Towards a unified analysis of brain maturation and aging across the entire lifespan: A MRI analysis

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Abstract: There is no consensus in literature about lifespan brain maturation and senescence, mainly because previous lifespan studies have been performed on restricted age periods and/or with a limited number of scans, making results instable and their comparison very difficult. Moreover, the use of non-harmonized tools and different volumetric measurements lead to a great discrepancy in reported results. Thanks to the new paradigm of BigData sharing in neuroimaging and the last advances in image processing enabling to process baby as well as elderly scans with the same tool, new insights on brain maturation and aging can be obtained. This study presents the analysis of the brain volume trajectory over the entire lifespan using the largest age range to date (from few months of life to elderly) and one of the largest number of subjects (N=2944). First, we found that white matter trajectory based on absolute and normalized volumes follows an inverted U-shape with a maturation peak around middle life. Second, we found that from 1 to 8-10y there is an absolute gray matter (GM) increase related to body growth followed by GM decrease. However, when normalized volumes were considered, GM continuously decreases all along life. Finally, we found that this observation holds for almost all the considered subcortical structures except for amygdala which is rather stable and hippocampus which exhibits an inverted U-shape with a longer maturation period. By revealing the entire brain trajectory picture, a consensus can be drawn since most of the previously discussed discrepancies can be explained.

Introduction

Brain development and aging are key topics in neuroscience. The study of normal brain maturation and age-related brain atrophy is crucial to better understand normal brain development and a large variety of neurological disorders. With the rise of the population age, it is becoming increasingly important to understand the cognitive changes that accompany aging, both normal and pathologic. Moreover, analyzing brain maturation and senescence during the entire lifespan may help to better understand the undergoing process on normal brain development and aging.

However, despite the important increase of studies dedicated to brain trajectory analysis over the last decades, an important disagreement remains between existing results (Walhovd, Westlye et al. 2011, Walhovd, Fjell et al. 2016). Some studies described early life increase of grey matter (GM) volumes followed by a decrease (Giedd, Blumenthal et al. 1999, Lenroot, Gogtay et al. 2007, Raznahan, Shaw et al. 2011) while others described decrease all along the lifespan (Ostby, Tamnes et al. 2009, Brain Development Cooperative 2012, Aubert-Broche, Fonov et al. 2013, Ducharme, Albaugh et al. 2016, Mills, Goddings et al. 2016). An extensive review of these inconstancies can be found in Walhovd et al. (2016). For white matter (WM) the picture is inverted, with a consensus for the early life period characterized by an increase. However, less consistent effect of age in adulthood has been reported (Jernigan, Baaré et al. 2011, Fjell, McEvoy et al. 2014). Time of brain maturation is also different according to the studies (Groeschel, Vollmer et al. 2010, Hedman, van Haren et al. 2012). Discrepancies also exist for the shape of trajectories for cortical and subcortical structures, sometimes described as linear, U-shaped (curvilinear) or as more complex polynomial curves. Finally, sometimes sexual dimorphism is described in these studies and sometimes no gender difference is observed (Giedd, Blumenthal et al. 1999, Suzuki, Hagino et al. 2005, Lenroot, Gogtay et al. 2007, Lenroot and Giedd 2010). The lack of consensus on brain development and aging prevents us to better understand these highly complex and multi-factor phenomena. The significant divergence between existing results is due to many factors.

First, the use of restricted life periods (e.g., childhood (Brain Development Cooperative 2012), adolescence (Lenroot and Giedd 2010, Vijayakumar, Allen et al. 2016), adulthood (Ziegler, Dahnke et al. 2012), etc.) makes difficult the comparison of results, and tends to favor simple models capturing only brain growth or aging. Thus, it prevents global understanding of brain modification across the entire lifespan. Up to now, no study covered the entire lifespan including babies from few months of life to elderly older than 90.

Second, the use of a limited number of scans at certain age ranges (especially at young ages) may produce unstable results limiting the reproducibility and accuracy of the estimations. The large majority of previous studies used less than 100 subjects (Walhovd, Westlye et al. 2011), some studies used several hundreds of subjects (Giedd and Rapoport 2010, Brain Development Cooperative 2012, Ziegler, Dahnke et al. 2012, Mills, Goddings et al. 2016) and very few studies used more than 1000 subjects (Fjell, Westlye et al. 2013, Potvin, Mouiha et al. 2016).

In addition, the use of non-harmonized acquisition protocols, segmentation tools, labelling protocols (Walhovd, Fjell et al. 2016) and volumetric measurements such as absolute volume (Brain Development Cooperative 2012) or normalized volumes (with intracranial volume (Good, Johnsrude et al. 2002, Mills, Goddings et al. 2016), GM

volume (Ziegler, Dahnke et al. 2012) or using z-scores (Ostby, Tamnes et al. 2009, Walhovd, Westlye et al. 2011), etc.) lead to a great discrepancy in reported results (Walhovd, Westlye et al. 2011). Moreover, some studies are based on cross-sectional data while others on longitudinal ones. Consequently, this heterogeneity makes difficult the definition of normative values (Potvin, Mouiha et al. 2016) stressing the need of using harmonized protocols over large samples covering the entire lifespan.

