Subcortical Volume Trajectories across the Lifespan: Data from 18,605 healthy individuals aged 3-90 years

Danai Dima[1,2], Efstathios Papachristou[3], Amirhossein Modabbernia[4], Gaelle E Doucet[5], Ingrid Agartz[6-8], Moji Aghajani[9], Theophilus N Akudjedu[10], Anton Albajes-Eizagirre[11,12], Dag Alnæs[6,13], Kathryn I Alpert[14], Micael Andersson[15,16], Nancy Andreasen[17], Ole A Andreassen[6,7], Philip Asherson[18], Tobias Banaschewski[19], Nuria Bargallo[20], Sarah Baumeister[19], Ramona Baur-Streubel[21], Alessandro Bertolino[22], Aurora Bonvino[22], Dorret I Boomsma[23], Stefan Borgwardt[24], Josiane Bourque[25], Daniel Brandeis[19], Alan Breier[26], Henry Brodaty[27], Rachel M Brouwer[28], Jan K Buitelaar[29-31], Geraldo F Busatto[32], Randy L Buckner[33,34], Vincent Calhoun[35-38], Erick J Canales-Rodríguez[11,12], Dara M Cannon[10], Xavier Caseras[39], Francisco X Castellanos[40], Simon Cervenka[8,41], Tiffany M Chaim-Avancini[32], Christopher RK Ching[42], Vincent P Clark[43,44], Patricia Conrod[45], Annette Conzelmann[46], Benedicto Crespo-Facorro[12,47], Fabrice Crivello[48], Eveline AM Crone[49], Anders M Dale[50-52], Cristopher Davey[53,54], Eco JC de Geus[23], Lieuwe de Haan[55], Greig I de Zubicaray[56], Anouk den Braber[23], Erin W Dickie[57,58], Annabella Di Giorgio[59], Nhat Trung Doan[6], Erlend S Dørum[6,60,61], Stefan Ehrlich[62], Susanne Erk[63], Thomas Espeseth[60], Helena Fatouros-Bergman[8], Simon E Fisher[64], Jean-Paul Fouche[65], Barbara Franke[29,31], Thomas Frodl[66], Paola Fuentes-Claramonte[11,12], David C Glahn[67], Ian H Gotlib[68], Hans-Jörgen Grabe[69], Oliver Grimm[70], Nynke A Groenewold[65,71], Dominik Grotegerd[72], Oliver Gruber[73], Patricia Gruner[74,75], Rachel E Gur[25,76,77], Ruben C Gur[25,76,77], Ben J Harrison[78], Catharine A Hartman[79], Sean N Hatton[51,80], Andreas Heinz[63], Dirk J Heslenfeld[81],Derrek P Hibar[82], Ian B Hickie[80], Beng-Choon Ho[17], Pieter J Hoekstra[83], Sarah Hohmann[19], Avram J Holmes[84], Martine Hoogman[31,85], Norbert Hosten[86], Fleur M Howells[65,71], Hilleke E Hulshoff Pol[28], Chaim Huyser[87], Neda Jahanshad[42], Anthony James[88], Jiyang Jiang[27], Erik G Jönsson[6,8], John A Joska[65], Rene Kahn[4], Andrew Kalnin[89], Ryota Kanai[90], Sim Kang[91], Marieke Klein[31,85], Tatyana P Klushnik[92], Laura Koenders[55], Sanne Koops[28], Bernd Krämer[73], Jonna Kuntsi[18], Jim Lagopoulos[93], Luisa Lázaro[94,95], Irina Lebedeva[96], Won Hee Lee[4], Klaus-Peter Lesch[97], Christine Lochner[98], Marise WJ Machielsen[55], Sophie Maingault[48], Nicholas G Martin[99], Ignacio Martínez-Zalacaín[12,100], David Mataix-Cols[8,41], Bernard Mazoyer[48], Colm McDonald[10], Brenna C McDonald[26], Andrew M McIntosh[101], Katie L McMahon[102], Genevieve McPhilemy[10], José M Menchón[12,100], Sarah E Medland[99], Andreas Meyer-Lindenberg[103], Jilly Naaijen[30,31,85], Pablo Najt[10], Tomohiro Nakao[104], Jan E Nordvik[105], Lars Nyberg[15], Jaap Oosterlaan[106], Víctor Ortiz-García de la Foz[12,107,108], Yannis Paloyelis[2], Paul Pauli[21,109], Giulio Pergola[22], Edith Pomarol-Clotet[11,12], Maria J Portella[12,110], Steven G Potkin[111], Joaquim Radua[8,95,112], Andreas Reif[70], Joshua L Roffman[113], Pedro GP Rosa[32], Matthew D Sacchet[114], Perminder S Sachdev[27], Raymond Salvador[11,12], Pascual Sánchez-Juan[107,115], Salvador Sarró[11,12], Theodore D Satterthwaite[25], Andrew J Saykin[26], Mauricio H Serpa[32], Lianne Schmaal[53,54], Knut Schnell[116], Gunter Schumann[18,117], Jordan W Smoller[118], Iris Sommer[119], Carles Soriano-Mas[12,100], Dan J Stein[98], Lachlan T Strike[120], Suzanne C Swagerman[23], Christian K Tamnes[121], Henk S Temmingh[65], Sophia I Thomopoulos[42], Alexander S Tomyshev[92], Diana Tordesillas-Gutiérrez[12,122], Julian N Trollor[27], Jessica A Turner[35], Anne Uhlmann[65], Odille A van den Heuvel[9], Dennis van den Meer[6,13,123], Nic JA van der Wee[124,125], Neeltje EM van Haren[126], Dennis van 't Ent[23], Theo GM van Erp[111,127], Ilya M Veer[63], Dick J Veltman[9], Henry Völzke[128], Henrik Walter[63], Esther Walton[129], Lei Wang[130], Yang Wang[131], Thomas H Wassink[17], Bernd Weber[132], Wei Wen[27], John D West[26], Lars T Westlye[60], Heather Whalley[101], Lara M Wierenga[133], Steven CR Williams[2], Katharina Wittfeld[134], Daniel H Wolf[25], Amanda Worker[2], Margaret J Wright[120], Kun Yang[135], Yulyia Yoncheva[40], Marcus V Zanetti[32], Georg C Ziegler[136], Paul M Thompson[42], Sophia Frangou[4,137]

