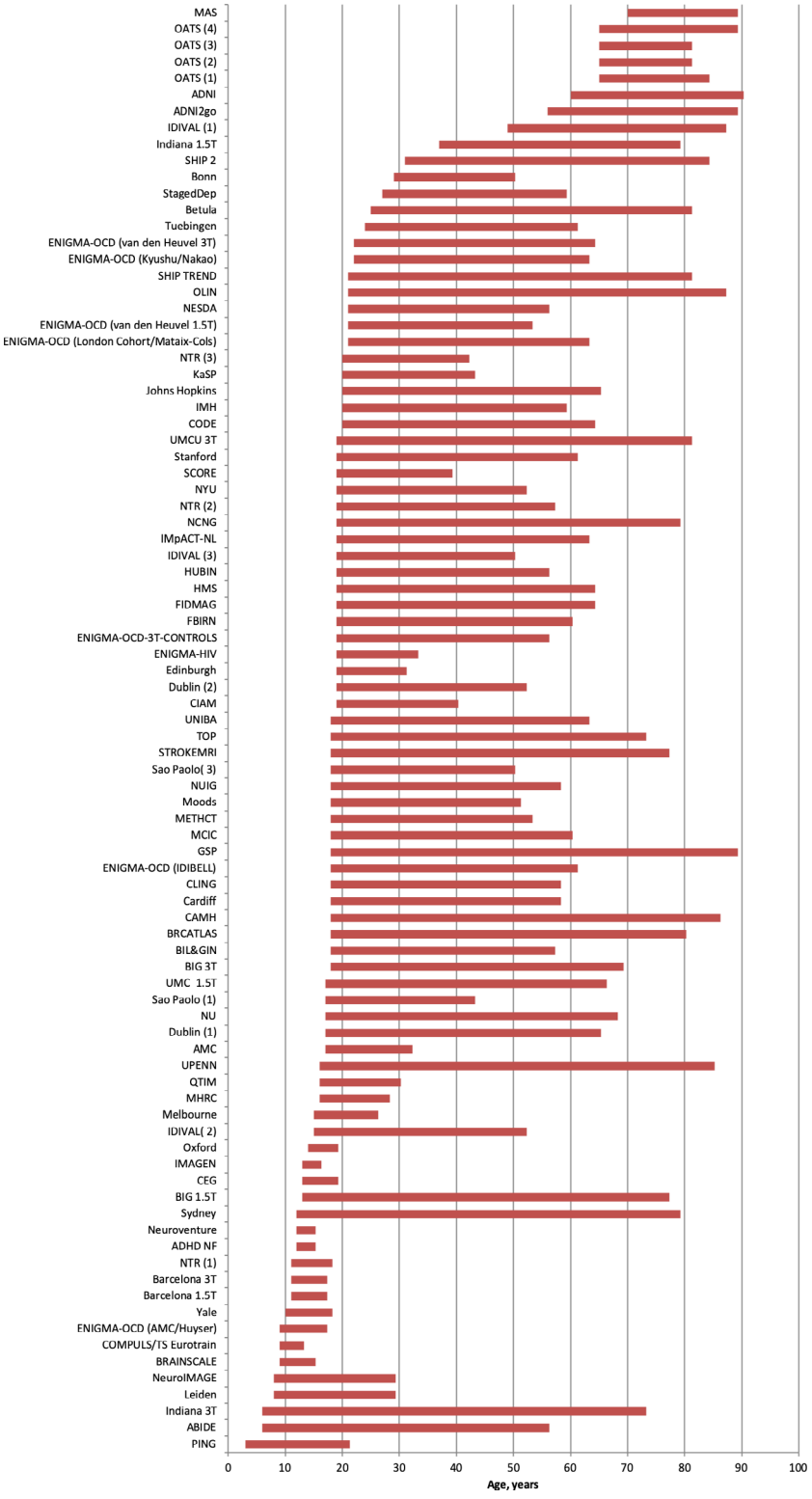

FIGURE 1 ENIGMA lifespan samples. Details of each sample are provided Table 1 and in the supplemental material. Abbreviations are provided in Table 1

observations in each age-group (t). The residuals (e_i) were normally distributed suggesting good fit of the model without having over- or under-fitted the data. Upon calculating the square root of the squared residuals we used the natural logarithm to account for the positive skewness of the new distribution. Then the mean inter-individual variability between early (6–29 years), middle (30–59 years) and late-life (60–90 years) age-groups was compared using between-groups omnibus tests for the residual variance around the identified best-fitting nonlinear fractional polynomial model of each structure. We conducted 16 tests (one for each structure) and accordingly the critical alpha value was set at 0.003 following Bonferroni correction for multiple comparisons.