Finally, the use of an exigent quality control in the whole measurement process plays a major role in the quality of the final estimated brain models. This step is often not considered enough, while the model estimation greatly depends on a careful quality control (Ducharme, Albaugh et al. 2016).

Therefore, one of the most important challenges in neuroscience is to provide a consensual and unified vision of brain maturation and aging. In this study, we have addressed the previously mentioned limiting factors. First, thanks to the new paradigm of BigData sharing in neuroimaging (Poldrack and Gorgolewski 2014), we have been able to use a very high number of samples (N=3296) covering the largest lifespan period never studied (from few months to advanced age). Moreover, all the considered MRI scans obtained from several freely available databases were processed using the same advanced MRI processing pipeline (Manjon and Coupe 2016). Thanks to the last advances in image processing, images from different age ranges can be analyzed with the same tool. To get insight on brain maturation and aging at global (i.e., absolute volume) and brain scale (i.e., normalized volume), we have extensively analyzed our results using absolute volumes and relative volumes (normalized by Total Intracranial Volume, TIV). Moreover, to prevent the estimated models to be affected by wrongly processed images (Ducharme, Albaugh et al. 2016), we have used a demanding three stages quality control process. Finally, to be able to present a unified analysis of brain development and brain aging at the same time we used a hybrid model. Contrary to previous studies based on linear or low order polynomial models, we also considered models enable to capture fast growth and complex degenerative processes. This is achieved by combining cumulative exponential function to model rapid growth with saturation resulting from maturation and low order polynomial function to model volume decreases caused by aging.

By putting all these elements together, we are able to show for the first time a global picture of brain trajectory across the entire lifespan. Our results suggest that most of the previous marked disagreements can be explained by the proposed analysis. Previous divergences mainly seem to result from restricted investigations over short periods of the entire life history. Indeed, as shown in the following, the analysis of subjects bellow 8 years of age is important to detect the maturation peak. Similarly, the analysis of subjects older than 80 years is necessary to observe the accelerated atrophy occurring at this age. We hope that the proposed unified analysis will help to reach a consensus on normal brain trajectory.

Material and Methods

Datasets

In this study, we used 3D T1-weight MRI obtained from nine different freely available databases covering the entire lifespan. All the considered subjects are normal controls. The summary of used databases is detailed in Table 1 while details are provided latter in this section. The used images have been acquired on 1.5T and 3T over 103 sites. After quality control, 2944 MRI were kept from the 3296 considered subjects. The gender proportion of these selected subjects is 47% of female. The covered age starts from 9 months to 94 years, with an average age of 39.65 year and a standard deviation of 26.62.

Figure 1 shows the age distribution of the used subjects after quality. At least three different datasets are used for all the considered periods except for extreme ages (i.e., [0-4] year and [90-94] year) where only 2 datasets are available. Moreover, more than 50 subjects by 5-years interval are used at the exception of the last [90-94] interval.

In the following, more details about the different datasets used in this study are presented.

- **C-MIND (N=266, after QC N=236):** The images from the C-MIND dataset (https://research.cchmc.org/c-mind/) used in this study were obtained on 266 control subjects. All the images are acquired at the same site on a 3T scanner. The MRI are 3D T1-weighted MPRAGE high-resolution anatomical scan of the entire brain with spatial resolution of 1 mm^3 acquired using a 32 channel SENSE head-coil.
- **NDAR (N=612, after QC N=382):** The Database for Autism Research (NDAR) is a national database funded by NIH (https://ndar.nih.gov). This database included 13 different cohorts acquired on 1.5T MRI and 3T scanners. In our study we used 415 images of control subjects from the NIHPD (http://www.bic.mni.mcgill.ca/nihpd/info/data_access.html) dataset and 197 images of control subjects from the Lab Study 19 of National Database for Autism Research. For the NIHPD, T1-weighted images were acquired at six different sites with 1.5 Tesla systems by General Electric (GE) and Siemens Medical Systems. The MRI are 3D T1-weighted spoiled gradient recalled (SPGR) echo sequence with following parameters: TR = 22–25 ms, TE = 10–11 ms, flip angle = 30◦, FoV = 256 mm IS × 256 mm AP, matrix size = 256 × 256: 1 × 1 × 1 mm^3 voxels, 160–180 slices of sagittal orientation. The participants chosen from the Lab Study 19 of National Database for Autism Research (NDAR) were scanned using a 3T Siemens Tim Trio scanner at each site. The MRI are 3D MPRAGE sequence (voxel dimensions: 1.0 × 1.0 × 1.0 mm^3; image dimensions: 160 × 224 × 256, TE = 3.16 ms, TR = 2400 ms).
- **ABIDE (N=528, after QC N=492):** The images from the Autism Brain Imaging Data Exchange (ABIDE) dataset (http://fcon_1000.projects.nitrc.org/indi/abide/) used in this study were obtained on 528 control subjects acquired at 20 different sites on 3T scanner. The MRI are T1-weight MPRAGE image and the details of acquisition, informed consent, and site-specific protocols are available on the website.
- **ICBM (N=308, after QC N=294)**: The images from the International Consortium for Brain Mapping (ICBM) dataset (http://www.loni.usc.edu/ICBM/) used in this study were obtained on 308 normal subjects obtained through the LONI website. The MRI are T1-weighted MPRAGE (fast field echo, TR = 17 ms, TE = 10 ms, flip

angle = 30 °, 256×256 matrix, 1 mm^2 in plane resolution, 1 mm thick slices) acquired on a 1.5T Philips GyroScan imaging system (Philips Medical Systems, Best, The Netherlands).

