

SHORT REPORT

Changes of gray matter volumes of subcortical regions across the lifespan: a Human Connectome Project study

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Abstract

We assessed changes in gray matter volume (GMV) of nine subcortical regions (accumbens, amygdala, brainstem, caudate, cerebellar cortex, pallidum, putamen, thalamus, and ventral diencephalon) across the lifespan in a large sample of participants in the Human Connectome Project ($n = 2,458$, 5–90 yr old, 1,113 males and 1,345 females). 3T MRI data were acquired using a harmonized protocol and were processed in an identical way for all brains. GMVs of individual regions were adjusted for estimated total intracranial volume and regressed against age. We found highly statistically significant changes in GMV with age ($P < 0.001$) that were distinct among areas and mostly consistent between sexes, as follows. 1) The GMVs of accumbens, caudate, putamen, and cerebellum decreased with age in a linear fashion. The rate of decrease was steeper in males than in females for all regions. 2) The GMVs of the amygdala, pallidum, thalamus, ventral diencephalon, and brainstem changed with age in a quadratic fashion, i.e., increasing first and decreasing afterward. The estimated age at the peak (vertex) of the parabola was 51.8 yr for the brainstem and 28.0–37.9 yr for the other regions. The peak occurred earlier in males than in females, by an average of 8 yr, with the exception of the brainstem, where the age at the peak was very similar in both sexes. These results confirm previous findings and offer new insights into region-specific age-related changes in subcortical brain GMVs.

NEW & NOTEWORTHY We report mixed effects of age on subcortical grey matter volume (GMV) during lifespan ($n = 2458$, 5–90 yr old, 1113 male, 1345 female). Striatal and cerebellar GMVs decreased linearly with age, more steeply in males. In contrast, GMVs of the amygdala, pallidum, thalamus, ventral diencephalon, and brainstem changed in a quadratic fashion, increasing first and decreasing afterward, with males peaking earlier than females in all regions but the brainstem where they peaked at nearly the same time.

aging; Human Connectome Project; lifespan; subcortex

INTRODUCTION

Several studies have reported changes in the gray matter volumes (GMVs) of subcortical regions, combining and analyzing data from different studies (1–12). Sample sizes in different studies are moderate; and hardware (magnets), data acquisition protocols, and data processing pipelines typically differ across studies. Although some basic findings have been consistent (e.g., reports of both linear and nonlinear changes with age), comprehensive data from methodologically homogeneous (hardware and software) studies with large sample sizes are lacking. Similarly lacking are data from large samples of male and female brains. Such data have been recently provided by the Human Connectome Project (HCP) (13–15). These data were acquired from a large number of participants ($n = 2,458$) of ages 5–90 yr, comprising similarly large numbers of

male ($n = 1,113$) and female ($n = 1,345$) participants using similar Siemens 3T MRI hardware, a harmonized data acquisition protocol, and the same processing pipeline. To our knowledge, this is the first dataset of this magnitude, homogeneity, and sex representation to date. Here, we report on the analysis of changes with age in gray matter GMVs of nine subcortical regions and their comparison between males and females.

MATERIALS AND METHODS

Participants

We analyzed HCP data from 2,458 healthy participants for whom age was given (1,113 male and 1,345 female, age range 5–90 yr), comprising data from HCP-Development (HCP-D; 13), HCP-Young Adult (HCP-YA; 14), and HCP-Aging (HCP-A; 15);

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all data are publicly available from www.humanconnectome.org. Healthy participants were selected to represent the “typical” population reflecting the ethnic and racial composition of the U.S. and diverse socioeconomic status. Exclusion criteria included premature birth, lifetime history of serious medical or endocrine conditions, neurodevelopmental disorders, and clinical diagnoses of psychiatric and neurological disorders. All participants aged 18 yr and above provided written informed consent. For children under the age of 18 yr, a parent or a legal guardian provided informed, written permission for their child to participate in the study. The research and development committee of the Minneapolis Veterans Affairs Medical Center approved the analysis of these data.