The second approach entailed the quantification of the mean individual variability of each subcortical structure through a meta-analysis

of the *SD* of the adjusted volumes according to the method proposed by Senior, Gosby, Lu, Simpson, and Raubenheimer (2016).

2.5 | Centile curves

Reference curves for each structure by sex and hemisphere were produced from ICV- and site-adjusted volumes as normalized growth centiles using the parametric Lambda (λ), Mu (μ), Sigma (σ) (LMS) method (Cole & Green, 1992) implemented using the Generalized Additive Models for Location, Scale and Shape (GAMLSS) in R (http://cran.r-project.org/web/packages/gamlss/index.html) (Rigby & Stasinopoulos, 2005; Stasinopoulos & Rigby, 2007). LMS allows for the estimation of the distribution at each covariate value after a suitable transformation and is summarized using three smoothing parameters, the Box-Cox power λ, the mean μ and the coefficient of variation σ. GAMLSS uses an iterative maximum (penalized) likelihood estimation method to estimate λ, μ and σ as well as distribution dependent smoothing parameters and provides optimal values for effective degrees of freedom (edf) for every parameter (Indrayan, 2014). This procedure minimizes the Generalized Akaike Information Criterion (GAIC) goodness of fit index; smaller GAIC values indicate better fit of the model to the data. GAMLSS is a flexible way to derive normalized centile curves as it allows each curve to have its own number of edf while overcoming biased estimates resulting from skewed data

3 | RESULTS

3.1 | Fractional polynomial regression analyses

The volume of the caudate, putamen, globus pallidus and nucleus accumbens peaked early during the first decade of life and showed a linear decline immediately thereafter (Figure 2, Figures S2–S4). The association between age and the volumes of the thalamus, hippocampus and amygdala formed a flattened, inverted U-curve (Figure 3, Figures S5 and S6). Specifically, the volumes of these structures were largest during the first 2–3 decades of life, remained largely stable until the sixth decade and declined gradually thereafter (Table S2). The volume of the lateral ventricles increased steadily with age bilaterally (Figure S7). The smallest proportion of variance explained by age and its FP derivatives was noted in the right amygdala (7%) and the largest in the lateral ventricles bilaterally (38%) (Table S2).

Striatal volumes correlated negatively with age throughout the lifespan with the largest coefficients observed in the middle-life age-group (r = −0.39 to −0.20) and the lowest ($|r|$ < 0.05) in the late-life age-group, particularly in the caudate. The volumes of the thalamus, the hippocampus and the amygdala showed small positive correlations with age ($r \approx 0.16$) in the early-life age-group. In the middle-life age-group, the correlation between age and subcortical volumes became negative (r = −0.30 to −0.27) for the thalamus but remained largely unchanged for the amygdala and the hippocampus. In the late-life age-group, the largest negative correlation coefficients between age and volume were observed for the hippocampus bilaterally (r = −0.44 to −0.39). The correlation between age and lateral ventricular volumes bilaterally increased throughout the lifespan from r = 0.19 to 0.20 in early-life age-group to r = 0.40 to 0.45 in the late-life age-group (Table S3). No effect of sex was noted for any pattern of correlation between subcortical volumes and age in any age-group.

Inter-individual variability: For each structure, the mean inter-individual variability in volume in each age-group is shown in Table S5. Inter-individual variance was significantly higher for the hippocampus, thalamus amygdala and lateral ventricles bilaterally in the late-life age-group compared to both the early- and middle-life group.

