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ORIGINAL ARTICLE

Effects of aging on brain volumes in healthy individuals across adulthood

Iman Beheshti[1] · Norihide Maikusa[1] · Hiroshi Matsuda[1]

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Abstract

In this retrospective study, we analyzed the effects of age on brain volumes in healthy brains across adulthood. We investigated the correlations between brain volumes and age in the brains of 563 healthy individuals (age range: 20–86, 55% female) whose MRI scans and related information were drawn from the IXI database (brain-development.org/ixi-dataset/). We conducted a regression analysis to assess the effect of age on whole-brain volumes as well as selected regional volumetric measures. The whole-brain analysis revealed a negative linear relationship between gray matter (GM) and age as well as nonlinear patterns of the relationship between age and the white matter (WM), cerebrospinal fluid (CSF), and the GM/WM ratio across adulthood. The regional volumetric analysis showed linear and non-linear age-related regional volumetric changes with aging. Our present findings contribute to the understanding of how structures in the human brain change over the adult years and will help address the pathological age-related neural changes in age-related neural disorders such as Parkinson disease and Alzheimer disease.

Keywords Brain volume · Aging · Cognitive changes · Adulthood · Gray matter · White matter

Abbreviations

GM	gray matter
WM	white matter
CSF	cerebrospinal fluid
nGM	normalize GM
nWM	normalize WM
nCSF	normalize CSF
MRI	magnetic resonance imaging
VBM	voxel-based morphometry
TIV	total intracranial volume
ICV	intracranial volume
CAT	Computational Anatomy Toolbox

Introduction

Over the human lifespan, the brain undergoes marked changes, and high-resolution magnetic resonance imaging (MRI) data have been established as a powerful biomarker for assessing the alterations in brain volume that are associated with aging [1–3]. Several studies have reported the effects of the aging on gray matter (GM) changes, describing changes such as a decrease of GM volume in the neocortex involving mainly prefrontal regions and the parietal and temporal cortices [4–6] and age-related GM deficits in the insula, cerebellum, basal ganglia, and thalamus [7–9]. With respect to the association between white matter (WM) changes and aging, various studies have indicated a widespread decline in several WM structures of the brain with aging [2, 10, 11], whereas other studies reported a slight increase of WM with aging in some parts of the brain [12, 13]. Parallel to these studies, Potvin and colleagues [14] presented a comprehensive regional analysis on the basis of cortical normative data obtained from FreeSurfer procedure across adulthood. They additionally developed norms for predicting regional subcortical volumetric brain values through a statistical model, which sex, age, total intracranial volume, the scanner's manufacturer, and magnet strength field were considered as predictors [15].

In the present MRI study, we investigated the association between whole and regional volumetric alterations with increasing age in a large group of healthy humans ($n = 563$).

✉ Iman Beheshti
Beheshtiiman@gmail.com

[1] Integrative Brain Imaging Center, National Center of Neurology and Psychiatry 4-1-1, Kodaira, Tokyo 187-8551, Japan

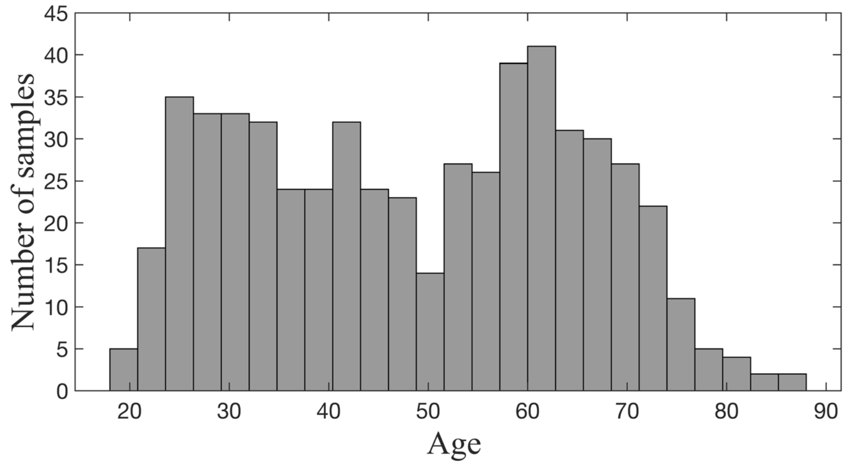

Fig. 1 Histogram showing the age distribution for the samples used in this study ($n = 563$)

In a whole-brain analysis, we used the voxel-based morphometry (VBM) procedure to calculate the whole-brain volumes (i.e., GM, WM, and cerebrospinal fluid [CSF]), and in a regional volumetric analysis, we used the *FreeSurfer* procedure to extract quantified regional brain volumes: the superior frontal, rostral middle frontal, putamen, precentral, insula, cuneus, hippocampus, amygdala, and para-hippocampal structures.