MRI Data Acquisition

For HCP-D and HCP-A projects, a standard Siemens 3T Prisma whole body scanner with an 80 mT/m gradient coil was used (16). The 32-channel head coil enables high acceleration factors via multislice acquisitions. For 5–7 yr old participants, the Ceresensa pediatric 32-channel head coil was used. This advanced scanning technology allows whole brain imaging with a submillimeter resolution of structural MRI. Acquired structural images are T1-weighted (T1w) multiecho MPRAGE and T2-weighted (T2w) SPACE with a volumetric navigator for prospective motion correction. Both structural scans use a sagittal field of view (FOV) $256 \times 240 \times 166$ mm and 0.8 mm isotropic voxels. Other parameters of acquisitions are: for T1w scan, TE = 1.8/3.6/5.4/7.2 ms multiecho, TR/TI = 2,500/1,000, flip angle = 8°; for T2w scan, TR/TE = 3,200/564 ms.

For HCP-YA, the T1w and T2w structural images were acquired using the HCP’s custom 3T Siemens Skyra with a 32-channel head coil (17). The T1w image was acquired using the three-dimensional (3-D) MPRAGE sequence with 0.7-mm isotropic resolution (FOV = 224 mm, matrix = 320, 256 sagittal slices), TR = 2,400 ms, TE = 2.14 ms, TI = 1,000 ms, FA = 8, echo spacing = 7.6 ms. The T2w image was acquired using the variable flip angle turbo spin-echo sequence (Siemens SPACE) with 0.7 mm isotropic resolution (same matrix, FOV, and slices as in the T1w), TR = 3,200 ms, TE = 565 ms.

MRI Data

The HCP structural pipeline processed the high-resolution anatomical T1w and T2w images in three consequent steps: PreFreeSurfer, FreeSurfer, and PostFreeSurfer. It is important that all three datasets be processed identically. The available data through the HCP structural pipeline used FreeSurfer 6.0 for the HCP-D and HCP-A datasets but used FreeSurfer 5.3.0 (17) for the HCP-YA set. To achieve uniformity, we reanalyzed the HCP-YA unprocessed data with the same HCP structural pipeline used for HCP-D and HCP-A using FreeSurfer 6.0.

In addition, single acquisitions of T1w and T2w images of group HCP-YA were used as input, as was done for HCP-D and HCP-A datasets.

The GMV of the brainstem was extracted and the right and left GMVs of cerebellar cortices, nucleus accumbens, amygdala, caudate, pallidum, putamen, thalamus proper, and ventral diencephalon were extracted and averaged.

Statistical Analyses

Standard statistical methods were used to analyze the data, including analysis of covariance (ANCOVA), linear and quadratic regression, *t* test, etc.

GMVs

To correct for variation in estimated total intracranial volume (eTIV), we computed the fraction of the GMV of individual regions over eTIV and expressed it as a percentage:

$$\text{GMV as percent of eTIV} : g = 100 \frac{\text{GMV}}{\text{eTIV}} \% \quad (1)$$

Since prior studies have reported nonlinear changes of subcortical GMVs with age (1, 8, 9), we analyzed the relation between GMV and age using linear and quadratic regression to choose the appropriate model for further analyses.

Linear Regression

The linear regression equation was:

$$g^L = a + by, \quad (2)$$

where *y* denotes the year and *a* and *b* are regression coefficients. The estimated percent change of *g* per year was:

$$g_y^L = 100 \frac{b}{a} \% \quad (3)$$

Quadratic Regression

The quadratic equation was:

$$g^Q = d + ey + fy^2, \quad (4)$$

where *y* denotes the year and *d*, *e*, and *f* are regression coefficients. The estimated location (year) of the vertex of the parabola was:

$$V = -\frac{e}{2f} \text{ years.} \quad (5)$$

MRI data processing was performed using MATLAB (v. R2016) and statistical analyses using the IBM-SPSS statistical package (v. 27). All *P*-values reported are two-sided.