- **OASIS (N=315, after QC N=298):** The images from the Open Access Series of Imaging Studies (OASIS) database (http://www.oasis-brains.org) used in this study were obtained on 315 control subjects. The MRI are T1-weighted MPRAGE image (TR = 9.7 ms, TE = 4 ms, TI = 20 ms, flip angle = 10 degrees, slice thickness = 1.25 mm, matrix size = 256×256, voxel dimensions = 1×1×1.25 mm^3 resliced to 1 mm^3, averages = 1) acquired on a 1.5-T Vision scanner (Siemens, Erlangen, Germany).
- **IXI (N=588, after QC N=573)**: The images from the Information eXtraction from Images (IXI) database (http://brain-development.org/ixi-dataset/) used in this study were obtained on 588 normal subjects. The MRI are T1weighted images collected at 3 sites with 1.5 and 3T scanners (FoV = 256 mm × 256 mm, matrix size = 0.9375 × 0.9375 × 1.2 mm^3).
- **ADNI1 (N=228, after QC N=223):** The images from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (http://adni.loni.usc.edu) used in this study were obtained on 228 control subjects from the 1.5T baseline collection. These images were acquired on 1.5T MR scanners at 60 different sites across the United States and Canada. A standardized MRI protocol to ensure cross-site comparability was used. Typical MRI are 3D sagittal MPRAGE (repetition time (TR): 2400 ms, minimum full TE, inversion time (TI): 1000 ms, flip angle: 8°, 24 cm field of view, and a 192×192×166 acquisition matrix in the x-, y-, and z-dimensions, yielding a voxel size of 1.25×1.25×1.2 mm^3, later reconstructed to get 1 mm^3 isotropic voxel resolution).
- **ADNI2 (N=213):** The images from the ADNI2 database (second phase of the ADNI project) were obtained on 215 control subjects. Images were acquired on 3T MR scanners with the standardized ADNI-2 protocol, available online (www.loni.usc.edu). Typical MRI are T1-weighted 3D MPRAGE sequence (repetition time 2300 ms, echo time 2.98 ms, flip angle 9°, field of view 256 mm, resolution 1.1 x 1.1 x 1.2 mm^3).
- **AIBL (N=233)**: The Australian Imaging, Biomarkers and Lifestyle (AIBL) database (http://www.aibl.csiro.au/) used in this study consists of 236 control subjects. The imaging protocol was defined to follow ADNI's guideline on the 3T scanner (http://adni.loni.ucla.edu/research/protocols/mri-protocols) and a custom MPRAGE sequence was used on the 1.5T scanner.

Image processing

All the images were processed with volBrain online software pipeline (http://volbrain.upv.es). The volBrain system is a web-based online tool that is able to provide automatic brain volumetry in around 10 minutes (including the generation of a pdf volumetry report summarizing the volumetric results). Since its deployment (less than 2 years) volBrain has processed online almost 30.000 brains for approximately 1000 users. Recently, volBrain pipeline was compared with two well-known tools used on MR brain analysis (FSL and Freesurfer) showing significant improvements in terms of both accuracy and reproducibility for intra and inter-scanner scan rescan acquisition (Manjon and Coupe 2016). The volBrain pipeline consists of a set of steps aimed to improve the quality of the MR images to analyze and to locate them in a common geometric and intensity space prior to perform at several anatomical levels (Manjon and Coupe 2016). In more details, volBrain pipeline includes the following preprocessing steps: 1) denoising using spatially adaptive non-local means (Manjon, Coupe et al. 2010), 2) rough inhomogeneity correction using N4 method (Tustison, Avants et al. 2010), 3) affine registration to

MNI152 space using ANTS software (Avants, Tustison et al. 2011), 4) SPM based fine inhomogeneity correction (Ashburner and Friston 2005) and 5) histogram based intensity standardization. After the preprocessing, the intracranial cavity is segmented using NICE method (Manjon, Eskildsen et al. 2014), tissue classification is performed using TMS method (Manjón, Tohka et al. 2010) and finally subcortical structures are estimated using an extended version of the non-local label fusion method (Coupe, Manjon et al. 2011). All the segmentation methods of volBrain use a library of 50 experts manually labelled cases (covering almost the whole lifespan) needed to perform the labeling process at different levels. More details can be found in (Manjon and Coupe 2016).