1.Department of Psychology, School of Arts and Social Sciences, City, University of London, UK
2.Department of Neuroimaging, Institute of Psychiatry, Psychology and Neuroscience, King's College London, UK
3.Psychology and Human Development, Institute of Education, University College London, UK
4.Department of Psychiatry, Icahn School of Medicine at Mount Sinai, USA
5. Boys Town National Research Hospital, University of Nebraska Medical Center, USA
6.Norwegian Centre for Mental Disorders Research (NORMENT), Institute of Clinical Medicine, University of Oslo, Norway
7.Department of Psychiatric Research, Diakonhjemmet Hospital, Norway
8. Centre for Psychiatric Research, Department of Clinical Neuroscience, Karolinska Institutet, Sweden
9.Department of Psychiatry, Amsterdam University Medical Centre, Vrije Universiteit, Netherlands
10.Clinical Neuroimaging Laboratory, Centre for Neuroimaging and Cognitive Genomics and NCBES Galway Neuroscience Centre, National University of Ireland, Ireland
11.FIDMAG Germanes Hospitalàries, Spain
12.Mental Health Research Networking Center (CIBERSAM), Spain
13.Division of Mental Health and Addiction, Institute of Clinical Medicine, University of Oslo, Norway
14.Radiologics, INC, USA
15.Umeå Center for Functional Brain Imaging, Umeå University, Sweden
16.Department of Integrative Medical Biology, Umeå University, Sweden
17.Department of Psychiatry, Carver College of Medicine, University of Iowa, USA
18.Social, Genetic and Developmental Psychiatry Centre, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
19.Department of Child and Adolescent Psychiatry and Psychotherapy, Central Institute of Mental Health, Heidelberg University, Germany
20.Imaging Diagnostic Centre, Barcelona University Clinic, Spain
21.Department of Psychology, Biological Psychology, Clinical Psychology and Psychotherapy, University of Würzburg, Germany
22.Department of Basic Medical Science, Neuroscience and Sense Organs, University of Bari Aldo Moro, Italy
23.Department of Biological Psychology, Vrije Universiteit, Netherlands
24.Department of Psychiatry & Psychotherapy, University of Lübeck, Germany
25. Department of Psychiatry, University of Pennsylvania, Philadelphia, USA
26.Department of Radiology and Imaging Sciences, Indiana University School of Medicine, USA
27.Centre for Healthy Brain Ageing, University of New South Wales, Australia
28.Rudolf Magnus Institute of Neuroscience, University Medical Center Utrecht, Netherlands
29.Donders Center of Medical Neurosciences, Radboud University, Netherlands
30.Donders Centre for Cognitive Neuroimaging, Radboud University, Netherlands
31.Donders Institute for Brain, Cognition and Behaviour, Radboud University, Netherlands
32.Laboratory of Psychiatric Neuroimaging, Departamento e Instituto de Psiquiatria, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, Brazil
33.Department of Psychology, Center for Brain Science, Harvard University, USA
34.Department of Psychiatry, Massachusetts General Hospital, USA
35.College of Arts and Sciences, Georgia State University, USA
36.Computer Science, Math, Neuroscience and Physics at Georgia State University, USA
37.Electrical and Computer Engineering and Biomedical Engineering, Georgia Institute of Technology, USA
38. Neurology, Radiology, Psychiatry and Biomedical Engineering Emory University, USA
39.MRC Centre for Neuropsychiatric Genetics and Genomics, Cardiff University, UK
40.Department of Child and Adolescent Psychiatry, New York University, USA

