Brain charts for the human lifespan

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Abstract

Over the past 25 years, neuroimaging has become a ubiquitous tool in basic research and clinical studies of the human brain. However, no reference standards currently exist to quantify individual differences in neuroimaging metrics over the lifespan, in contrast to growth charts for anthropometric traits such as height and weight[1]. Here, we built an interactive resource (www.brainchart.io) to benchmark individual differences in brain morphology, measured from any current or future magnetic resonance imaging (MRI) study, against normative age-related trends. With the goal of basing these reference charts on the largest and most inclusive dataset available, we aggregated 123,984 MRI scans from 101,457 participants in over 100 studies – from 115 days post-conception through 100 postnatal years. Cerebrum tissue volumes and other global or regional MRI metrics were quantified by centile scores, relative to non-linear trajectories[2], demonstrating concurrent validity with non-MRI brain growth milestones, high stability over longitudinal assessments, and robustness to differences between studies. Brain charts identified previously unreported neurodevelopmental milestones[3], and centile scores had increased heritability compared to non-centiled MRI phenotypes. Crucially, for clinical purposes[4], centile scores provided a standardised and interpretable measure of deviation that revealed new patterns of neuroanatomical differences across neurological and psychiatric disorders. In sum, brain charts for the human lifespan are an essential first step towards robust, standardised quantification of deviation from age-related trends in multiple commonly-used neuroimaging phenotypes. Our global collaborative study provides such an anchorpoint for neuroimaging research and will facilitate implementation of quantitative standards in clinical studies.

Main

First published in the late 18th century[1], the simple framework of growth charts to quantify developmental change against a reference standard remains a cornerstone of paediatric care. Although a powerful example of 'personalised' or 'precision' medicine, growth charts exist mainly for a small set of anthropometric variables, e.g., height, weight and head circumference. Critically, brain growth and maturation continues well beyond developmental periods covered by anthropometric charts. The lack of brain reference standards is particularly relevant to psychiatric disorders that are increasingly considered to be disorders of neurodevelopment[4], and arguably represent the single highest current global health burden[5]. Furthermore, preterm infants and those born with congenital conditions – many with psychiatric sequelae – show marked morphological differences during early brain development[6,7] and even decades later during adulthood[7,8]. With ageing, neurodegeneration and accelerated changes in brain tissue volumes are hallmark signatures of Alzheimer's disease (AD)[9] and other types of dementia. Modernising the concept of growth charts to generate analogous life-spanning reference charts for the human brain would allow for standardised comparison across samples at scale, while simultaneously advancing our understanding of atypicality by providing benchmark reference points for individual differences in both typical development and ageing.

Such standards for neuroimaging-based reference charts have not yet materialised, likely due to the challenges of integration across studies targeting specific developmental epochs and clinical

conditions. In particular, the perinatal period is rarely incorporated in lifespan models, despite evidence that early biophysical and molecular processes shape brain growth trajectories[10,11] and vulnerability to psychiatric conditions[3]. Moreover, case-control comparisons are usually limited to a single disorder despite evidence of shared risk factors and convergent mechanisms, especially in psychiatry[12,13]. Compared to relatively simple anthropometric variables like height or weight, brain morphometrics derived from neuroimaging are more sensitive to methodological variation in scanner platforms, acquisition, and analytic strategy, which severely limits the generalisability of trajectories estimated from individual datasets[14]. Collaborative initiatives spurring collection of large-scale datasets[15,16], recent advances in neuroimaging data processing[17,18], and proven statistical frameworks[2,19,20] provide the building blocks for comprehensive, life-spanning reference charts of the human brain. Here, we present lifespan models of brain development and ageing that i) robustly capture the normative spectrum of age and sex; ii) identify previously unreported brain growth milestones; iii) increase sensitivity to genetic and early life events; iv) provide standardised effect-size deviations that reveal new patterns of neuroanatomical differences across multiple clinical disorders; and v) represent a global resource for future neuroimaging studies to leverage the benefits of normative benchmarks for precise, quantitative assessment of individual differences in brain structure.

Mapping normative brain growth

We created brain charts for the human lifespan using generalised additive models for location, scale and shape (GAMLSS)[2,19], a robust and flexible framework for modelling non-linear growth trajectories recommended by the World Health Organization[19]. Models were fitted to structural MRI data from control subjects for the four main tissue volumes of the cerebrum (total cortical grey matter volume [GMV] and total white matter volume [WMV], total subcortical grey matter volume [sGMV], and total ventricular cerebrospinal fluid volume [Ventricles or CSF]). See **Online Methods**, **Supplementary Table** [**ST**] **1.1-1.7** for details on acquisition, processing and demographics of the dataset. See **Supplementary Information** [**SI**] for details regarding GAMLSS model specification and estimation (**SI1**), image quality control (**SI2**), model stability and robustness (**SI3-4**), phenotypic validation against non-imaging metrics (**SI3 & SI5.2**), inter-study harmonisation (**SI5**) and assessment of cohort effects (**SI6**).

Our models extend previously reported growth curves in multiple ways. Lifespan curves (**Fig.1**; **ST2.1**) show an initial strong increase in GMV from mid-gestation onwards, peaking at $5.9_{\text{CI-Bootstrap:5.8-6.1}}$ years, followed by a near-linear decrease. This peak was observed 2-3 years later than prior reports relying on smaller, more age-restricted samples[21,22]. WMV also increased rapidly from mid-gestation through early childhood peaking at $28.7_{\text{CI-Bootstrap:28.1-29.2}}$ years postnatal, with subsequent accelerated decline in WMV after 50 years. Subcortical GMV showed an intermediate growth pattern compared to GMV and WMV, peaking in adolescence at $14.4_{\text{CI-Bootstrap:14.0-14.7}}$ years. Both the WMV and sGMV peaks are consistent with prior neuroimaging and postmortem reports[23,24]. In contrast, CSF showed an increase until age 2, followed by a plateau until age 30, and then a slow linear increase that exponentiated in the sixth decade of life. Previously reported growth curves have not generally modelled age-related changes in the variability of brain structure. Age-related variance (**Fig.1D**), explicitly estimated by GAMLSS, formally quantifies developmental changes in between-subject variability. There was an early

developmental increase in GMV variability that peaked at 4 years, whereas subcortical volume variability peaked in late adolescence. WMV variability peaked during the fourth decade of life, and CSF was maximally variable at the end of the human lifespan.