RESULTS

The percent of variance explained by linear and quadratic fits for each region is shown in Table 1. It can be seen that for four regions (accumbens, putamen, caudate, and cerebellum) quadratic fits offered a very small improvement over the linear fit (<2%), whereas for the remaining five regions (brainstem, amygdala, pallidum, thalamus, and ventral diencephalon) the quadratic fit offered a substantial improvement (45–300%). Therefore, we analyzed the data for these two groups of regions separately, using linear and quadratic fits.

Quadratic Dependence of GMV on Age

As mentioned earlier, the GMVs of the brainstem, amygdala, pallidum, thalamus, and ventral diencephalon showed a quadratic relation to age, such that GMVs increased up to a certain age (up to the vertex of the quadratic function) and decreased afterward. This is shown in the scatterplots of Fig. 1, A–E and is illustrated in Fig. 1F. The regression fits were highly significant (*P* < 0.001) for all regions and both sexes.

Table 1. Percent of variance explained by linear and quadratic fits

Region	r^2 Linear	R^2 Quadratic	Quadratic Improvement Over Linear $100 \frac{R^2 - r^2}{r^2} \%$
Accumbens	0.405	0.405	0.0
Caudate	0.105	0.107	1.9
Putamen	0.251	0.254	1.2
Cerebellum	0.089	0.090	1.1
Brainstem	0.030	0.090	200.0
Amygdala	0.180	0.334	85.5
Pallidum	0.030	0.121	303.3
Thalamus	0.224	0.326	45.5
Ventral diencephalon	0.120	0.253	110.8

$P < 0.001$ for all regression fits; bold type indicates a better fit. See text for details.

The year (V) corresponding to the vertex (peak of the quadratic function) is given in Table 2 and is indicated by a vertical white line in the scatterplots of Fig. 1, A–E. It is shown as a region-coded colored line in Fig. 1 and summarized for the two sexes in Fig. 2F. We found the following. 1) For the brainstem, the peak occurred late, at 51.8 yr, close to the middle of the lifespan, and it was very similar for males and females (Fig. 2F). 2) For the thalamus, the peak occurred early, at 28 yr, and much earlier in males (at 18.7 yr) than in females (at 31.3 yr) (Table 2, Fig. 2F). 3) For the remaining regions (amygdala, pallidum, and ventral diencephalon) the peak occurred during the third decade but consistently earlier in males than in females (Table 2, Fig. 2F). 4) These results indicate that,

with the exception of the brainstem, the first, GMV-increasing period lasts 27.7 yr on the average, whereas the GMV-decreasing period lasts $90 - 27.7 = 57.3$ yr, i.e., twice as long.

Linear Dependence of GMV on Age

The GMVs of accumbens, caudate, putamen, and cerebellum decreased with age in a linear and highly statistically significant fashion (Table 2 and scatterplots in Fig. 2, A–D; $P < 0.001$ for all regressions). The percent GMV reduction per year was highest for accumbens, followed by putamen, caudate, and cerebellum and was consistently and statistically significantly higher in males than in females (Fig. 2E and Table 2; mean difference $\pm$ SE: -0.06175 ± 0.00626 , $P = 0.002$, paired t test).