To model the influence of aging on brain volumes (i.e., whole and regional brain volumes), we performed a regression analysis. We sought to determine the patterns of aging-related changes of whole and regional brain volumes using a range of volumetric measures. Investigations of the volumetric changes over these two age ranges may contribute to the understanding of the mechanisms underlying brain atrophy and could help monitor the clinical treatment effects in many age-related neural disorders such as Alzheimer disease [16] and Parkinson disease [17].

Methods

Subjects and image acquisition

We used data acquired from the IXI database (http://brain-development.org/ixi-dataset/), which contains nearly 600 MRI scans and related information for healthy individuals. The MRI scans were acquired from three different hospitals in London on a 1.5-T Philips scanner and GE and 3-T Philips scanners. Details of the IXI data and scan parameters can be found at (http://biomedic.doc.ic.ac.uk/brain-development/index.php?n= Main.Datasets).

We selected the MRI scans and related information of the brains of 563 healthy individuals at ages ranging from 20 to 86 years (mean age ± sd: 48.66 ± 16.47, 55% female). Figure 1 shows the age distribution of the samples used in this study.

MRI preprocessing and statistical analysis

For the whole-brain analysis, we used Statistical Parameter Mapping (SPM; http://www.fil.ion.ucl.ac.uk/spm) software ver. 12 and the Computational Anatomy Toolbox (CAT12; http://dbm.neuro.uni-jena.de/cat) [18] to extract the whole-brain volumes including GM, WM, CSF, and total intracranial volume (TIV) of each individual. For an adjustment of the data in light of the variations in the subjects' head size, the normalized GM, WM, and CSF values are calculated through dividing the global GM, WM, and CSF volumes of all the individual brains by the TIV of the respective subjects.

Table 1 The whole-brain and regional-brain variables

Whole-brain variables	Regional-brain variables		
GM	Superior frontal	Posterior cingulate	Paracentral
WM	Rostral middle frontal	Supramarginal	Cuneus
CSF	Lateral orbitofrontal	Inferior parietal	Lateral occipital
GM/WM	Accumbens area	Cerebellum cortex	Postcentral
	Precuneus	Isthmus cingulate	Hippocampus
	Thalamus proper	Rostral anterior cingulate	Amygdala
	Superior temporal	Insula	Para- hippocampal
	Precentral	Putamen	