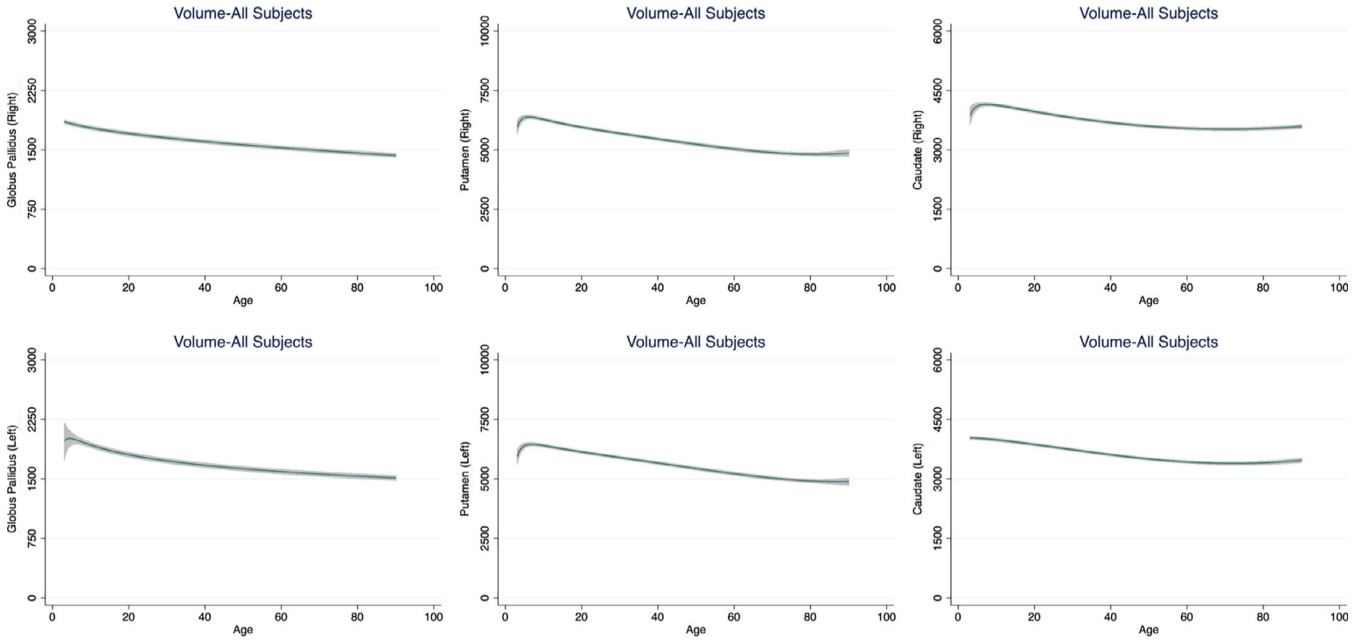

FIGURE 2 Fractional polynomial plots for the volume of the basal ganglia. Fractional Polynomial plots of adjusted volumes (mm^3) against age (years) with a fitted regression line (solid line) and 95% confidence intervals (shaded area)