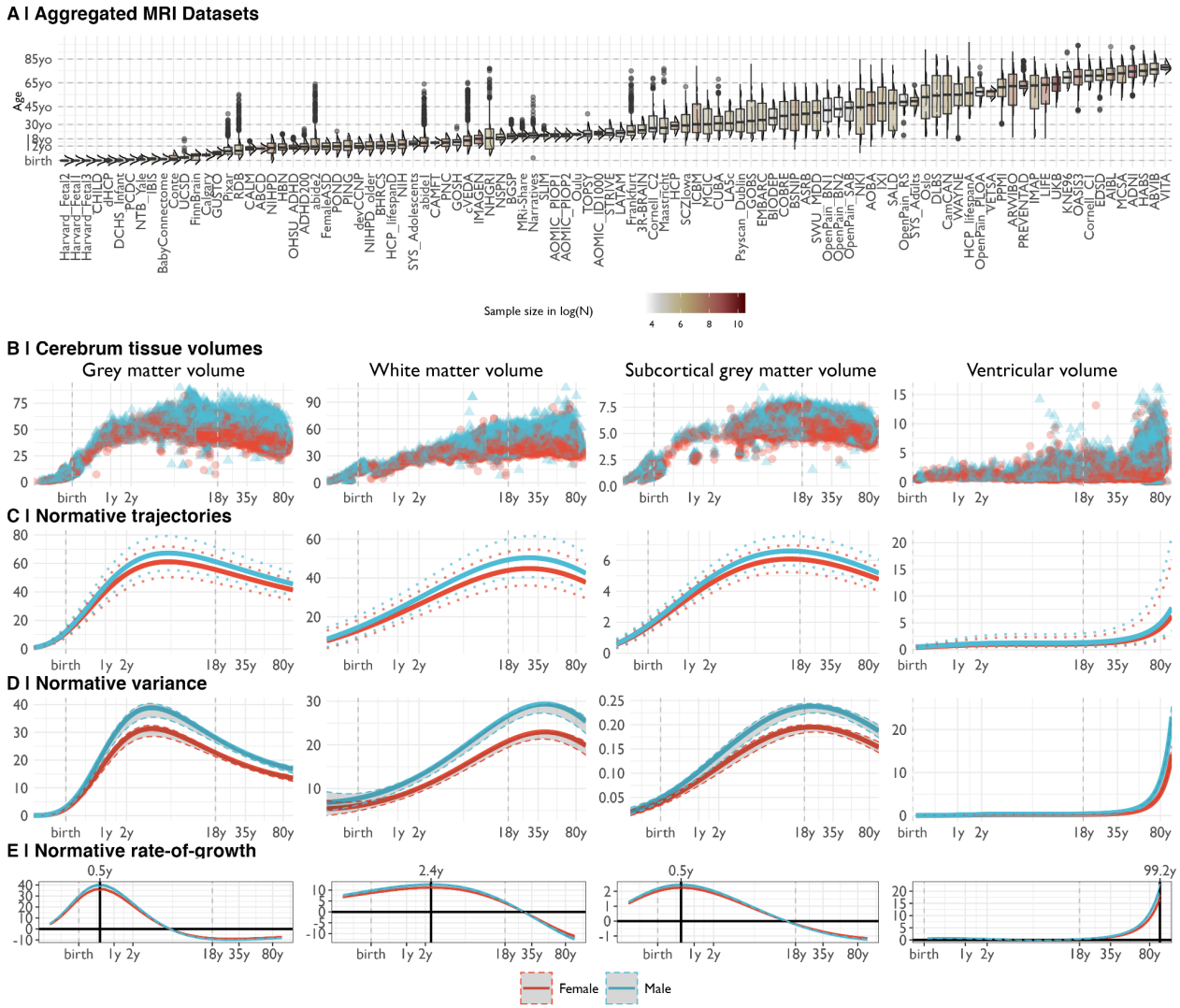

Fig. 1. Human brain charts. *A | MRI data were aggregated from 100 primary studies comprising 123,984 scans that collectively spanned the age range from late pregnancy to 100 postnatal years. Box-violin plots show age distributions (log-scaled) for each study coloured by its relative sample-size (log-scaled) B | Non-centiled bilateral cerebrum tissue volumes (right to left: grey matter, white matter, subcortical grey matter and ventricles) are plotted for each cross-sectional control scan, point-coloured by sex, as a function of age (log-scaled). C | Normative brain growth curves, analogous to paediatric growth charts, were estimated by generalised additive modelling for location scale and shape (GAMLSS), accounting for site- and study-specific batch effects, and stratified by sex (female/male curves coloured red/blue). All four cerebrum tissue volumes demonstrated distinct, non-linear trajectories of their medians and 95% centile boundaries as a function of age over the life-cycle. Demographics for each cross-sectional sample of healthy controls included in the reference dataset for normative GAMLSS modeling of each MRI phenotype are detailed in* ***ST1.2-1.7.*** *D | Trajectories of median between-subject variability and 95% confidence intervals for four cerebrum issue volumes were estimated by sex-stratified bootstrapping (1,000 times; see* ***SI3*** *for details). E | Rates of volumetric change across the lifespan for each tissue volume, stratified by sex, were estimated*

*by the first derivatives of the median volumetric trajectories. For solid (parenchymal) tissue volumes, the solid horizontal line (y=0) indicates when the volume of each tissue stops growing and starts shrinking; the solid vertical line indicates the age of maximum growth of each tissue. See **ST2.1** for all neurodevelopmental milestones and their confidence intervals. Note that y-axes in panels B-E are scaled in units of 10,000 mm^3 (10ml).*

Extended brain MRI phenotypes

To extend the scope of brain charts beyond the four cerebrum tissue volumes, we used the same GAMLSS modeling approach to estimate normative trajectories for additional MRI phenotypes including other geometric properties at a similar scale (mean cortical thickness and total surface area) and regional volume at each of 34 cortical areas[25] (**Fig.2, SI7-9, ST1-2**). We found, as expected, that total surface area closely tracked the development of total cerebrum volume (TCV) across the lifespan (**Fig.2A**), with both metrics peaking at ~11-12 years (SA $10.97_{\text{CI-Bootstrap:10.42-11.51}}$; TCV $12.5_{\text{CI-Bootstrap:12.14-12.89}}$). In contrast, cortical thickness peaked distinctly early at $1.7_{\text{CI-Bootstrap:1.3-2.1}}$ years, which reconciles prior observations that cortical thickness increases during the perinatal period[26] and declines during later development[27]. We also found evidence for regional variability in volumetric neurodevelopmental trajectories. Compared to GMV's peak at 5.9 years, the age of peak regional volume varied considerably – from approximately 2 to 10 years – across 34 cortical areas. Primary sensory regions reached peak volume earliest, and fronto-temporal association cortical areas matured later (**Fig.2B; SI8**). In general, earlier maturing ventral-caudal regions also showed faster post-peak declines in cortical volume, and later maturing dorsal-rostral regions showed slower post-peak declines (**Fig.2B; SI8.2**). Notably, this spatial pattern recapitulates a gradient from sensory-to-association cortex that has been previously associated with multiple aspects of brain structure and function[28].