Statistical Analysis

The statistical analysis was performed with Matlab© software. In order to determine the best general models for each structure, several models were tested from the simplest to the most complex on all the dataset (i.e., female and male at the same time). A model is kept as a potential candidate only when F-statistic based on ANOVA for model vs. constant model is significant ($p<0.05$) and when all its coefficients are significant using t-statistic ($p<0.05$). At the end of the selection procedure, we used the Bayesian Information Criterion (BIC) to select the best model among models being significant compared to constant model and having all coefficients significant. BIC provides a measure of the trade-off between bias and variance and thus select the model explaining most the data with minimum parameters. Afterwards, this general model type is applied on female and male separately to estimate gender specific models. At the end, to study trajectory difference in terms of volume and shape between both female and male, $\beta_i Sex + \beta_j Sex.Age$ interactions are tested over the selected general model. All the reported parameters (t-statistic, F-statistic, BIC and R^2) were internally estimated by Matlab© using default parameters. The following models were considered as potential candidates:

1. Linear model

$$Vol = \beta_0 + \beta_1 Age + \varepsilon$$

2. Quadratic model

$$Vol = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \varepsilon$$

3. Cubic model

$$Vol = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Age^3 + \varepsilon$$

4. Linear hybrid model: exponential cumulative distribution for growth with linear model for aging

$$Vol = \beta_4 . \left(1 - e^{-Age/\beta_5}\right) + \beta_0 + \beta_1 Age + \varepsilon$$

5. Quadratic hybrid model: exponential cumulative distribution for growth with quadratic model for aging

$$Vol = \beta_4 . \left(1 - e^{-Age/\beta_5}\right) + \beta_0 + \beta_1 Age + \beta_2 Age^2 + \varepsilon$$

6. Cubic hybrid model: exponential cumulative distribution for growth with cubic model for aging

$$Vol = \beta_4 . \left(1 - e^{-Age/\beta_5}\right) + \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Age^3 + \varepsilon$$

In the literature, structure trajectories have been mainly modeled using low order polynomial function (see (Walhovd, Westlye et al. 2011) for review). However, to follow structure trajectories across the entire lifespan, we propose to consider hybrid models able to track rapid growth during childhood and to capture complex volume decrease from adulthood to elderly. In the past, fast growth modelling occurring during childhood has been achieved using Poisson curve (Lebel, Gee et al. 2012) or Gompertz-like function (Makropoulos, Aljabar et al. 2016). Here, we propose to combine a cumulative exponential function in place of Gompertz-like function, and to combine it with low order polynomial function. At the end, our hybrid models can model fast growth process and complex volume decreases at the same time.

Quality Control

As recently shown, the quality control (QC) of image processing pipeline has a critical impact on trajectory results (Ducharme, Albaugh et al. 2016). Therefore, in this study we decided to use a demanding multi-stage QC procedure for a careful selection of the involved subjects. First, a visual assessment of input image quality was done for all considered subjects. This assessment was performed by checking screen shots of one sagittal, one coronal and one axial slice in middle of the 3D volume. This step led to remove 219 subjects from the 3296 considered subjects in our study (6.6%). Next, a visual assessment of the image processing quality for all remaining subjects was performed using volBrain reports (see an example of report here: http://volbrain.upv.es/example_report.pdf). This report provides screenshots of one sagittal, one coronal and one axial slice at middle of the 3D volume for each step of the processing pipeline. All these steps (full head coverage including cerebellum, registration to MNI space, TIV extraction, tissue classification, subcortical structure segmentation, etc.) were carefully checked. This step led to remove 83 subjects from our study (2.5%). Finally, a last control was performed by individually checking all outliers detected using estimated trajectories. A volume was considered as outlier when its value was higher/lower than 2 standard deviations of the estimated model. For each detected outlier, the segmentation map was opened and displayed over the MRI using a 3D viewer (Yushkevich, Piven et al. 2006). A careful inspection was performed over the 3D volume. In case of segmentation failure, the subject was removed from the study. This last QC step led to remove 50 subjects (1.5%). Therefore, 2944 of the 3296 considered subjects were kept after our QC procedure.

Results

Maturation and aging of brain tissues

Global gray matter and white matter trajectories

At the global scale (i.e., absolute volumes), we observe an increase of WM volume until 30-40y followed by a volume decrease (see Fig. 2). As can be noticed, the WM growth at early ages is faster than the senescence at late ages. This is assessed by the selected hybrid model ($p<0.001$) combining an exponential cumulative distribution model for growth and a cubic model for aging (see Tab. 2). On the other hand, although the same model is selected for GM ($p<0.0001$), its trajectory is more complex. We observed a 4 stages trajectories composed of a fast growth until 8-10y followed by a fast decrease until 40ys, then a plateau and finally an accelerated aging-related decrease is visible around 80ys. At the brain scale (i.e., normalized

volumes in % to the TIV), the main difference is found for the GM trajectory. Indeed, at this scale, we observe a decrease of GM all along the lifespan (see Fig. 3) following a cubic model ($p<0.0001$) (see Tab. 3). The decrease of normalized volumes also follows a complex shape with 3 stages composed of a rapid decrease from 0 to 20y, a plateau from 40 to 80y and a rapid decrease after 80y. It is interesting to note that despite the normalization, the WM growth remains very fast at the brain scale for early age with a hybrid model using an exponential cumulative distribution model for growth. Finally, at global and brain scales, we observe that WM have almost an inverted U-shape model although an asymmetry exists with a faster volume increase related to maturation than volume decrease caused by aging.