41.Stockholm Health Care Services, Stockholm County Council, Karolinska University Hospital, Sweden
42.Imaging Genetics Center, Mark and Mary Stevens Neuroimaging and Informatics Institute, Keck School of Medicine, University of Southern California, Marina del Rey, USA
43.Department of Psychology, University of New Mexico, USA
44.Mind Research Network, USA
45.Department of Psychiatry, Université de Montréal, Canada
46.Department of Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy, University of Tübingen, Germany
47.HU Virgen del Rocio, IBiS, University of Sevilla, Spain
48.Groupe d'Imagerie Neurofonctionnelle, Institut des Maladies Neurodégénératives, UMR5293, Université de Bordeaux, France
49.Faculteit der Sociale Wetenschappen, Instituut Psychologie, Universiteit Leiden, Netherlands
50.Center for Multimodal Imaging and Genetics, University of California San Diego, USA
51.Department of Neurosciences, University of California San Diego USA
52. Department of Radiology, University of California San Diego, USA
53. Centre for Youth Mental Health, University of Melbourne, Australia
54.Orygen, Australia
55.Academisch Medisch Centrum, Universiteit van Amsterdam, Netherlands
56.Faculty of Health, Institute of Health and Biomedical Innovation, Queensland University of Technology, Australia
57.Kimel Family Translational Imaging Genetics Research Laboratory, University of Toronto, Canada
58.Campbell Family Mental Health Research Institute, The Centre for Addiction and Mental Health, University of Toronto, Canada
59.Department of Experimental and Clinical Medicine, Università Politecnica delle Marche, Italy
60.Department of Psychology, University of Oslo, Norway
61.Sunnaas Rehabilitation Hospital HT, Nesodden, Norway
62.Klinik und Poliklinik für Kinder und Jugendpsychiatrie und Psychotherapie, Universitätsklinikum Carl Gustav Carus an der TU Dresden, Germany
63.Division of Mind and Brain Research, Department of Psychiatry and Psychotherapy, Charité-Universitätsmedizin Berlin, Germany
64.Language and Genetics Department, Max Planck Institute for Psycholinguistics, Netherlands
65.Department of Psychiatry and Mental Health, University of Cape Town, South Africa
66.Department of Psychiatry and Psychotherapy, Otto von Guericke University Magdeburg, Germany
67.Department of Psychiatry, Tommy Fuss Center for Neuropsychiatric Disease Research Boston Children's Hospital, Harvard Medical School, USA
68.Department of Psychology, Stanford University, USA
69.Department of Psychiatry and Psychotherapy, University Medicine Greifswald, University of Greifswald, Germany
70.Department for Psychiatry, Psychosomatics and Psychotherapy, Universitätsklinikum Frankfurt, Goethe Universitat, Germany
71.Neuroscience Institute, University of Cape Town, South Africa
72.Department of Psychiatry and Psychotherapy, University of Muenster, Germany
73.Section for Experimental Psychopathology and Neuroimaging, Department of General Psychiatry, Heidelberg University, Heidelberg, Germany
74.Department of Psychiatry, Yale University, USA
75. Learning Based Recovery Center, VA Connecticut Health System, USA
76.Lifespan Brain Institute, Perelman School of Medicine, University of Pennsylvania, USA

77.Children's Hospital of Philadelphia, University of Pennsylvania, USA
78.Melbourne Neuropsychiatry Center, University of Melbourne, Australia
79.Interdisciplinary Center Psychopathology and Emotion regulation, University Medical Center Groningen, University of Groningen, Netherlands
80.Brain and Mind Centre, University of Sydney, Australia
81.Departments of Experimental and Clinical Psychology, Vrije Universiteit Amsterdam, Netherlands
82.Personalized Healthcare, Genentech, Inc., USA
83.Department of Psychiatry, University Medical Center Groningen, University of Groningen, Netherlands
84.Department of Psychology, Yale University, USA
85.Radboud University Medical Center, The Netherlands
86.Norbert Institute of Diagnostic Radiology and Neuroradiology, University Medicine Greifswald, University of Greifswald, Germany
87.Bascule, Academic Centre for Children and Adolescent Psychiatry, Netherlands
88.Department of Psychiatry, Oxford University, UK
89.Depart of Radiology, The Ohio State University College of Medicine, USA
90.Department of Neuroinformatics, Araya, Inc., Japan
91.Institute of Mental Health, Singapore
92.Laboratory of Neuroimaging and Multimodal Analysis, Mental Health Research Center, Russian Academy of Medical Sciences, Russia
93.Sunshine Coast Mind and Neuroscience, Thompson Institute, University of the Sunshine Coast, Australia
94.Department of Child and Adolescent Psychiatry and Psychology, Barcelona University Clinic, Spain
95.August Pi i Sunyer Biomedical Research Institut (IDIBAPS), Spain
96.Mental Health Research Center, Moscow, Russia
97.Department of Psychiatry, Psychosomatics and Psychotherapy, Julius-Maximilians Universität Würzburg, Germany
98.SA MRC Unit on Risk and Resilience in Mental Disorders, Department of Psychiatry, Stellenbosch University, South Africa
99.Queensland Institute of Medical Research, Berghofer Medical Research Institute, Australia
100.Department of Psychiatry, Bellvitge University Hospital-IDIBELL, University of Barcelona, Spain
101.Division of Psychiatry, University of Edinburgh, UK
102.Herston Imaging Research Facility, Queensland University of Technology, Australia
103.Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Heidelberg University, Germany
104.Department of Clinical Medicine, Kyushu University, Japan
105.CatoSenteret Rehabilitation Hospital, Norway
106.Department of Clinical Neuropsychology, Amsterdam University Medical Centre, Vrije Universiteit Amsterdam, Netherlands
107.Department of Psychiatry, University Hospital “Marques de Valdecilla”, Instituto de Investigación Valdecilla (IDIVAL), Spain
108.Instituto de Salud Carlos III, Spain
109.Centre of Mental Health, University of Würzburg, Germany
110.Department of Psychiatry, Hospital de la Santa Creu i Sant Pau, Institut d'Investigació Biomèdica Sant Pau, Universitat Autònoma de Barcelona, Spain
111.Department of Psychiatry, University of California at Irvine, USA
112.Department of Psychosis Studies, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK
113.Department of Psychiatry, Massachusetts General Hospital, USA
114.Center for Depression, Anxiety, and Stress Research, McLean Hospital, Harvard Medical School, USA