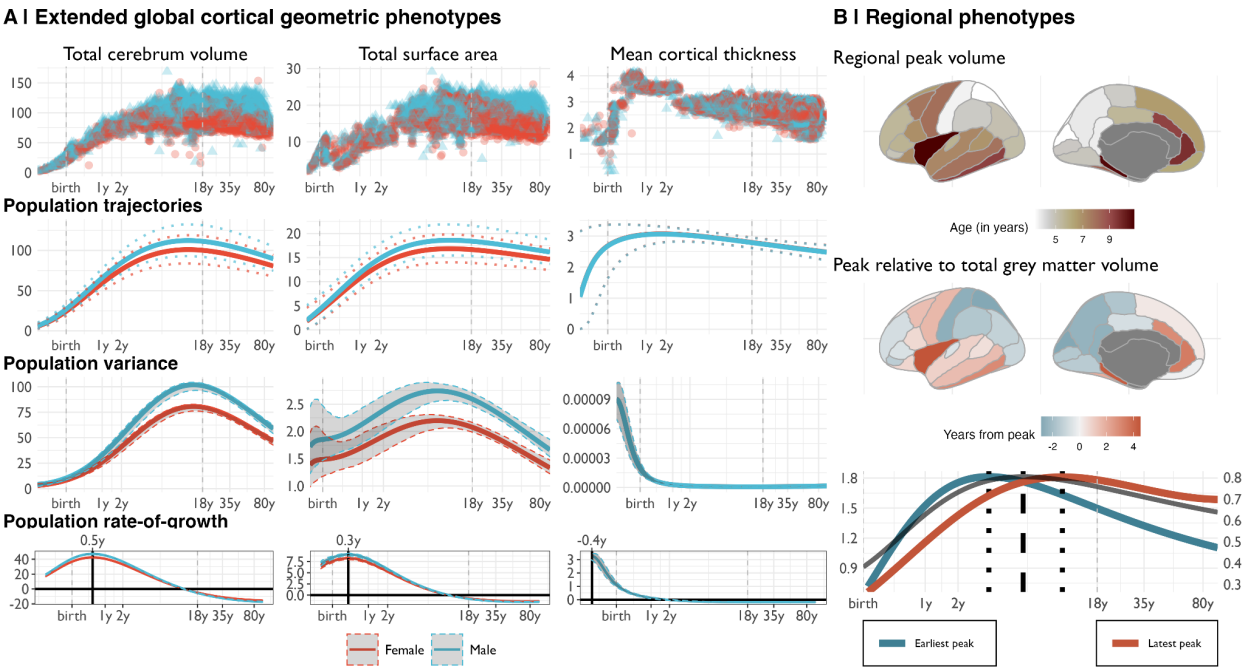

Fig 2. Extended global and regional cortical geometric phenotypes. *A | Trajectories for total cerebrum volume (TCV; left column), total surface area (SA; middle column), and mean cortical thickness (CT; right column). For each global cortical geometric MRI phenotype, the following sex-stratified results are shown as a function of age over the life-span, from top to bottom rows: raw, non-centiled data, population trajectories of the median (with 2.5% and 97% centiles; dotted lines), between-subject variance (and 95% confidence intervals), and rate-of-growth (the first derivatives of the median trajectory and 95% confidence interval). All trajectories are plotted on log-scaled age (x-axis) and y-axes are scaled in units of the corresponding MRI metrics (10,000 mm^3 for TCV, 10,000 mm^2 for SA and mm for CT). B | Regional variability of cortical volume trajectories for 34 bilateral brain regions as defined in the Desikan Killiany parcellation[25], averaged across sex (see also* ***SI7-8*** *for details). From top to bottom panels: cortical map of age at peak regional volume (range 2-10 years); cortical map of age at peak regional volume relative to age at peak GMV (5.9 years), highlighting regions that peak earlier (blue) or later (red) than GMV; and illustrative trajectories for the earliest peaking region (superior parietal lobe) and the latest peaking region (insula), showing the range of regional variability. Regional volume peaks are denoted as dotted vertical lines either side of the global peak denoted as a dashed vertical line in the bottom panel. Left hand y-axis on the bottom panel refers to the earliest peak, the right hand y-axis refers to the latest peak, and both are in units of 10,000 mm^3.*

Developmental milestones

Neuroimaging milestones are defined by inflection points of the tissue-specific volumetric trajectories (**Fig.3; Online Methods**). Relative to traditional pubertal age milestones[29], among the total tissue volumes only GMV peaked before typical pubertal onset, with sGMV peaking mid-puberty and WMV peaking in young adulthood (**Fig.3**). The rate-of-growth (velocity) peaked for GMV ($5.08_{CI\text{-}Bootstrap:4.85\text{-}5.22}$ months), sGMV ($5.65_{CI\text{-}Bootstrap:5,75\text{-}5.83}$ months) and WMV ($2.4_{CI\text{-}Bootstrap:2.2\text{-}2.6}$ years) in infancy and early childhood. TCV velocity peaked between the maximum velocity for GMV and WMV at ~7 months. Two major milestones of TCV and sGMV (peak velocity and size; **Fig.3**) coincided with the early neonatal and adolescent peaks of height and weight velocity[30,31]. The velocity of mean cortical thickness peaked even earlier, in the prenatal period at $-0.38_{CI\text{-}Bootstrap:-0.4\ to\ -0.34}$ years (relative to birth), corresponding approximately to the second half of pregnancy. This very early peak in cortical thickness velocity has not been reported previously, probably due to the unprecedented aggregation of foetal MRI data allowing precise estimation of early human brain growth in the current study[23,32]. Similarly, the exact timing of the GMV:WMV differentiation in early development, due to changes in myelination and synaptic proliferation[33–37], has not been clearly demarcated by prior studies. In contrast, lifespan curves indicated an early period of GMV:WMV differentiation, beginning with the switch from WMV to GMV as the dominant tissue compartment in the first month after birth (GMV/WMV ratio=1), and ending when the absolute difference of GMV and WMV peaked around 3 postnatal years (**SI9**). This epoch of GMV:WMV differentiation encompasses dynamic changes in brain metabolites[38] (0-3 postnatal months), resting metabolic rate (RMR; minimum=7 months, maximum=4.2 years)[39], the typical period of acquisition of motor capabilities and other early paediatric milestones[40], interneuron migration, and the most rapid change in TCV (**Fig.3**).