Cortical and subcortical gray matter trajectories

To study trajectory differences between cortical and deep gray matter, we performed complementary analyses. First, we estimated the deep GM volume by adding the GM volume of the considered deep structures (i.e., caudate, thalamus, accumbens, globus pallidus, putamen, hippocampus and amygdala). The cortical GM was estimated as the global GM volume (as used in the paper) minus the deep GM volume. Supplementary Figure 2 shows the estimated trajectories using absolute volume and normalized volume in % of TIV. At the global scale, we can observe that after their maturation peaks, deep and cortical GM volume decreases. However, deep GM volume decreases with almost a constant rate while cortical GM volume follows a more complex trajectory similar to the 4 stages pattern already described for global GM. Similarly, at the brain scale, while the cortical GM follows the 3 stages detailed for global GM, the deep GM follows an almost linear decrease all along the lifespan with accelerated atrophy after 80y.

Cerebrum and cerebellum trajectories

Finally, we investigated trajectories for cerebrum and cerebellum separately. At global scale, selected models for cerebrum and cerebellum are the same and they are similar to the models selected for global GM and WM (see supplementary Tab. 2 and Tab. 3). Moreover, gender differences were found for cerebrum and cerebellum when using absolute volumes. Visually, both structures follow similar trajectories (see supplementary Fig. 3 and supplementary Fig. 4). However, some differences can be observed. First, the cerebellum has a shorter GM volume decrease after maturation peak. In addition, the magnitude of GM and WM increase during maturation is smaller for the cerebellum than for cerebrum. Finally, the cerebellum has a less pronounced WM decrease after 80y and a reduced atrophy rate over this period. At the brain scale, selected models are different between cerebrum WM and cerebellum WM. The hybrid model selected for WM cerebrum indicates a faster volume increase for this structure compared to WM cerebellum. The faster maturation during childhood of WM cerebrum is also visible on supplementary Figure 3 and supplementary Figure 4. The 3 stages trajectory obtained for global GM is observed for cerebellum GM and cerebrum GM. However, the plateau occurring at adulthood appears earlier for cerebellum than for cerebrum. Finally, the atrophy rate of normalized cerebrum volume is faster than cerebellum one.

Deep gray matter structure trajectories

Thalamus, accumbens, caudate, putamen and globus pallidus trajectories

At global scale, we observe that thalamus, accumbens, caudate and putamen follow similar trajectories with fast growth until 10-12y followed by a volume decrease. All selected hybrid models combine an exponential cumulative distribution for growth followed by low polynomial order for volume loss during aging, cubic for caudate ($p<0.0001$) and putamen ($p<0.0001$), quadratic for thalamus ($p<0.0001$) and linear for accumbens ($p<0.0001$) (see Tab. 2). On the other hand, globus pallidus volume decreases from birth all along lifespan (quadratic model with $p<0.0001$). Unexpected slight increases of caudate and putamen volumes are visible after 80y. At the brain scale, we can see that thalamus, accumbens, caudate, putamen and globus pallidus show a volume decrease across the entire lifespan. First, thalamus and accumbens exhibit almost monotonous decrease although cubic models have been selected (both with $p<0.0001$). Second, caudate and putamen present similar slowdown decreases after 50y. The similar trajectories of the caudate and putamen are consistent with their shared nature as dorsal striatal structures (Paxinos and Mai 2004). The model selected for these structures is cubic for caudate ($p<0.0001$) and quadratic for putamen ($p<0.0001$) (see Tab. 3). Finally, globus pallidus follows a cubic model ($p<0.0001$) showing a fast decrease between 1y-30y, followed by a plateau between 30y and 80y and then by an accelerated atrophy after 80y.

Amygdala and hippocampus trajectories

At the global scale, amygdala volume shows a slight increase until 18y-20y followed by a long plateau which ends around 70y, followed by an age related atrophy. The selected hybrid model combines a volume increase following an exponential cumulative distribution and a volume decrease following cubic model ($p<0.0001$). The hippocampus shows a fast volume increase until 8y-10y followed by a slow volume increase until 40y-50y before an atrophic period. Here, the selected hybrid model mixes a volume increase following an exponential cumulative distribution and then an inverted U-shape volume decrease ($p<0.0001$). At the brain scale, amygdala volume trajectory follows a cubic model ($p<0.0001$) presenting a plateau until 70y followed by an atrophy. This result seems to indicate that absolute increase of amygdala volume during childhood is mainly related to brain growth. Moreover, using relative volume, hippocampus exhibit its very specific inverted U-shape trajectory compared to the other subcortical structures analyzed. In our study, the hippocampus is the only structure showing volume increase until the middle period of human life. To better investigate this point, we performed a complementary analysis between 18y and 70y. We found that the impact of age on absolute HC volume is significant ($p<0.0001$) and that the selected model is an inverted U-shape trajectory over this restricted period. According to our results, the hippocampal maturation stops around 50y.