115. Centro de Investigacion Biomedica en Red en Enfermedades Neurodegenerativas (CIBERNED), Spain
116. Department of Psychiatry and Psychotherapy, University Medical Center Göttingen, Germany
117. Centre for Population Neuroscience and Precision Medicine, Institute of Psychiatry, Psychology & Neuroscience, King's College London, UK
118. Center for Genomic Medicine, Massachusetts General Hospital, USA
119. Department of Biomedical Sciences of Cells and Systems, Rijksuniversiteit Groningen, University Medical Center Groningen, Netherlands
120. Queensland Brain Institute, University of Queensland, Australia
121. PROMENTA Research Center, Department of Psychology, University of Oslo, Norway
122. Neuroimaging Unit, Technological Facilities, Valdecilla Biomedical Research Institute IDIVAL, Spain
123. School of Mental Health and Neuroscience, Faculty of Health, Medicine and Life Sciences, Maastricht University, Netherlands
124. Department of Psychiatry, Leiden University Medical Center, Netherlands
125. Leiden Institute for Brain and Cognition, Netherlands
126. Department of Child and Adolescent Psychiatry/Psychology, Erasmus University Medical Center, Sophia Children's Hospital, Rotterdam, The Netherlands
127. Center for the Neurobiology of Learning and Memory, University of California Irvine, USA
128. Institute of Community Medicine, University Medicine, Greifswald, University of Greifswald, Germany
129. MRC Integrative Epidemiology Unit, Population Health Sciences Bristol Medical School, Bristol University, UK
130. Department of Psychiatry and Behavioral Sciences, Feinberg School of Medicine, Northwestern University, USA
131. Department of Radiology, Medical College of Wisconsin, USA
132. Institute for Experimental Epileptology and Cognition Research, University of Bonn, Germany
133. Developmental and Educational Psychology Unit, Institute of Psychology, Leiden University, Netherlands
134. German Center for Neurodegenerative Diseases (DZNE), Rostock/Greifswald Site, University of Greifswald, Germany
135. National High Magnetic Field Laboratory, Florida State University, USA
136. Division of Molecular Psychiatry, Center of Mental Health, University of Würzburg, Germany
137. Department of Psychiatry, Djavad Mowafaghian Centre for Brain Health, University of British Columbia, Canada

¥ Corresponding authors:
Sophia Frangou, Department of Psychiatry, Icahn School of Medicine at Mount Sinai, 1425 Madison Avenue, New York, New York 10029, USA. Email:sophia.frangou@mssm.edu
Danai Dima, City, University of London, Northampton Square, London EC1V 0HB; Email: danai.dima@city.ac.uk

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 capitalised on the resources of the Enhancing Neuroimaging Genetics through Meta-Analysis (ENIGMA) Consortium to examine the age-related morphometric trajectories 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 early in life; the volume of the basal ganglia showed a gradual monotonic decline thereafter while the volumes of the thalamus, amygdala and the hippocampus remained largely stable (with some degree of decline in thalamus) until the sixth decade of life followed by a steep decline thereafter. The lateral ventricles showed a trajectory of continuous enlargement throughout the lifespan. Significant age-related increase in inter-individual variability was found for the hippocampus and amygdala and the lateral ventricles. These results were robust to potential confounders and could be used to derive risk predictions for the early identification of diverse clinical phenotypes.