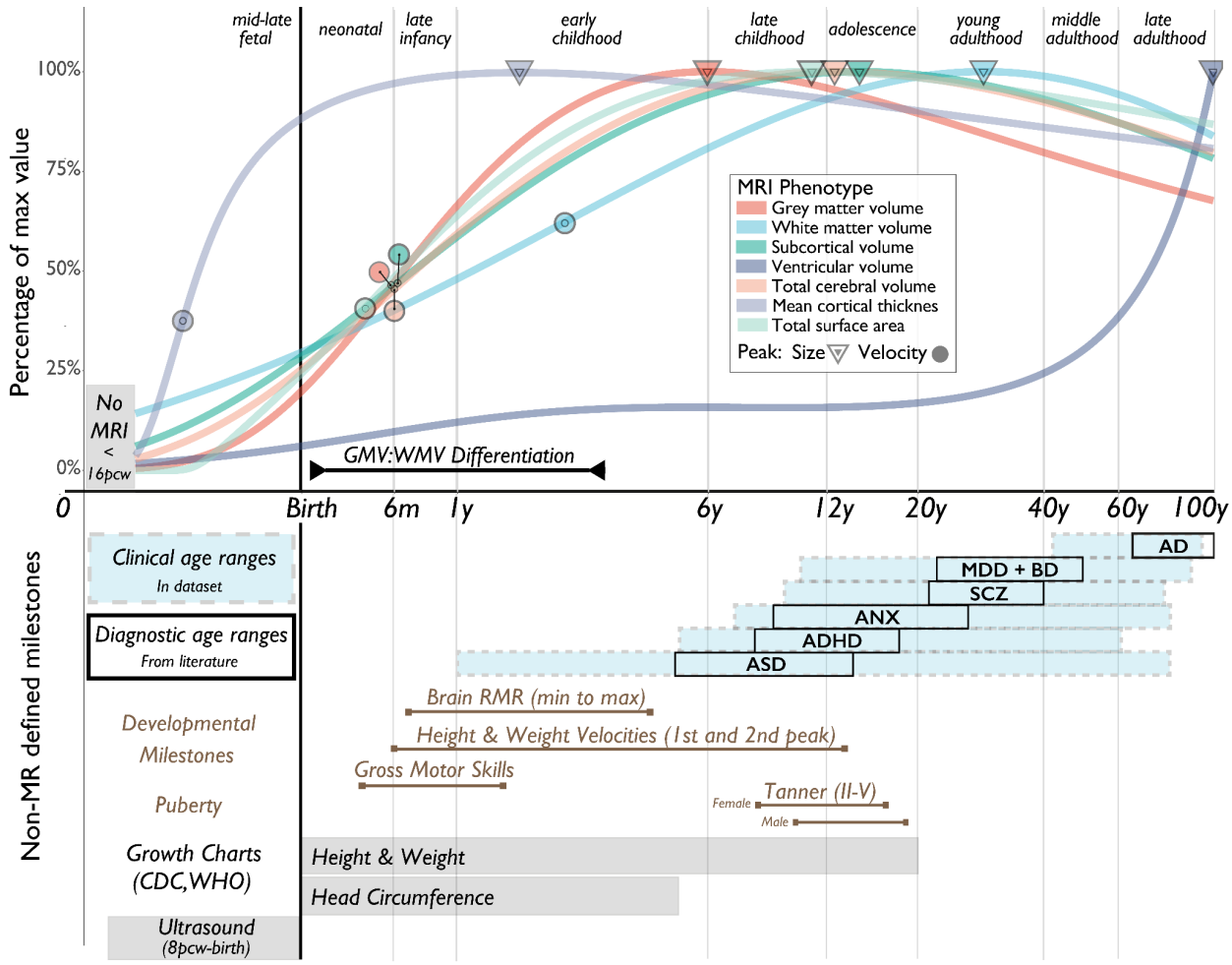

Fig. 3. Neurodevelopmental milestones. *Top panel: A graphical summary of the normative trajectories of the median,i.e., 50th centile, for each global MRI phenotype, and key developmental milestones, as a function of age (log-scaled). Circles depict the peak rate-of-growth milestones for each phenotype (defined by the maxima of the first derivatives of the median trajectories; see* ***Fig.1E****). Triangles depict the peak volume of each phenotype (defined by the maxima of the median trajectories), definition of GMV:WMV differentiation is detailed in* ***SI9.1****. Bottom panel: A graphical summary of additional MRI and non-MRI developmental stages and milestones. From top to bottom: blue shaded boxes denote the age-range of incidence for each of the major clinical disorders represented in the MRI dataset; black boxes denote the age at which these conditions are generally diagnosed as derived from literature[41] (****Online Methods****); brown lines represent the normative intervals for developmental milestones derived from non-MRI data, based on previous literature and averaged across males and females (****Online Methods****); grey bars depict age ranges for existing (WHO and CDC) growth charts of anthropometric and ultrasonographic variables. Across both panels, light grey vertical lines delimit lifespan epochs (labelled above the top panel) previously defined by neurobiological criteria[42]. Abbreviations: resting metabolic rate (RMR), Alzheimer's disease (AD), attention deficit hyperactivity disorder (ADHD), anxiety or phobic disorders (ANX), autism spectrum disorder (ASD, including high-risk individuals with confirmed diagnosis at a later age), major depressive disorder (MDD), bipolar disorder (BD), and schizophrenia (SCZ).*

Individualised centile scores in clinical samples

We computed individualised centile scores that benchmarked each individual scan in the context of normative age-related trends (**SI1-6**). The clinical diversity of the aggregated dataset allowed

us to comprehensively investigate case-control differences in individually-specific centile scores. Relative to the control group (CN), there were highly significant differences in centile scores across large (N>500) diagnostic groups of multiple disorders (**Fig.4A; SI10**, **ST3-4**). The pattern of these centile differences varied across tissue types and disorders. Clinical differences in cortical thickness and surface area generally followed the same trend as volume differences (**SI10**). AD showed the greatest overall difference, with a maximum difference localised to gray matter in biologically female patients (36% difference from CN median; **Fig.4A**). In addition, we generated a cumulative deviation metric, the "centile Mahalanobis distance" (CMD), across all brain phenotypes relative to the CN mean, to summarise a comparative assessment of brain morphology (**Fig.4B**; **SI1.6**). Notably, schizophrenia (SCZ) ranked third overall behind AD and mild cognitive impairment (MCI), based on CMD (**Fig.4C**). Assessment across diagnostic groups, based on profiles of the multiple centile scores and CMD, highlighted shared and distinct patterns across clinical conditions (**SI10-11**). However, when examining cross-disorder similarity, hierarchical clustering yielded three clusters broadly comprising neurodegenerative, mood/anxiety, and neurodevelopmental disorders (**SI11**). Overall, these analyses highlight the complementary use-cases for examining both absolute and relative differences in centile scores within and across conventional diagnostic categories.