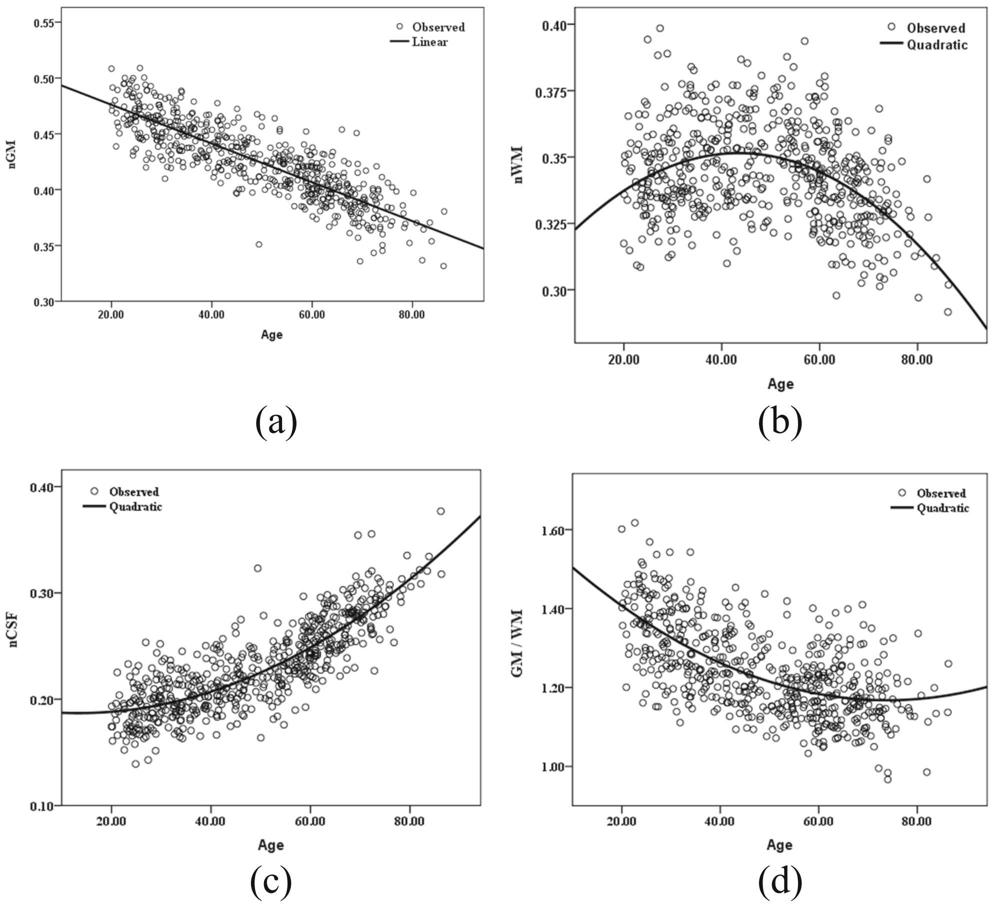

Fig. 2 Cross-sectional estimates of whole-brain volume change vs. age including best fit regression lines across adulthood ($n = 563$). **a** Normalized GM, **b** normalized WM, **c** normalized CSF, and **d** the GM/WM ratio

In the regional analysis, we used the *FreeSurfer* segmentation software (ver. 5.3.0, default parameters) to produce the respective reginal volumetric variables from 3D T1-weighted MRI scans of all of the subjects. We selected a total of 23 regions, and for each region, the respective volumes of the left and right sides are calculated by *FreeSurfer* and added together. All regional volumetric variables are adjusted by the individual subject's intracranial volume (ICV). The technical details of the *FreeSurfer* analysis are described elsewhere [19–21]. Table 1 provides the list of whole and regional variables used in this study. To evaluate the associations of the global and regional brain volume changes with aging, we examined six models (i.e., linear, quadratic, cubic, logarithmic, inverse, and power) to find the best-fitting model. We selected the model with the best-fitting robustness to display the data.

Results

Whole-brain variables

As described above in section "Methods", we calculated normalized brain volumes (i.e., nGM, nWM, and nCSF) as well as the GM/WM ratio for each subject by using the CAT12 toolbox. We used a regression model to examine the linear and nonlinear correlations of whole-brain variable changes with increasing age. Figure 2 illustrates the association of whole-brain variables with aging in terms of nGM, nWM, nCSF, and GM/WM ratio. The normalized GM values manifested a significant linear correlation with aging, whereas a nonlinear correlation was observed between each of the parameters nWM, nCSF, and GM/WM ratio with aging. The details of the best fitting model for nGM, nWM, nCSF, and the GM/WM ratio measures over the age are summarized in Table 2.

Table 2 Best fitting regression models for whole-brain volumes over the age

Variable	Best-fitting model	R^2
nGM	Linear	0.71
nWM	Quadratic	0.18
nCSF	Quadratic	0.70
GM/WM	Quadratic	0.40

GM normalized gray matter, *nWM* normalized white matter, *nCSF* normalized cerebrospinal fluid

All variables showed a significant association with age (i.e., $p < 0.001$)