Introduction

Over the last 20 years, studies using structural magnetic resonance imaging (MRI) have confirmed that brain morphometric measures changes 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 et al. 2005; Good et al. 2001; Pfefferbaum et al. 2013; Pomponio et al., 2019; Raz et al. 2005; Raznahan et al. 2014; Resnick et al. 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 et al. 2014) but they are also involved in other aspects of cognition particularly memory, inhibitory control, reward and salience processing (Chudasama and Robbins 2006; Richard et al. 2013; Scimeca and Badre 2012; Tremblay et al. 2015). The role of the hippocampus has been most clearly defined in connection to declarative memory (Eichenbaum, 2004; Shohamy and 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 et al. 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 et al. 2015; Krain and Castellanos 2006), psychiatric (Kempton et al. 2011; Hibar et al. 2016; 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 age-related trajectories of 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 in age-related trajectories derived from smaller samples (Dickie et al. 2013; Raz et al. 2010).

Materials and Methods

Study Samples

The study data comes from 88 samples and 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).

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 et al. 2002, 2012). Prior to data pooling, images were visually inspected at each site to exclude participants whose scans were improperly segmented. After merging the samples, outliers were identified and excluded using Mahalanobis distances. In each sample, 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 x (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., 2019 this issue). 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.

Fractional polynomial regression analyses

The effect of age on each ICV- and site-adjusted subcortical volume was modelled using high order fractional polynomial regression (Royston and Altman 1994; Sauerbrei et al. 2006) in each hemisphere. Because the effect of site (and thus scanner and Freesurfer version) were adjusted using ComBat, we only included sex as a covariate in the regression models. Fractional polynomial regression is currently considered the most advantageous

modelling strategy for continuous variables (Moore et al. 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 and Altman 1994; Royston et al. 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 over-fitting at ages with more data points, we used the stricter 0.01 level of significance as the cut-off for each respective likelihood-ratio tests, rather than adding powers, until the 0.05 level was reached. For ease of interpretation we centred 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.

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 non-linear best fitting regression line, and n the number of 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 non-linear fractional polynomial model of each structure. 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 standard deviation of the adjusted volumes according to the method proposed by Senior et al. 2016.

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 and Green, 1992) implemented using the Generalised Additive Models for Location, Scale and Shape (GAMLSS) in R (http://cran.r-project.org/web/packages/gamlss/index.html)(Rigby and Stasinopoulos, 2005; 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.

Results

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 age-related trajectories of the thalamic, hippocampal and amygdala volumes followed a flattened, inverted U-curve (Figure 3, Figures S5-S6). Specifically, the volumes of these structures were largest during the first 2-3 decades of life, remained largely stable until the 6th decade and declined gradually thereafter (Table S2). The volume of the lateral ventricles bilaterally increased steadily with age (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≈0.16) in the early-life age-group. In the middle-life age-group, the correlation between age and subcortical volumes became more 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. These findings were recapitulated when data were analysed using a meta-analytic approach (Figure 4 and Figure S8).

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

Discussion

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

We found three distinct age-related trajectories. 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 till the 6th decade of life, before they also started to decline. The trajectories defined here represent a close approximation to a

normative reference dataset and are in line with findings from Pomponio et al (2019) who also used harmonised multi-site MRI data from 10,323 individuals aged 3-96 years. Similar findings were reported by Douaud and colleagues (2014) who analysed volumetric data from 484 healthy participants aged 8 to 85 years; they also noted the similarity in the age-related trajectories of the thalamus, hippocampus and the amygdala. Our results also underscore the acceleration in age-related decline from the 6th 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 non-genetic exposures, biological or otherwise (Eyler et al. 2011; Somel et al. 2010; Wardlaw et al. 2011). Our findings of high age-related inter-individual variability 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 6th decade onwards.

In medicine, biological measures from each individual are typically categorised as normal or otherwise in reference to a population 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 very large-scale datasets that could eventually lead to normative range for brain volumes for well-defined reference populations. 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 our sample that our 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 et al. 2010) that are likely to operate in single site studies.

In conclusion, we used existing data to derive 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 to derive clinically meaningful predictors of risk of adverse health outcomes.

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Conflict of interest

None of the authors reports any conflict of interest in connection to this manuscript.

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.

Table 1. ENIGMA samples

Sample	Age, Mean (Years)	Age, SD (Years)	Age Range (Years)	Sample Size (N)	Male (N)	Female (N)
ADHD NF	13.4	0.9	12-15	12	6	6
AMC	23	3.4	17-32	94	60	34
Barcelona 1.5T	15	1.8	11-17	25	12	13
Barcelona 3T	14.5	2.2	11-17	37	18	19
Betula	62.5	12.8	26-81	263	123	140
BIG	28.4	14.3	13-82	1311	651	660
BIG	24.1	8.1	18-71	1275	537	738
BIL&GIN	26.7	7.7	18-57	451	219	232
CAMH	43.6	19.3	18-86	141	72	69
Cardiff	25.2	7.1	18-58	290	78	212
CEG	15.6	1.7	13-19	32	32	0
CIAM	26.1	4.8	19-40	27	13	14
CLiNG	25.2	5.3	18-58	316	130	186
CODE	39.7	13.3	20-64	72	31	41
ENIGMA-HIV	24.7	4.5	19-33	30	15	15
ENIGMA-OCD (1)	14.9	2	12-17	6	2	4
ENIGMA-OCD (2)	34.5	12.7	18-61	23	11	12
ENIGMA-OCD (3)	38.9	10.9	26-63	20	8	12
ENIGMA-OCD (4)	39.5	12.4	26-63	17	3	14
ENIGMA-OCD (5)	33.9	9.3	24-53	19	6	13
ENIGMA-OCD (6)	39.7	8.2	24-53	17	8	9
ENIGMA-OCD (7)	31.5	10.9	20-56	22	8	14
FBIRN	37.6	11.3	19-60	173	123	50
FIDMAG	37.5	10.1	19-64	123	54	69
GSP	27.2	16.5	18-90	1996	882	1114
HMS	39.6	12.2	19-64	55	21	34
HUBIN	42	8.8	19-56	102	69	33
IMH	31.9	10.1	20-59	78	49	29
Indiana 1.5T	62.5	11.7	37-84	49	9	40
Indiana 3T	27.7	20.1	6-87	199	95	104
KaSP	27.5	5.7	20-43	31	14	17