Between-subject variation in centile scores also showed strong associations with development, early-life events, and shared genetic architecture. Across individual lifespan epochs, CMD was consistently greater in cases relative to controls, irrespective of diagnostic category, with the largest difference found in adolescence and late adulthood across epochs[42] (**SI10.3**). Adolescence also represented the greatest period of overlap across diagnostic categories in our dataset and is well-recognised as a period of overall vulnerability for neuropsychiatric disease (**Fig.4**; **SI10-11**). Across 5 primary studies covering the lifespan, average centile scores were related to two metrics of premature birth (gestational age at birth: t=13.164, P<2e-16; birth weight: t=36.395, P<2e-16; **SI12**). Centile scores also showed increased twin-based heritability in two independent studies (total N=913 twin-pairs) compared to non-centiled phenotypes (11.8% mean difference in h^2; **Fig.4C**, **SI13**). In summary, centile normalisation of brain metrics reproducibly detected case-control differences and genetic effects on brain structure, as well as long-term sequelae of adverse birth outcomes even in the adult brain[8].

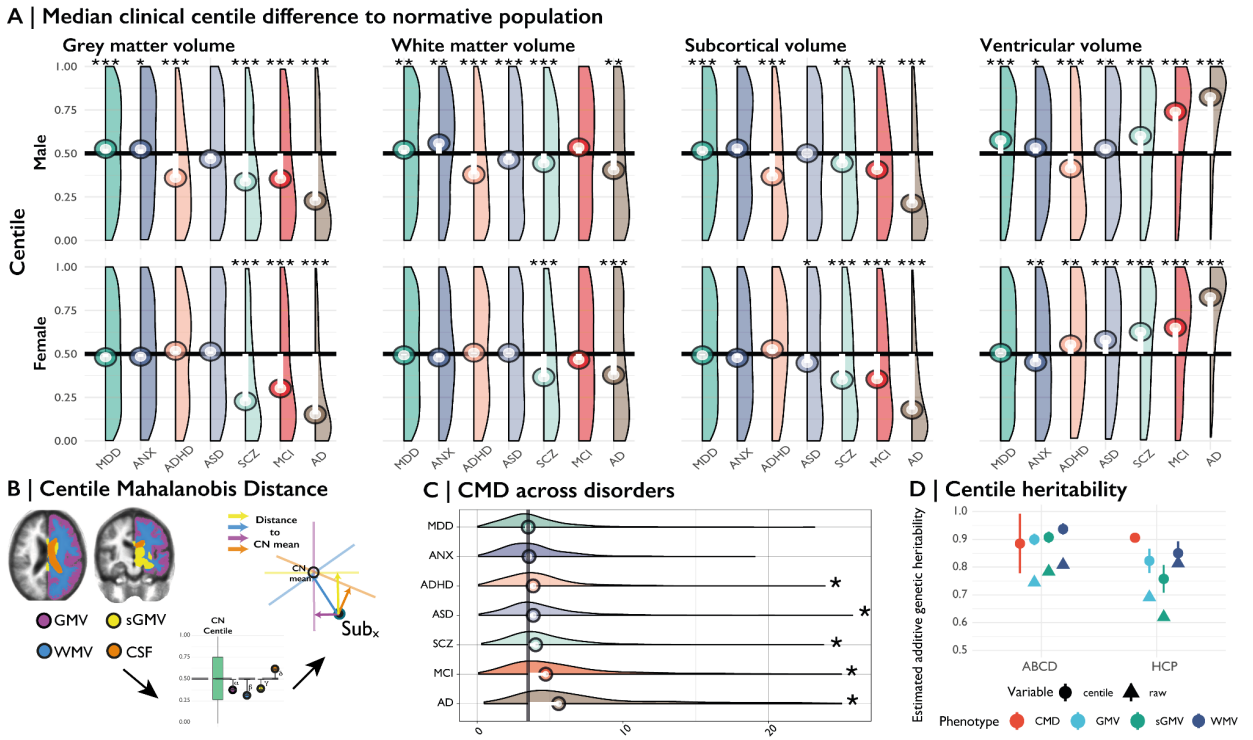

Fig. 4. Case-control differences and heritability of centile scores. *A | Centile score distributions for each diagnostic category of clinical cases relative to the control group median (depicted as a horizontal black line). The median deviation of centile scores in each diagnostic category is overlaid as a lollipop plot (white line with circle corresponding to the median centile score for each group of cases). Pairwise tests for significance were based on Monte-Carlo resampling (10,000 permutations) and P-values were adjusted for multiple comparisons using the Benjamini-Hochberg False Discovery Rate (FDR) correction across all possible case-control differences. Only significant deviations from the control group median (with corrected P<0.001) are highlighted with an asterisk. For a complete overview of all pairwise comparisons, see* ***SI10*** *and* ***ST3****. Groups are ordered by their multivariate distance from the control group (see panel C and* ***SI10.3****). B | The centile Mahalanobis distance (CMD) is a summary metric of multivariate deviation that quantifies the aggregate atypicality of an individual scan in terms of all MRI phenotypes. The schematic shows segmentation of four cerebrum tissue volumes, followed by estimation of univariate centile scores, leading to the orthogonal projection of a single subject (Sub_x) onto the four principal components of the control group (CN; coloured axes and arrows): the CMD for Sub_x is then the sum of its distances from the CN group mean on all 4 dimensions of the multivariate space. C | Probability density plots of CMD across disorders. Vertical black line depicts the median CMD of the control group. Asterisks indicate an FDR-corrected significant difference from the CN group (P < 0.001). D | Heritability of raw volumetric phenotypes and their centile scores across two twin studies (ABCD and HCP). All dots have error bars for the standard error, but in some cases these are too narrow to be observed. Abbreviations: control (CN), Alzheimer's disease (AD), attention deficit hyperactivity disorder (ADHD), anxiety or phobia (ANX), autism spectrum disorder (ASD), mild cognitive impairment (MCI), major depressive disorder (MDD), schizophrenia (SCZ); grey matter volume (GMV), subcortical grey matter volume (sGMV), white matter volume (WMV), centile Mahalanobis distance (CMD).*