DISCUSSION

Our results are in keeping with those of other studies (1–12) documenting linear and nonlinear changes of subcortical GMVs with age across the lifespan, depending on the region. The present study was based on HCP MRI data acquired and preprocessed with the harmonized protocol, thus eliminating variability stemming from differences in such protocols, a potential issue shared by studies combining and/or analyzing data collected by various MRI systems and preprocessed in various ways. The homogeneity of data acquisition and preprocessing, combined with the same participant recruitment protocol and the large sample size (total and for both sexes) yielded three clear-cut results, as follows. First, the

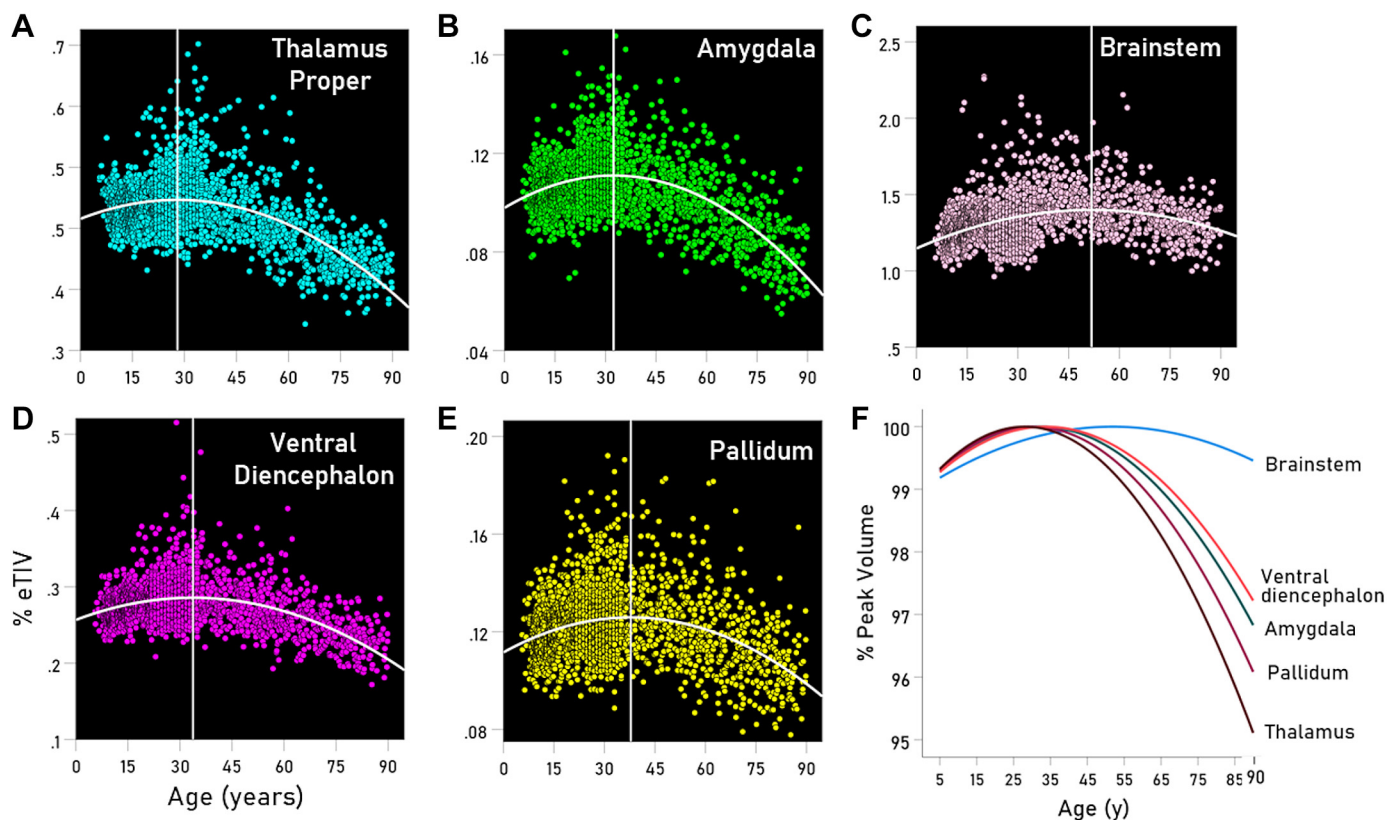


Figure 1. A–E: scatterplots of volume vs. age (years) and fitted quadratic functions for the regions indicated. F: fitted quadratic functions color-coded for the regions indicated and normalized for the function maximum at the parabola peak. See text for details.