Table 1. ENIGMA samples

Sample	Age, Mean (Years)	Age, SD (Years)	Age Range (Years)	Sample Size (N)	Male (N)	Female (N)
MAS	78.4	4.7	70-90	528	240	288
MCIC	32.5	12.1	18-60	91	61	30
Melbourne	19.9	2.9	15-26	79	46	33
METHCT	26.5	6.8	18-53	59	45	14
NESDA	40.3	9.7	21-56	65	23	42
NeuroIMAGE	16.7	3.6	8-28	345	155	190
Neuroventure	13.7	0.6	12-15	130	55	75
NU	32.8	14.8	14-68	79	46	33
NUIG	36.1	11.6	18-58	92	53	39
NYU	31.1	8.7	19-52	49	29	20
Olin	36	13.1	21-87	590	236	354
Oxford	16.2	1.4	14-19	38	18	20
QTIM	22.6	3.4	16-30	306	92	214
Sao Paolo (3)	30.5	8.4	18-50	76	42	34
SCORE	25.5	4.3	19-39	44	17	27
SHIP-2	54.4	12	32-81	190	99	91
SHIP TREND	50	13.5	22-79	425	229	196
StagedDep	46.9	8.4	27-58	19	4	15
Stanford	37	10.6	19-61	40	13	27
STROKEMRI	45.2	22.1	18-78	52	19	33
Sydney	39.1	22.1	12-84	157	65	92
TOP	35.4	9.9	18-73	303	159	144
TS-Eurotrain	10.9	1.1	9-13	45	29	16
Tuebingen	40.5	11.9	24-61	50	22	28
UMCU	39.7	14.5	19-65	66	26	40
UNIBA	27.4	9.1	18-63	128	64	64
UPENN	36.3	14	16-85	176	77	99
Yale	14.2	2.3	10-18	22	11	11
Total	**32.9**	**18.3**	**6-90**	**11550**	**5334**	**6216**

N=number; SD= standard deviation; Abbreviations of sample names: ADHD-NF=Attention Deficit Hyperactivity Disorder- Neurofeedback Study; AMC=Amsterdam Medisch Centrum; 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; 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; 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; IMH=Institute of Mental Health, Singapore; Indiana=Indiana University School of Medicine; KaSP=The Karolinska Schizophrenia Project;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=methamphetamine use, University of Cape Town; 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); NU=Northwestern University; NUIG=National University of Ireland Galway; NYU=New York University; 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