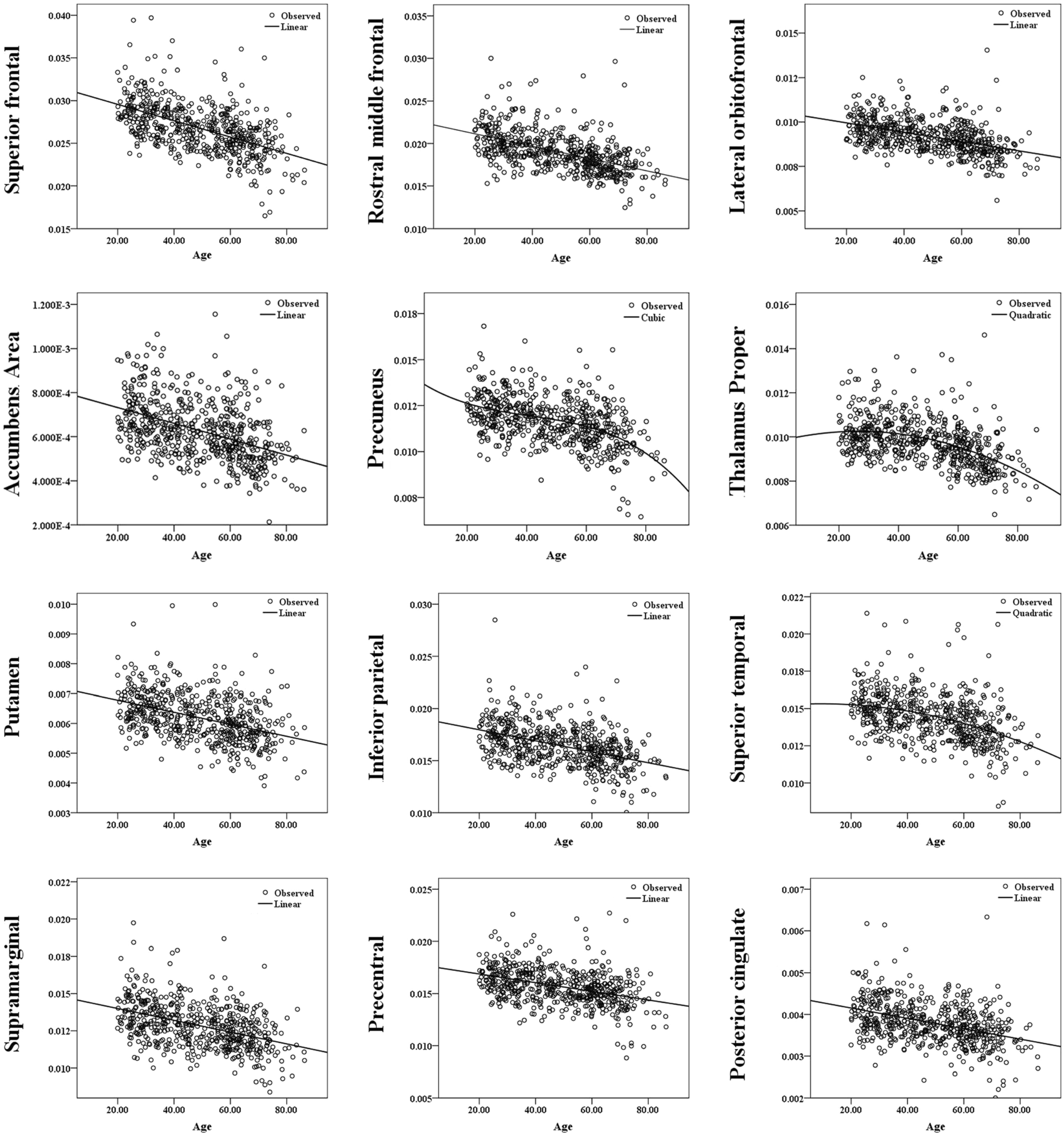

Fig. 3 Cross-sectional estimates of regional volumetric change versus age including best-fit regression lines across adulthood ($n = 563$)

Regional-brain variables

As described above, we used the *FreeSurfer* segmentation software to produce the regional volumetric measurements from 3D MRI scans. Figure 3 and Table 3 show the results for the regression analyses of selected regional-brain variables versus age, revealing that there were different volumetric change patterns in the selected regions with aging.

Discussion

The scope of this study was to investigate the effects of age on whole and regional brain volumes in healthy