Sexual dimorphism

At the global scale, we observe that males have bigger volumes than females for all considered structures (sex interaction with $p<0.0001$, see Tab. 2) with the exception of accumbens. Finally, increased atrophy rates for males after 80y is assessed by CSF trajectory, which is the only brain compartment showing significant age*sex ($p<0.0001$) over the entire lifespan using the considered model. At the brain scale, almost all gender volume differences vanish, except in favor of females for caudate

(p=0.05) and thalamus (p=0.05) with marginal significance, and for accumbens (p=0.02) (see Tab. 3). Visually, we can observe bigger relative volume for female hippocampus almost significant (p=0.07) (see Tab. 3 and Fig. 3). Finally, for global GM, caudate, thalamus, globus pallidus and amygdala, the trajectories of females seem to indicate a better resistance to the accelerated age-related atrophy occurring after 80y. To investigate this point, we studied sex and sex*age interaction using all subjects with age > 70 years (i.e., 637 subjects composed of 292 males and 345 females). Models estimated using all the subjects (see Tab. 2) are applied over this considered restricted period to evaluate sex and sex*age interactions. We found that using normalized volumes, almost all studied structures show significant sex and sex*age interaction after 70y with the exception of WM and amygdala (see Tab. 4).

Discussion

One of the main questions related to brain tissue properties deals with gray and white matter development/maturation and age-related gray and white matter atrophy. Knowing the time when brain tissues stop to mature and when they start to degenerate are key questions in neurology (Sowell, Peterson et al. 2003). In the past, both questions have been usually treated separately in the literature, preventing us to get a global picture of these join phenomena. Moreover, discrepancies between used volumetric measurements (absolute or relative) made difficult to reach a consensus on crucial questions about synaptogenesis and synaptic pruning, myelination and aging.

Towards a consensus?

Marked discrepancies exist in the literature about the best fitting models to describe brain trajectories either in pediatric phase (Ducharme, Albaugh et al. 2016) or adulthood (Fjell, Westlye et al. 2013). In our study, hybrid models mixing exponential cumulative distribution growth with low order polynomial senescence are the most suitable for 8/10 of the investigated brain regions when absolute volumes are used. Moreover, the absolute global GM volume (mainly due to cortical GM) follows a complex trajectory with 4 phases: 1) rapid increase from 0 to 8-10y, 2) rapid decrease until 40, 3) a plateau from 40-80y and 4) a rapid decrease after 80y. On the other hand, low order polynomial models better fit when volumes normalized by TIV are used, except for WM (see Tab. 2 and Tab. 3). When global growth effect is corrected, normalized global GM volumes decrease all over lifespan and follow a complex shape with 3 phases: 1) a rapid decrease from 0 to 20y, 2) a plateau from 40 to 80y and 3) a rapid decrease after 80y. This decline of the normalized global GM volume is consistent with the well-known fact that most of the neurogenesis is a prenatal phenomenon (Stiles and Jernigan 2010). In contrast, WM presents a shape close to the usually described inverted U-shape (Walhovd, Westlye et al. 2011) which persists after controlling for head size. This result indicates that during the early phase of brain development WM expansion exceeds general growth. The fast simultaneous WM maturation and GM decrease at brain scale from childhood to adolescence are consistent with brain myelination period and cortical thinning process previously observed *ex-vivo* (Huttenlocher and Dabholkar 1997). When considering cortical GM and deep GM separately, they exhibit a different pattern at both global and brain scales. At brain scale, deep GM shows almost a linear decrease while cortical GM trajectory follows the 3 identified stages for the global GM (see supplementary Fig. 2). The steep decrease in the normalized volume of cortical GM in the 0-20y period (compared to the almost linear dynamics of the deep GM) is

probably due to the very high pruning rate of the exuberant connectivity generated in the cerebral cortex (Stiles and Jernigan 2010) or is due to myelination of nearby subcortical WM fibers (Jernigan, Baaré et al. 2011).