FIGURES

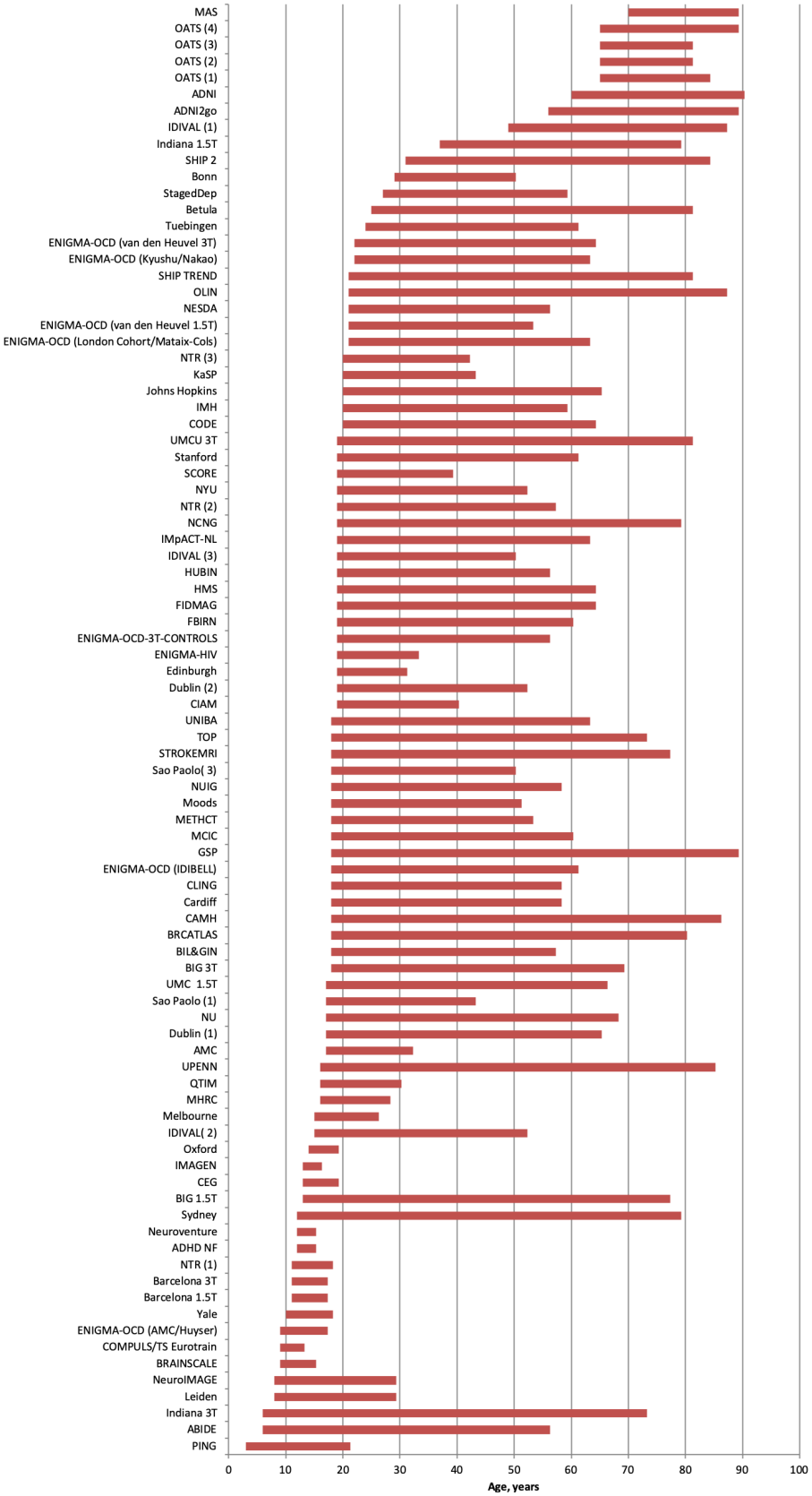

Figure 1. ENIGMA Lifespan Samples

Details of each sample are provided Table 1 and in the supplemental material. Abbreviations are provided in Table 1.

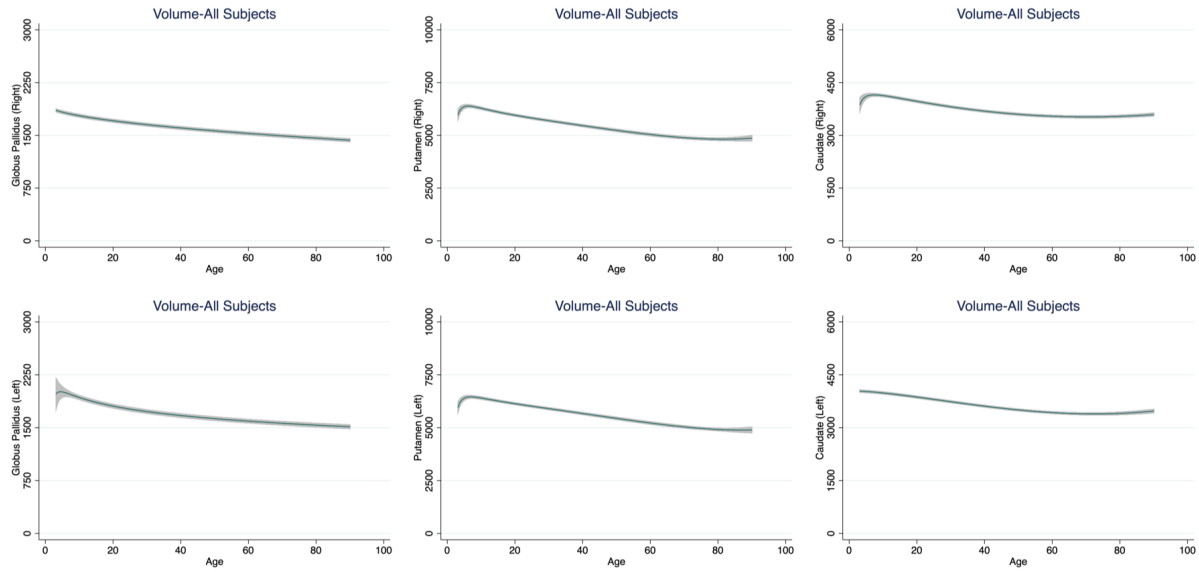

Figure 2. Fractional Polynomial Plots for the Volume of the Basal Ganglia

Fractional Polynomial plots of adjusted volumes (mm^3) against age (years) with a fitted regression line (solid line) and 95% confidence intervals (shaded area).