Longitudinal centile changes

Due to the relative paucity of longitudinal imaging data (~10% of the reference dataset), normative models were estimated from single cross-sectional time points. However, the generalisability of cross-sectional models to longitudinal assessment is important for potential clinical utility. Within-subject variability of centile scores derived from longitudinally repeated scans, measured with

the interquartile range (IQR; **SI1.7**), was low across both clinical and control groups (all median <0.05 centile), indicating that centile scoring of brain structure was generally stable over time, although there was also some evidence of between-study and cross-disorder differences in within-subject variability (**SI14**). Notably, individuals who changed diagnostic categories showed small but significant increases in within-subject variability of centile scores (**SI14**; **ST5-6**). Within-subject variability was also slightly higher in younger samples (**SI14**), which could reflect increased noise due to the technical difficulties associated with scanning younger individuals, but is also consistent with the evidence of increased variability in earlier development observed across other anthropometric traits[43].

Out-of-sample centile scoring of "new" MRI data

A key challenge for brain charts is the accurate centile scoring of out-of-sample MRI data, not represented in the normative distribution of trajectories. As such, we carefully evaluated the reliability and validity of brain charts for centile scoring of "new" scans. For each new MRI study, we used maximum likelihood to estimate study-specific statistical offsets from the age-appropriate epoch of the normative trajectory; then we estimated centile scores for each individual in the new study benchmarked against the offset trajectory (**Fig.5; SI1.8**). Extensive jack-knife and leave-one-study-out (LOSO) analyses indicated that a study size of N>100 scans was sufficient for stable and unbiased estimation of out-of-sample centile scores (**SI4**). Furthermore, out-of-sample centile scores proved highly reliable in multiple test-retest datasets and robust to variations in image processing pipelines (**SI4**).

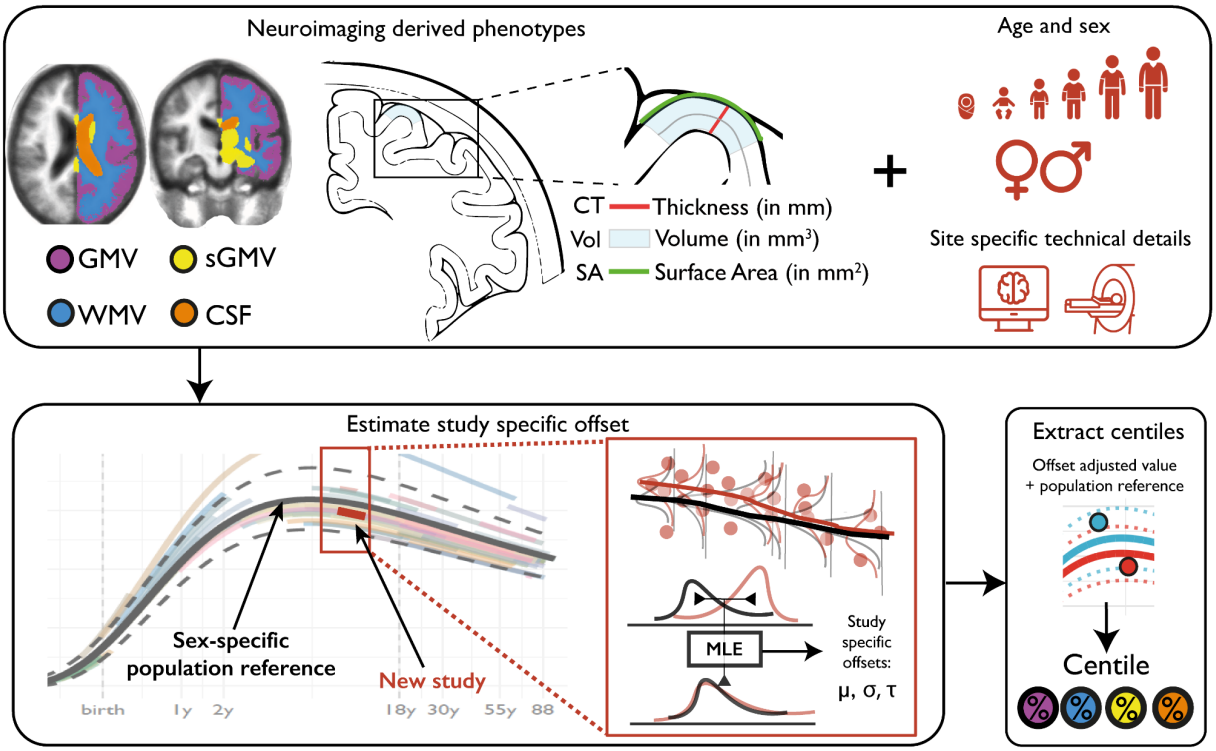

Fig. 5. Schematic overview of brain charts, highlighting methods for out-of-sample centile scoring. *Top panel: Brain phenotypes are measured in a reference dataset of MRI scans. GAMLSS modeling is*

*used to estimate the relationship between (global) MRI phenotypes and age, stratified by sex, and controlling for technical and other sources of variation between scanning sites and primary studies. Bottom panel: The normative trajectory of the median and confidence interval for each phenotype is plotted as a population reference curve. Out-of-sample data from a new MRI study are aligned to the corresponding epoch of the normative trajectory, using maximum likelihood to estimate the study specific offsets (random effects) for three moments of the underlying statistical distributions: mean (μ), variance (σ), and skewness (ν) in an age- and sex-specific manner. Centile scores can then be estimated for each scan in the new study, on the same scale as the reference population curve, while accounting for study-specific "batch effects" on technical or other sources of variation (see **SI1.8** for details).*

Discussion

We have aggregated the largest neuroimaging dataset to date to modernise the concept of growth charts for mapping typical and atypical human brain development and ageing. The ~100 year age range enabled the delineation of milestones and critical periods in brain maturation, revealing an early growth epoch across its constituent tissue classes -- starting before 17 post-conception weeks, when the brain is at ~10% of its overall size and ending at ~80% by age 3. Individual centile scores benchmarked by normative neurodevelopmental trajectories were significantly associated with neuropsychiatric disorders as well as with individual differences in birth outcomes and fluid intelligence (**SI5.2** and **SI12**). Furthermore, imaging-genetics studies[44] may benefit from the increased heritability of centile scores compared to raw volumetric data (**SI13**). Perhaps most importantly, GAMLSS modeling enabled harmonisation across technically diverse studies (**SI5**), and thus leveraged the potential power of aggregating MRI datasets at scale.