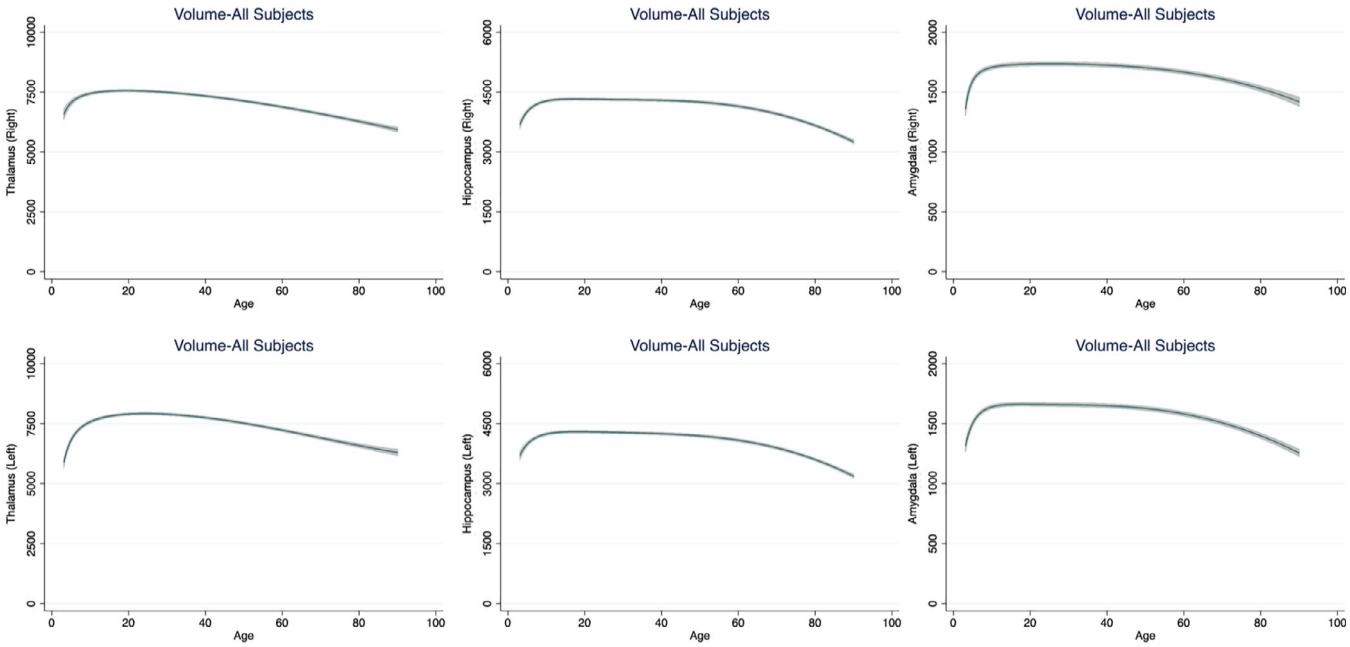

FIGURE 3 Fractional polynomial plots for the volume of the thalamus, hippocampus and amygdala. Fractional polynomial plots of adjusted volumes (mm^3) against age (years) with a fitted regression line (solid line) and 95% confidence intervals (shaded area)

These findings were recapitulated when data were analyzed using a meta-analytic approach (Figure S8).

Normative Centile Curves: Centile normative values for each subcortical structure stratified by sex and hemisphere are shown in Figure 4 and Tables S6–S8.

4 | DISCUSSION

We analyzed subcortical volumes from 18,605 healthy individuals from multiple cross-sectional cohorts to infer age-related trajectories between the ages of 3 and 90 years. Our lifespan perspective and our large sample size complement and enrich previous age-related findings in subcortical volumes.

We found three distinct patterns of association between age and subcortical volumes. The volume of the lateral ventricles increased monotonically with age. Striatal and pallidal volumes peaked in childhood and declined thereafter. The volumes of the thalamus, hippocampuus and amygdala peaked later and showed a prolonged period of stability lasting until the sixth decade of life, before they also started to decline. These findings are in line with those of Pomponio et al. (2019), who also used harmonized multi-site MRI data from 10,323 individuals aged 3–96 years, and those reported by Douaud et al. (2014) who analyzed volumetric data from 484 healthy participants aged 8 to 85 years. Notably, both studies reported similarity in the age-related changes of the thalamus, hippocampus and the amygdala. Our results also underscore the significantly steeper negative association between subcortical volumes and age from the sixth decade of life onwards. This effect seemed relatively more pronounced for the hippocampus, compared to the other subcortical regions, as observed in other studies (Jernigan et al., 2001; Pomponio et al., 2019; Raz et al., 2010).

The trajectories of subcortical volumes are shaped by genetic and nongenetic exposures, biological or otherwise (Eyler et al., 2011; Somel et al., 2010; Wardlaw et al., 2011). Our findings of higher inter-individual variability with age in the volumes of the thalamus, hippocampus and amygdala suggest that these structures may be more susceptible to person-specific exposures, or late-acting genes, particularly from the sixth decade onwards.

The unique strengths of this study are the availability of age-overlapping cross-sectional data from healthy individuals, lifespan coverage and the use of standardized protocols for volumetric data extraction across all samples. Study participants in each site were screened to ensure mental and physical wellbeing at the time of scanning using procedures considered as standard in designating study participants as healthy controls. Although health is not a permanent attribute, it is extremely unlikely given the size of the sample that the results could have been systematically biased by incipient disease

A similar longitudinal design would be near infeasible in terms of recruitment and retention both of participants and investigators. Although multisite studies have to account for differences in scanner type and acquisition, lengthy longitudinal designs encounter similar issues due to inevitable changes in scanner type and strength and acquisition parameters over time. In this study, the use of age-overlapping samples from multiple different countries has the theoretical advantage of diminishing systematic biases reflecting cohort and period effects (Glenn, 2003; Keyes, Utz, Robinson, & Li, 2010) that are likely to operate in single site studies.