One of the most marked discrepancy in the literature is about the cortical GM trajectory over childhood (Walhovd, Fjell et al. 2016). First studies reported an increase with maturation peak in early school age (Giedd, Blumenthal et al. 1999, Lenroot, Gogtay et al. 2007, Raznahan, Shaw et al. 2011). However, mainly monotonic decrease from early childhood have been recently published (Ostby, Tamnes et al. 2009, Brain Development Cooperative 2012, Aubert-Broche, Fonov et al. 2013, Ducharme, Albaugh et al. 2016, Mills, Goddings et al. 2016). The first factor that could explain this pronounced divergence is the used measurement. In this study, we showed that absolute GM volume follows a 4 stages trajectory with a maturation peak while normalized GM volume follows a 3 stages trajectory exhibiting a decrease all along the lifespan. Therefore, our results are in line with (Giedd, Blumenthal et al. 1999, Shaw, Kabani et al. 2008, Groeschel, Vollmer et al. 2010, Raznahan, Shaw et al. 2011) for absolute measurements and are consistent with (Ostby, Tamnes et al. 2009, Mills, Goddings et al. 2016) for normalized measurements. However, several studies reported monotonic decrease using absolute cortical GM volume over childhood (Sowell, Peterson et al. 2003, Brain Development Cooperative 2012, Aubert-Broche, Fonov et al. 2013, Ducharme, Albaugh et al. 2016, Mills, Goddings et al. 2016, Walhovd, Fjell et al. 2016). This result is in contradiction with studies dedicated to newborn period that report an increase of absolute GM over the first months of life (Groeschel, Vollmer et al. 2010, Holland, Chang et al. 2014, Makropoulos, Aljabar et al. 2016). The fact that several studies did not detect GM maturation peak using absolute measurements seems to be related to two main factors, the lack of subjects younger than 5y and the use of low order polynomial models. Indeed, most of the studies presenting monotonic decrease did not include subjects younger than 4y making difficult the detection of GM volume increase over the first years of life. Moreover, this implies that the model fitting was mainly driven by subjects with already mature brains (Sowell, Peterson et al. 2003, Brain Development Cooperative 2012, Aubert-Broche, Fonov et al. 2013, Ducharme, Albaugh et al. 2016, Mills, Goddings et al. 2016, Walhovd, Fjell et al. 2016). In addition to this potential issues on the used age range, most of these studies were using linear, quadratic or cubic models. Low order polynomial models are not well-designed to capture complex shape such as fast growth with saturation before nonlinear decrease. In our study, we tried to address these two limitations by using subjects younger than 4y old and by considering hybrid models enable to handle complex brain change occurring during the first years of life. Finally, it is interesting to note that our results are in line with another study presenting GM trajectory from infancy to young adulthood based on nonlinear piecewise polynomial model (Groeschel, Vollmer et al. 2010).

Deep GM structures are the focus of a great interest due to their important role in various neurodegenerative diseases, and thus have been intensively studied in the past (Fjell, Westlye et al. 2013). Non-linear trajectories of these structures have been previously described for adulthood (Ziegler, Dahnke et al. 2012, Fjell, Westlye et al. 2013). More recently, studies taking advantage of the “BigData sharing” in neuroscience started to analyze subcortical structure volumes from 20y up to advanced ages to define normative values for adult lifespan (Potvin, Mouiha et al. 2016). However, the limited age range of these studies made impossible to estimate full lifespan models. In this study, we have addressed this important problem by considering subjects covering the entire lifespan. Moreover, we extensively analyzed structure trajectories using both absolute and normalized volumes. Therefore, our results present at the same time the structure maturation peaks occurring during

childhood based on absolute volumes and the accelerated atrophy related to aging occurring after 80y obtained using normalized volumes. In addition, when deep GM structures are considered at the brain scale, their trajectories present a similar global decrease all along life, except for the medio-temporal regions with a late decrease for amygdala (after 70 years old) and an inverted U-shape for hippocampus. Moreover, unexpected slight increases of caudate and putamen absolute volumes are visible after 80y. Such observations have been already reported and questioned in several studies (Walhovd, Westlye et al. 2011, Fjell, Westlye et al. 2013, Potvin, Mouiha et al. 2016). Different hypotheses have been proposed such as bias related to survival of subjects with bigger structures, cohort effect, image artifact related to aging or a real phenomenon (Potvin, Mouiha et al. 2016). In our opinion, such volume increases at late ages can be also related to the use of global parametric model with less samples for very old subjects.

The understanding of the amygdalo-hippocampal complex is of key importance in neurology since it is related to crucial tasks such as memory, spatial navigation or emotional behavior. Moreover, hippocampus has been largely studied due to its use as an early biomarker in several neurodegenerative diseases such as Alzheimer's disease (Fox, Warrington et al. 1996, Jack, Petersen et al. 1997) and also because it is the main location of adult neurogenesis (Eriksson, Perfilieva et al. 1998, van Praag, Schinder et al. 2002). Noteworthy, while amygdala and hippocampus are often associated due to their respective contribution to the limbic system, it appears that they present different trajectories. This fact has been previously reported in recent studies (Ziegler, Dahnke et al. 2012, Fjell, Westlye et al. 2013, Pfefferbaum, Rohlfing et al. 2013, Potvin, Mouiha et al. 2016). The long maturation period of the hippocampus may be related to the adult neurogenesis, and in fact it has been shown that neurogenesis in the human hippocampus is substantial until at least the fifth decade of life (Spalding, Bergmann et al. 2013), a finding consistent with our analysis. In contrast to the hippocampus, early maturation of the amygdala is consistent with its known function in emotional learning, which allows individuals to avoid aversive events and pursue rewarding experiences (Phelps and LeDoux 2005). Accordingly, the amygdala in humans has been shown to be functional early in life (Tottenham and Sheridan 2009). Our results on amygdala are in accordance with most of the previous studies highlighting a minor effect of aging over adulthood (Walhovd, Westlye et al. 2011).