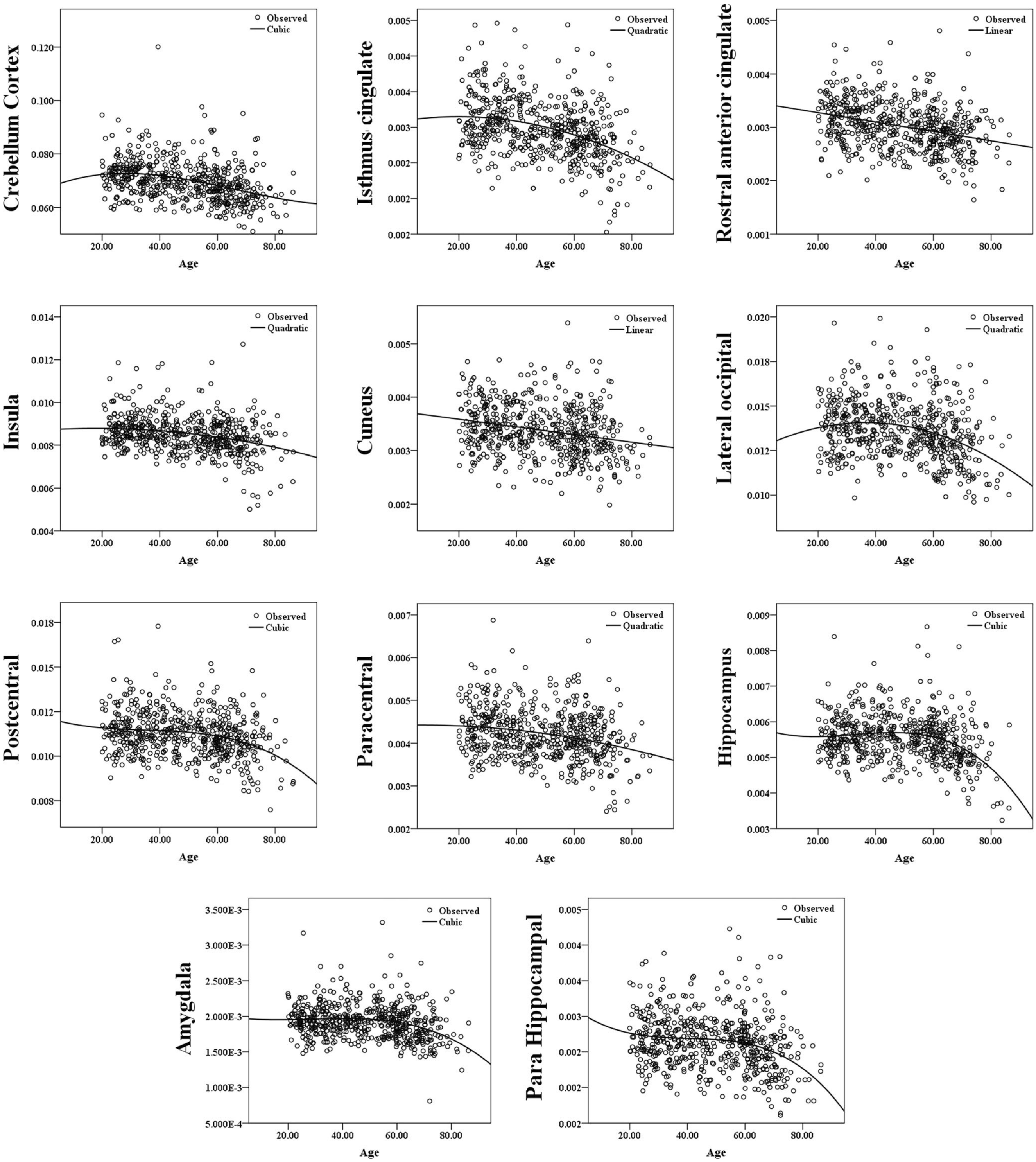

Fig. 3 (continued.)

individuals across adulthood, and our findings are summarized as follows.

Whole-brain analysis

In our study, the nGM values declined significantly over the age range 20 to 86 years, with best fit by a linear model ($R^2 = 0.71$, $p < 0.001$). This finding demonstrates that significant age-related GM loss occurs with advancing age.

Regarding the nWM, we observed a nonlinear relationship (i.e., an inverted U-shape) within the age range 20–86 years which were best fit by a quadratic model ($R^2 = 0.18$, $p < 0.001$). As can be seen in Fig. 2b, the nWM values increased

Table 3 Best fitting regression models for regional volumetric variables over the age

Variable	Best fitting model	R^2	Variable	Best fitting model	R^2
Superior frontal	Linear	0.29	Rostral middle frontal	Linear	0.27
Lateral orbitofrontal	Linear	0.21	Accumbens area	Linear	0.19
Precuneus	Cubic	0.22	Thalamus proper	Quadratic	0.21
Putamen	Linear	0.17	Inferior parietal	Linear	0.19
Superior temporal	Quadratic	0.17	Supramarginal	Linear	0.17
Precentral	Linear	0.15	Posterior cingulate	Linear	0.16
Cerebellum cortex	Cubic	0.13	Isthmus cingulate	Quadratic	0.14
Rostral anterior cingulate	Linear	0.10	Insula	Quadratic	0.07
Cuneus	Linear	0.06	Lateral occipital	Quadratic	0.10
Postcentral	Cubic	0.80	Paracentral	Quadratic	0.60
Hippocampus	Cubic	0.11	Amygdala	Cubic	0.07
Para hippocampal	Cubic	0.07			