In medicine, biological measures from each individual are typically categorized as normal or otherwise in reference to a population

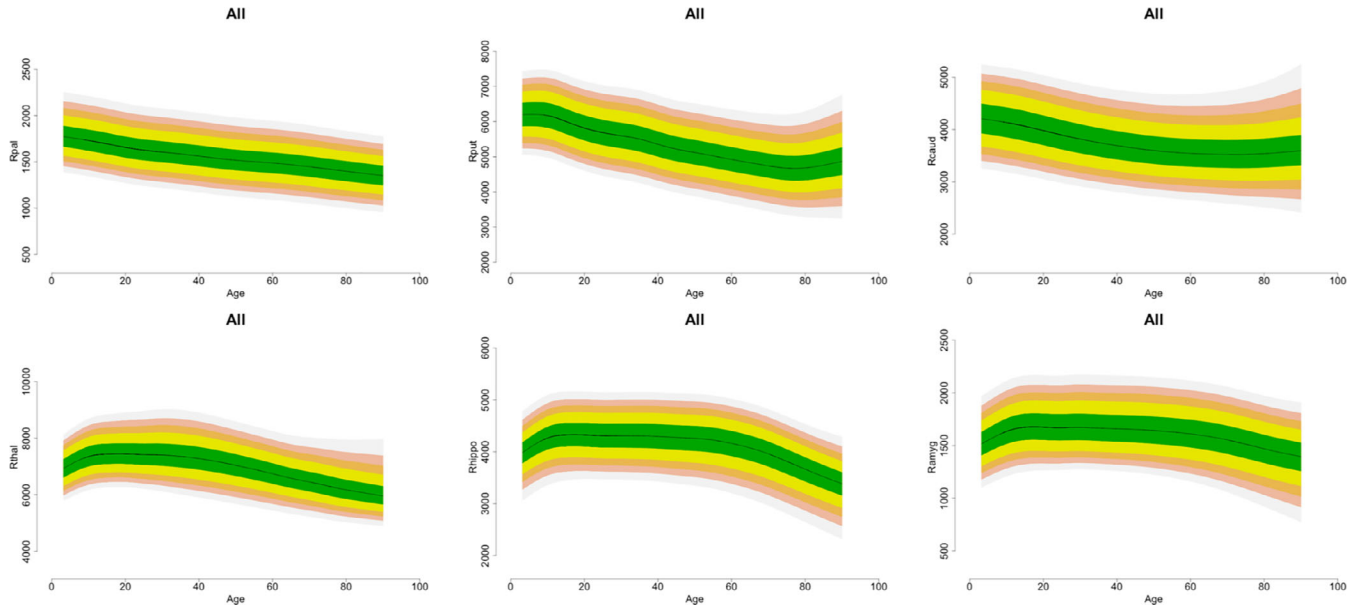

FIGURE 4 Centile values for subcortical volumes; Additional details in Tables S6-S9

derived normative range. This approach is yet to be applied to neuroimaging data, despite the widespread use of structural MRI for clinical purposes and the obvious benefit of a reference range from the early identification of deviance (Dickie et al., 2013; Pomponio et al., 2019). Alzheimer's disease provides an informative example as the degree of baseline reduction in medial temporal regions, and particularly the hippocampus, is one of the most significant predictors of conversion from mild cognitive impairment to Alzheimer's disease (Risacher et al., 2009). The data presented here demonstrate the power of international collaborations within ENIGMA for analyzing large-scale datasets that could eventually lead to normative range for brain volumes for well-defined reference populations. The centile curves presented here are a first-step in developing normative reference values for neuroimaging phenotypes and further work is required in establishing measurement error and functional significance (see Supplement). These curves are not meant to be used clinically or to provide valid percentile measures for a single individual.

In conclusion, we used existing cross-sectional data to infer age-related trajectories of regional subcortical volumes. The size and age-coverage of the analysis sample has the potential to disambiguate uncertainties regarding developmental and aging changes in subcortical volumes while the normative centile values could be further developed and evaluated.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

The ENIGMA Lifespan Working Group welcomes expression of interest from researchers in the field who wish to use the ENIGMA samples. Data sharing is possible subsequent to consent for the principal investigators of the contributing datasets. Requests should be directed to the corresponding authors.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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