The current results also bode well for future progress towards individualised prediction[45]. By providing an age- and sex-normalised metric, centile scores enable trans-diagnostic comparisons between disorders that emerge at different stages of the lifespan (**SI10-11**). The generally high stability of centile scores across longitudinal measurements also enabled assessment of documented changes in diagnosis such as the transition from MCI to AD (**SI14**), which provides one example of how centile scoring could be clinically useful in quantitatively predicting or diagnosing progressive neurodegenerative disorders. The analogy to paediatric growth charts is not meant to imply a predetermined or immediate application for brain charts in a typical clinical setting. However, our provision of appropriate normative growth charts and on-line tools creates an opportunity to quantify atypical brain structure, precisely benchmarked against age- and sex-typical distributions, and thus to enhance diagnostic yield from clinical scans as well as neuroimaging research studies.

Presently, even the current large and diverse dataset is not fully representative of the global population at all ages. For example, foetal, neonatal and mid-adulthood (30-40y) epochs were under-represented (**SI17-19**); and, as is also common in existing genetic datasets, ethnicity and geography were heavily biased towards European and North American populations. While our statistical modeling approach was designed to mitigate study- or site-specific bias in centile scores, further increasing diversity in MRI research will enable more population-representative normative trajectories[46,47] that can be expected to improve the accuracy and strengthen the interpretation of centile scores in relation to demographically appropriate norms. Our decision to

stratify the lifespan models by sex followed the analogous logic of sex-stratifed anthropometric growth charts. Males have larger brain tissue volumes than females in absolute terms (**SI16**) but this is not indicative of any difference in clinical or cognitive outcome. Future work would also benefit from more detailed and dimensional self-report variables relating to sex and gender[48].

We have focused primarily on charts of global brain phenotypes, which were measurable in the largest aggregated sample over the widest age range, with the fewest methodological, theoretical and data sharing constraints. However, we have also provided proof-of-concept brain charts for regional grey matter volumetrics, demonstrating plausible heterochronicity of cortical patterning, and illustrating the generalisability of this approach to a more diverse range of fine-grained MRI phenotypes. As ongoing and future efforts provide increasing amounts of high quality MRI data, we predict an iterative process of improved brain charts for the human lifespan, potentially representing multi-modal MRI phenotypes and enabling out-of-sample centile scoring of smaller samples or individual scans. In the hope of facilitating progress in this direction, we have provided interactive tools to explore these statistical models and to derive normalised centile scores for new datasets across the lifespan at www.brainchart.io

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Data and code availability

All code is made available on https://github.com/ucam-department-of-psychiatry/Lifespan and summary statistics are provided in the supplementary tables and through www.brainchart.io. Sharing or re-sharing MRI scans aggregated here is through application procedures at the discretion of each contributing study individually.

Contributions

RAIB, JS, SRW, ETB and AFA-B designed the study, conducted analyses, wrote and edited the manuscript. All other authors consulted on the study design, collected, processed and contributed data and edited the manuscript. JV and KA additionally contributed to the data analysis.

Disclosures

ETB serves on the scientific advisory board of Sosei Heptares and as a consultant for GlaxoSmithKline. The other authors have no conflicts of interest to disclose. The research was reviewed by the Cambridge Psychology Research Ethics Committee (PRE.2020.104) and The

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Online methods: Brain charts for the human lifespan

To accurately and comprehensively establish standardised brain reference charts across the lifespan, it is crucial to leverage multiple independent and diverse datasets, especially those spanning prenatal and early postnatal life. Here we sought to chart normative brain development and ageing across the largest age-span and largest aggregated neuroimaging dataset to date using a robust and scalable methodological framework[1,2]. We leveraged these normative reference charts in clinical cohorts to generate individualised assessments of age-relative centiles. These centiles were then leveraged to investigate cross-diagnostic and longitudinal atypicalities of brain morphology across the lifespan. We used generalised additive models for location, scale and shape (GAMLSS)[1] to estimate cross-sectional normative age-related trends from 100 studies (see supplementary tables [**ST**] **1.1-1.7** for full demographic information and supplementary information [**SI**] **19** for dataset descriptions). The GAMLSS approach allows not only modelling of age-related changes in brain phenotypes but also age related-changes in the variability, in the form of both linear and nonlinear changes over time, thereby overcoming potential limitations of conventional additive models that only allow additive means to be modelled[1]. In addition, site-specific offsets (mean and variance) for each brain phenotype are also modelled. These modelling criteria are particularly important in the context of establishing growth references as recommended by the World Health Organisation[2], as it is reasonable to assume the distribution of higher order moments (e.g., variance) changes with age, sex, site/study and pre-processing pipeline—especially given the impossibility of fully comprehensive longitudinal data for individuals spanning the ~100 year age range. Furthermore, recent studies suggest that changes in across-individual variability might intersect with vulnerability for developing a mental health condition[3]. The use of data spanning the entire age range is also critical, as estimation from partial age-windows can lead to biased estimations when extrapolated to the whole lifespan. In summary, using a sex-stratified approach[2], age, preprocessing pipeline and study were each included in the GAMLSS model estimation of first order (μ) and second order ($\boldsymbol{\sigma}$) distribution parameters of a generalised gamma distribution using fractional polynomials to model nonlinear trends. See **Supplementary Information** [**SI**] for more details regarding GAMLSS model specification and estimation (**SI1**), image quality control (**SI2**), model stability and robustness (**SI3-4**), phenotypic validation against non-imaging metrics (**SI3 & SI5.2**), inter-study harmonisation (**SI5**) and assessment of cohort effects (**SI6**).