Table 2. Volume changes during aging

Linear Group				
	g_y^L %, $n = 2,458$	g_y^{LM} %, $n = 1,113$	g_y^{LF} %, $n = 1,345$	$\%g_y^{LM} - \%g_y^{LF}$
Accumbens	-0.510	-0.543	-0.483	-0.060
Caudate	-0.190	-0.183	-0.134	-0.049
Cerebellum	-0.155	-0.347	-0.288	-0.059
Putamen	-0.314	-0.235	-0.156	-0.080
Quadratic Group				
Region	V , yr, $n = 2,458$	V_M , $n = 1,113$	V_F , $n = 1,345$	$V_M - V_F$
Amygdala	32.4	28.8	34.4	-5.6
Brainstem	51.8	53.0	51.5	1.5
Pallidum	37.9	31.0	40.9	-9.9
Thalamus	28.0	18.7	31.3	-12.6
Ventral diencephalon	32.7	31.0	35.0	-4.0

Top: linear percent volume change per year for males (M) and females (F). $P < 0.001$ for all male and female volume vs. age regressions. Bottom: estimated age (year) V at the vertex of the quadratic function (Eq. 5). V_M , V_F estimates for males and females, respectively.

striatal regions (accumbens, caudate, and putamen) and cerebellar cortex showed a linear decrease of GMV with age ranging from -0.510% per year for accumbens to -0.155% per year for cerebellum (Table 2). Second, all the other regions (thalamus, amygdala, pallidum, ventral diencephalon, and brainstem) showed a quadratic relation (parabola concave downward), i.e., an increase in GMV in younger ages, followed by a decrease later. The first period lasted ~ 50 yr for the brainstem and ranged from 28 to 38 yr for the rest, depending on the region (Table 2). Third, females showed less steep GMV decrease rates for all regions with linear fits (Fig. 2E) and later quadratic peaks, except for the brainstem (Fig. 2F). We discuss these results briefly.

The study by Bethlehem et al. (1) has provided the most comprehensive account of brain GMV trajectories over the lifespan, based on >100 primary studies. The plot of total subcortical GMV (Fig. 1 in Ref. 1) shows a single peak at 14.4 yr, and that of cortical GMV at 5.9 yr. The data are plotted against a logarithmic time scale and, hence, do not permit evaluation of fit for a quadratic or other function, nor has curve-fitting been described in the paper. Although overall lifespan GMV trajectories are useful, they come at the price of losing information about individual areas that commonly have different GMV trajectories, as evidenced by the results of this and previous studies (4, 18, 19).