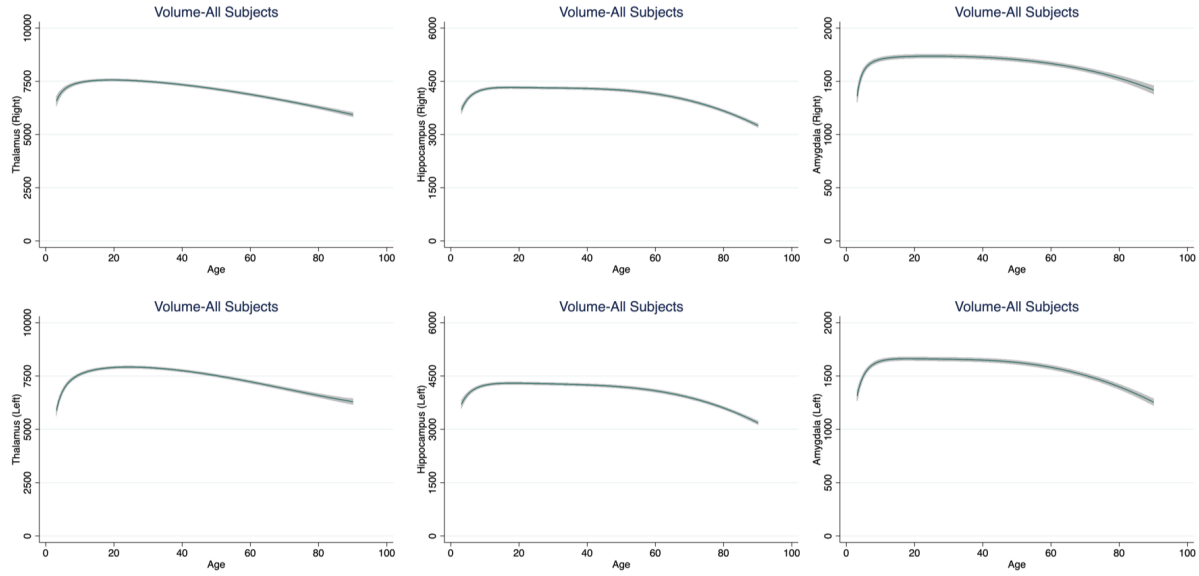

Figure 3. Fractional Polynomial Plots for the Volume of the Thalamus, Hippocampus and Amygdala

Fractional Polynomial plots of adjusted volumes (mm^3) against age (years) with a fitted regression line (solid line) and 95% confidence intervals (shaded area).

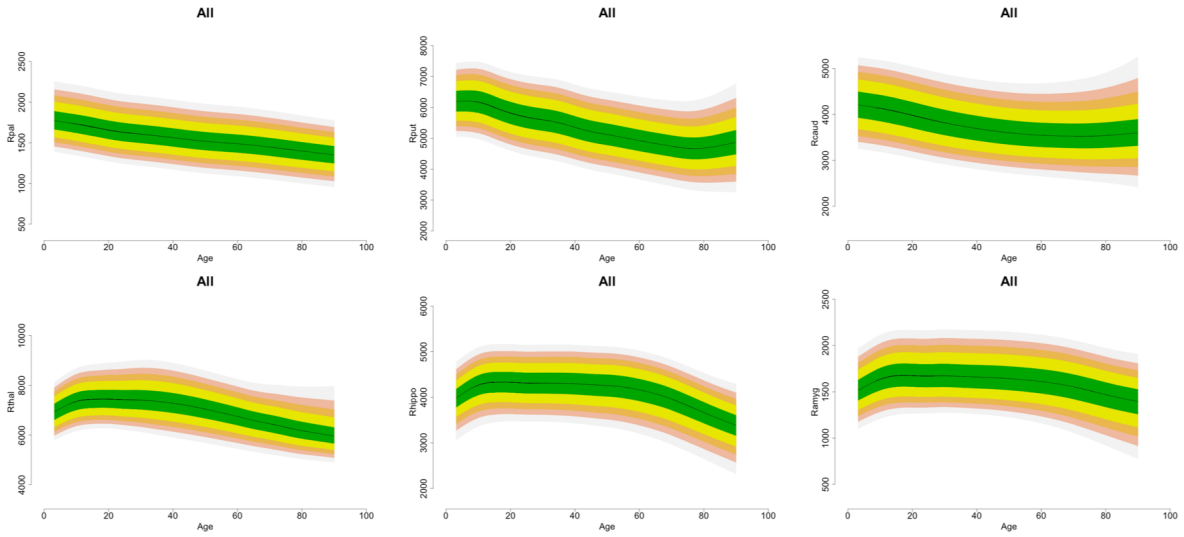

Figure 4. Mean Inter-individual Variability of Subcortical Volumes

Mean individual variability for each subcortical structure was estimated by means of a meta-analysis of the standard deviation of the adjusted volumes in each age-group.

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