In general, the GAMLSS framework can be specified in the following way:

$$
\begin{aligned}
Y &\sim \mathcal{F}(\mu, \sigma, \nu, \tau) \\
g_\mu(\mu) &= X_\mu \beta_\mu + Z_\mu \gamma_\mu + \sum_i s_{\mu,i}(x_i) \\
g_\sigma(\sigma) &= X_\sigma \beta_\sigma + Z_\sigma \gamma_\sigma + \sum_i s_{\sigma,i}(x_i) \\
g_\nu(\nu) &= X_\nu \beta_\nu + Z_\nu \gamma_\nu + \sum_i s_{\nu,i}(x_i) \\
g_\tau(\tau) &= X_\tau \beta_\tau + Z_\tau \gamma_\tau + \sum_i s_{\tau,i}(x_i)
\end{aligned}
\tag{1}
$$

Here, the outcome vector, Y, follows a probability distribution D parameterised by up to four parameters, (μ, σ, ν, τ). The four parameters, depending on the parameterisation of the probability density function, may correspond to the mean, variance, skewness, and kurtosis (i.e., the first four moments); however, for many distributions there is not a direct one-to-one correspondence. Each component is linked to a linear equation through a link-function, $g_\cdot()$, and each component equation may include three types of terms: fixed effects, $\beta_\cdot$(with design matrix, $X_\cdot$); random-effects, $\gamma_\cdot$ (with design matrix, $Z_\cdot$); and non-parametric smoothing functions, $s_{\cdot,i}$ applied to the ith covariate. The nature of the outcome distribution determines the appropriate link-functions and which components are used. In principle any outcome distribution can be used, from well-behaved continuous and discrete outcomes, through to mixtures and truncations.

Within this paper we consider fractional polynomials as a flexible, yet limited in complexity, approach to modelling age-related changes. Although non-parametric smoothers are more flexible, they can become unstable and infeasible, especially in the presence of random-effects. Hence, the fractional polynomials enter the model within the $X_\cdot$terms, with associated coefficients in $\beta_\cdot$. The GAMLSS framework includes the ability to estimate the most appropriate powers within the iterative fitting algorithm, searching across the standard set of powers, $p \in \{-2, -1, -0.5, 0, 0.5, 1, 2, 3\}$, where the design matrix includes the covariate (in our setting, age) raised to the power, namely, x^p. Fractional polynomials naturally extend to higher-orders, for example a second-order fractional polynomial of the form, $x^{p_1} + x^{p_2}$.

There are several options for including random-effects within the GAMLSS framework depending on the desired covariance structures. We consider the simplest case, including a factor-level (or group-level) random-intercept, where the observations are grouped by the study covariate. The random-effects are drawn from a normal distribution with zero mean and variance to be estimated, $\gamma_\cdot \sim N(0, \delta_\cdot^2)$. The ability to include random-effects is fundamental to accounting for co-dependence between observations. It is therefore possible to take advantage of the flexibility of "standard" GAMLSS, as typically used to develop growth charts[2,4,5], while accounting for co-dependence between observations using random-effects. The typical applications of GAMLSS assume independent and identically distributed outcomes; however within our context it is

essential to account for within-study covariance implying the observations are no longer independent.

This model allowed us to leverage the aggregated life-spanning neuroimaging dataset to derive developmental milestones (i.e., peaks of trajectories) and compare them to existing literature. These sex-stratified models incorporated variation in study and processing pipeline to allow computation of standardised reference charts. The cerebrum tissue classes from 100 studies (**Fig. 1A, ST1.1-1.7**, **SI18**) showed clear, predominantly age-related trends, even prior to any modelling (**Fig. 1B**). Yet, marked heterogeneity of growth curves for individual studies (www.brainchart.io) reinforces the importance of using the full aggregated dataset to achieve representative norms not biased by individual studies. The validity of the models is supported by high stability under cross-validation and bootstrap resampling (**SI3**). Comparing these models to multiple non-MRI metrics of brain size demonstrated high correspondence across the lifespan (**SI3**). Peaks were determined based on the GAMLSS model output (50th centile) for each of the tissue classes and TCV, for both total tissue volumes (**Fig. 1B**) and rates of change or growth ("velocity"; **Fig. 1E**). Diagnostic age ranges from previous literature[6,7] were plotted (blue boxes in **Fig. 3**) to compare with empirical age ranges of patients with a given diagnosis across the aggregated neuroimaging dataset (black boxes in **Fig. 3**). Note that age of diagnosis is significantly later than age of symptom onset for many disorders[6]. Developmental milestones were re-plotted based on published work for brain resting metabolic rate (RMR)[8], from its minimum in infancy to its maximum in early childhood; anthropometric variables (height and weight), which reach a first peak in velocity during infancy and a second peak in velocity in adolescence[9]; and typical acquisition of the six gross motor capabilities[4]. Pubertal age ranges were taken from reported typical age ranges[10,11].

Furthermore, these neuroimaging-derived brain reference charts also enabled each individual to be quantified relative to a statistical distribution defined at the reference level for any point during the lifespan[12,13]. Individual centile scores were obtained relative to the reference curves, conceptually similar to traditional anthropometric growth charts. These normative scores represent a novel set of population and age standardised clinical phenotypes, providing the capacity for cross-phenotype, cross-study and cross-disorder comparison. A single summary deviation metric for each individual was also generated. Main group effects were analysed with a bootstrapped (500 bootstraps) non-parametric generalisation of Welch's one-way ANOVA. Pairwise, sex stratified, post-hoc comparisons were conducted using non-parametric Monte-Carlo permutation tests (10,000 permutations) and thresholded at a Benjamini-Hochberg false discovery rate (FDR) of $q < 0.05$.

To utilise the centiles in a diagnostically meaningful or predictive way, they need to be stable across multiple measuring points. To assess this intra-individual stability we calculated the subject specific interquartile range (IQR) of centiles across timepoints for the datasets that included longitudinal scans (n = 9,306, 41 unique studies). Exploratory longitudinal clinical analyses were restricted to clinical groups that had at least 50 subjects with longitudinal data to allow for robust group-wise estimates of longitudinal variability. In addition, there was a small subset of individuals with documented pathological progression across longitudinal scans, for instance from high risk

status to formal diagnosis. Here, we would expect an associated change in centile measurement. To test this hypothesis we assessed whether these individuals showed differences in centile variability (as assessed with IQR), and their approximate direction of change.

Finally, we provide an interactive tool (www.brainchart.io) and have made our code and models openly available (https://github.com/ucam-department-of-psychiatry/Lifespan). The tool not only allows the user to visualise the underlying datasets' demographics and reported reference charts in a much more detailed fashion than static images allow, it also provides the opportunity for interactive exploration of differences in centile scores across many clinical groups that is beyond the present manuscript. Perhaps most significantly, it includes an out-of-sample estimator of model parameters for novel data that enables the user to compute percentile scores for their own datasets without the computational or data-sharing hurdles involved in adding that data to the reference chart. All modelling included extensive validation, sensitivity analyses and multi-modal validation against existing growth chart references.

Though already based on the largest and most comprehensive neuroimaging dataset to date and supporting analyses of out-of-sample data, the underlying reference charts will also be updated as additional data is made available.

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