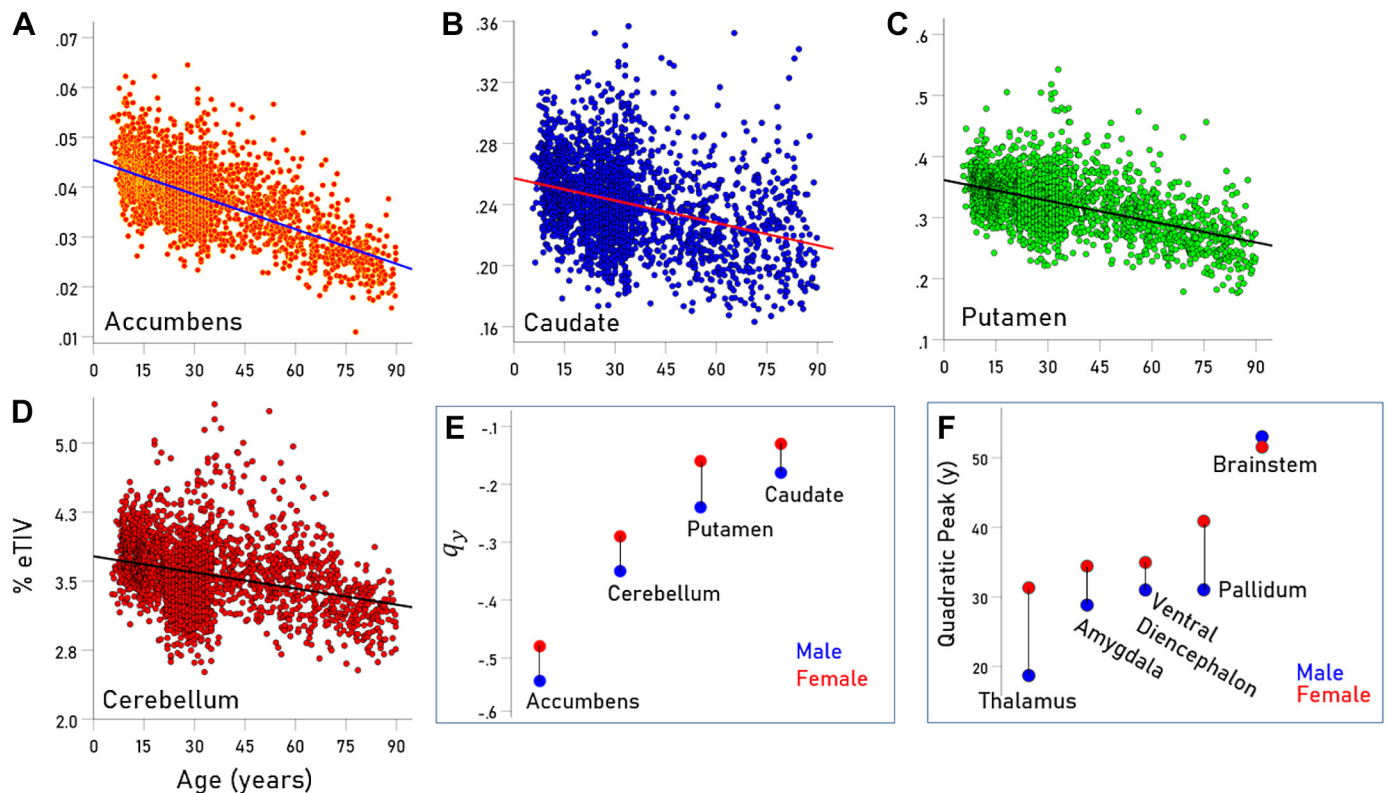


Figure 2. A–D: scatterplots of volume vs. age (years) and fitted linear functions for the regions indicated. E: rates of volume decrease for males and females for the regions indicated. F: year (V) at peak volume for males and females and regions indicated. See text for details.

With respect to linear GMV lifespan trajectories, all striatal regions (accumbens, caudate, and putamen) showed such trajectories, reflecting comparable GMV decreases in the cortex, which provides massive input to striatum. GMV decrease was steepest in the accumbens, in accord with its major inputs coming from the anterior cingulate and orbitofrontal cortex, areas with similarly steep volume decreases (18). It is possible that striatal changes are secondary to the cortical ones, mediated by anterograde neuronal degeneration, a hypothesis that remains to be investigated. Interestingly, the accumbens GMV trajectory during early childhood shows a $\cap$ -shaped peak at ~ 4 yr (20), which suggests that our result (starting from 5 yr onward) could be a continuation of GMV decrease that started earlier, at ~ 4 yr; neither caudate nor putamen GMVs showed such a $\cap$ -shaped pattern. Finally, among the remaining subcortical regions, the cerebellum was the only one with a linear volume decrease, as has been reported previously (10, 21).