Note: All variables showed a significant association with age (i.e., $p < 0.001$)

with the rising ages, reaching a peak in the fourth decade and a significant descent thereafter. This observation is broadly in line with other studies that describe a slight increase of WM during adulthood that is due to ongoing maturation of the white matter during normal aging [2, 13]. Statistical result shows that significant age-related WM loss occurs with advancing age.

Regarding the effect of aging on nCSF, a significant nonlinear relationship was revealed within the age range 20–86 years with the best fit by a quadratic model ($R^2 = 0.70$, $p < 0.001$). As Fig. 1c shows, the rate of total nCSF increases with advancing age, especially with a curve ascendance from the end of the fourth decade of age onwards. This may be due to the conversion of both GM and WM components into CSF, which occurs in later adulthood.

Regarding the GM/WM ratio, the rate of changes was significant within the age range 20–86, with the best fitting by a quadratic model ($R^2 = 0.40$, $p < 0.001$). We observed a significant decline in the GM/WM ratio until the fifth decade of life and a partly constant ratio after that. Our finding is in contrast with other research [22] describing a constant GM/WM ratio between older and younger subject groups.

Regional-brain analysis by *FreeSurfer*

In the regional volumetric analysis, we observed different patterns in different parts of the brain with age. As an example, we observed a linear steady decline in the superior frontal, rostral middle frontal, lateral orbitofrontal, accumbens area, putamen, inferior parietal, supramarginal and rostral anterior cingulate regions across the adult lifespan.

The regression volumetric analysis also showed that the precuneus, thalamus proper, superior temporal, cerebellum cortex, insula and lateral occipital regions followed nonlinear patterns with age. Regarding the isthmus cingulate, hippocampus, amygdala, and para-hippocampal regions, we observed curvilinear slopes; for example, in the isthmus cingulate region, the largest decline occurs after age 30 and in the hippocampus, amygdala and para-hippocampal regions, the largest declines occur after age 60. Several studies that used VBM described a preservation of the GM volume in limbic and paralimbic brain structures over the aging process [1, 8, 10, 23, 24]. The pattern observed in the hippocampus in the total series is in agreement with other studies that investigated the hippocampal volume changes with age [25, 26].

Several studies have investigated the impact of scanner characteristics (i.e., scanner field strength, manufacturer, upgrade, and pulse sequence) on MRI measurements [27, 28]. A limitation of present study might be that the effect of different scanner hardware and imaging protocol were not considered on our analysis, as the MRI data were collected from different sites.

Conclusion

We assessed the effect the age on whole and regional brain volume changes, using the MRI scans and related information of a series of 563 healthy individuals aged 20–86 years. Our analyses revealed the patterns of age-related global brain alternations that were best fit by a linear model for the normalized gray matter and by a nonlinear (i.e., quadratic) model for the normalized white matter, normalized cerebrospinal fluid, and the GM/WM ratio. We also observed different patterns in the regional analysis.

We were thus able to identify significant regression models that explain the effect of the aging on brain volume alternations. Our present findings contribute to the understanding of how structures in the human brain change over the adult years and will help address the pathological age-related neural changes in age-related neural disorders such as Parkinson disease and Alzheimer disease. The processes by which the brain matures and sometimes degenerates with aging remain to be further clarified by further studies using MRI and other imaging technology.

Authors' contributions IB designed the research, performed the statistical analysis, and drafted the manuscript. NM performed the volumetric segmentation. HM participated in the design of the study and supervised the statistical analysis. All authors read and approved the final manuscript.

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Availability of data and materials The dataset analyzed during this current study are available at http://brain-development.org/ixi-dataset/.

Compliance with ethical standards

Not applicable.

Competing interests The authors declare that they have no competing interests.

Consent for publication Not applicable.

Ethics approval This study was approved by the Institutional Review Board at the National Center of Neurology and Psychiatry, Tokyo, Japan.

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