In contrast to the linear striatal and cerebellar GMV decreases, the thalamus proper and regions connected with it (amygdala, pallidum, and ventral diencephalon) showed a quadratic pattern of GMV trajectory peaking around the 3rd decade (Fig. 1F). The first, ascending leg of the quadratic function lasted ~ 25 yr, whereas the second, descending leg lasted ~ 50 – 60 yr, with the result of a net reduction in GMV at the last decade. Remarkably, the ascending leg was very similar for all four regions, whereas the steepness of the second leg differed systematically among regions, with thalamus proper showing the steepest and ventral diencephalon the most shallow GMV decline (thalamus > pallidum > amygdala > ventral diencephalon) (Fig. 1F). It is not clear which are the mechanism(s) underlying this quadratic pattern and its variation among regions. With respect to cortical (linear) GMV decreases, we have hypothesized that they are partly due to low-grade neuroinflammatory processes (18, 19, 22, 23), possibly caused by intermittent reactivation of latent viruses (e.g., human herpes family) (19). Support for this hypothesis was provided by the finding that the Human Leukocyte Antigen (HLA) allele DRB1*13:02 protected against cortical and subcortical atrophy in healthy women (22). Given the known action of HLA molecules in adaptive immunity against viral and other foreign insults, this result suggested that the effective elimination of foreign insults by HLA was the mechanism involved. It is unclear whether such a mechanism may also underlie the decrease in subcortical GMVs observed in the second leg of the quadratic function, as suggested by the protection against subcortical atrophy afforded by HLA DRB1*13:02 (22). It is noteworthy that the neuroinflammatory response of brain regions to systemic administration of lipopolysaccharides (as measured by the activation of microglia) was very similar for cortical and subcortical regions (24), suggesting that the different profiles of GMV decreases [e.g., between accumbens (linear) and thalamus (quadratic)] cannot be explained by the same non-specific inflammatory response. At face value, the “infectious cause” hypothesis suggests that the detrimental effects of such insults appear earlier in cortical areas and later in subcortical areas, essentially causing the GMV declines following the early cortical peak and late subcortical peak. Since these effects are cumulative and local inflammatory (microglia) responses are comparable across cortical and subcortical regions (24), the different cortical versus subcortical trajectories imply the involvement of the following possible mechanisms, alone or

in combination, namely, 1) differential exposure of cortical and (quadratic) subcortical regions, due, e.g., to the differential tropism of insults (e.g., viruses being preferentially localized in cortical areas), 2) differential vulnerability of various regions to the insults due, e.g., to the differential vulnerability of specific neurons, variation in blood supply, etc., and 3) possible anterograde degeneration effects, such as those postulated about the cortico-striatal projection.

Finally, among the five regions with quadratic trajectories, the brainstem stands out as being the only one that ended up with a larger GMV (Fig. 1F). The brainstem comprises the midbrain, the pontine nuclei, and medulla oblongata. Apparently, those regions are resistant to long-term damage, the mechanism(s) of which remain to be investigated.

Limitations

This study used a cross-sectional sample, whereas a longitudinal sample would have been the better choice.

DATA AVAILABILITY

This paper is based on the three Human Connectome Project datasets. The HCP-Development 2.0 Release data used in this report came from <https://doi.org/10.15154/1520708>. HCP-Young Adult data were provided by the Human Connectome Project, WU-Minn Consortium (Principal Investigators: David Van Essen and Kamil Ugurbil; 1U54MH091657). The HCP-Aging 2.0 Release data used in this report came from <https://doi.org/10.15154/1520707>.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the authors.

DISCLAIMERS

The sponsors had no role in the study design, analysis, interpretation, or writing this paper. The contents do not represent the views of the U.S. Department of Veterans Affairs or the United States Government.

AUTHOR CONTRIBUTIONS

P.C. and A.P.G. conceived and designed research; P.C. and A.P.G. analyzed data; P.C. and A.P.G. interpreted results of experiments; A.P.G. prepared figures; P.C. and A.P.G. drafted manuscript; P.C. and A.P.G. edited and revised manuscript; P.C. and A.P.G. approved final version of manuscript.

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