Another important question about brain maturation and aging is related to sexual dimorphism. In the past, this question has been studied mainly over childhood development (Giedd and Rapoport 2010, Brain Development Cooperative 2012, Aubert-Broche, Fonov et al. 2013) or during adolescence (Lenroot, Gogtay et al. 2007, Ostby, Tamnes et al. 2009, Lenroot and Giedd 2010, Hu, Pruessner et al. 2013). As previously mentioned, studies on different limited time periods, using non harmonized tools and different volumetric measurements prevented reaching a consensus. In our study, when using absolute volume, we found that brain structure maturation peaks occur before for female than for male (between 1y-3y earlier). These earlier peaks in females in the maturational phase have been previously described (Giedd and Rapoport 2010) and were mainly explained by sex differences in growth. We also found a difference around 10-12% of brain size between sexes as previously reported by *in-vivo* or postmortem studies (Lenroot and Giedd 2010, Brain Development Cooperative 2012). On the other hand, when the impact of brain size is compensated for, both sexes exhibit more similar trajectories. Only the normalized volume of nucleus accumbens presents a marked sexual dimorphism. This region is a key structure in the neural circuitry of addiction, a phenomenon well known to show sex differences (Becker and Hu 2008). However, sexual dimorphism of the accumbens volume in humans has not been (to our knowledge) described before. In

rats, a higher density of dendritic spines has been shown in females (Forlano and Woolley 2010). If a similar sex difference would exist in humans, it would be so subtle that only very large experimental samples would reveal it, as it is the case in the present study. Finally, we found that for several structures males are more impacted by aging than females especially after 70y. The fact that women may be less vulnerable to age-related atrophy has been previously reported (Gur, Mozley et al. 1991, Coffey, Lucke et al. 1998, Carne, Vogrin et al. 2006). This phenomenon may be related to the protective effect of estrogens and progesterone (Green and Simpkins 2000) or related to the fact that women present fewer risk factors (hypertension, tobacco and alcohol consummation…).

Limitations

In our opinion, one of the strengths of our study is to use multiple datasets to be able to cover the entire lifespan. However, this point can be also viewed as a weakness since the use of multiple datasets may introduce bias. Indeed, pooling databases having different age ranges could lead to find artificial differences. It has to be noted that we limited this aspect by using at least 2 different overlapping databases for each 5y intervals. Moreover, the preprocessing pipeline of volBrain has been designed to limit the impact of acquisition protocol by proposing advanced denoising filter and tissue-based intensity normalization. Therefore, after preprocessing, images are better homogenized in terms of signal-to-noise ratio and tissue contrast limiting the impact of using different acquisition protocols and scanners. In addition, during our QC all images with motion and ghosting artifacts were removed as well as the image having high anisotropic voxel resolution. Finally, several studies showed that age-related volume differences are consistent between datasets when using the same analysis tool (Fjell, Westlye et al. 2009, Walhovd, Westlye et al. 2011, Mills, Goddings et al. 2016) and recent papers (Potvin, Mouiha et al. 2016, Potvin, Dieumegarde et al. 2017) based on a large scale study over adulthood, showed that the impact of MRI scanner manufacturer and magnetic strength is negligible compared to impact of age of the structure trajectories.

After our quality control step, no images of subjects younger than 9 months remained. Therefore, the newborn period is not well covered by our samples and thus obtained results before 9 months of life may be inaccurate. Few studies have been published on brain structure trajectory for this period (Gilmore, Lin et al. 2007, Groeschel, Vollmer et al. 2010, Gilmore, Shi et al. 2012, Holland, Chang et al. 2014, Makropoulos, Aljabar et al. 2016) since the acquisition is difficult and the image analysis is very challenging due to low contrast before 6 months and fast myelination progression during the first 2 years of life. Specific tools have been proposed to analyze the newborn life period (Makropoulos, Gousias et al. 2014, Wang, Shi et al. 2014). Nevertheless, up to now, no large period lifespan study integrates newborn period with childhood, adolescence, adulthood and elderly.

We described here different lifespan trajectories for deep versus cortical structures. Since previous studies also described different trajectories according to the different parts of the cortex (Sowell, Peterson et al. 2003, Fjell, Westlye et al. 2009, Pfefferbaum, Rohlfing et al. 2013, Walhovd, Fjell et al. 2016, Potvin, Dieumegarde et al. 2017), this should be investigated in a future study.

Finally, to study brain trajectory over the entire lifespan, we used cross-sectional analysis in our study. Using cross-sectional data to analyze a dynamic process can be suboptimal. However, some evidences show that cross-sectional and longitudinal data produce similar age-related patterns (Fjell, Westlye et al. 2013). Moreover, the reported lack of consensus is also observed among different longitudinal studies. For

instance, the volume of cortical gray matter is highest in childhood according to some longitudinal studies (Mills, Goddings et al. 2016), but peaks at puberty according to others (Lenroot, Gogtay et al. 2007). Therefore, the longitudinal or cross-sectional nature of the study is another factor introducing variability but it is not the unique factor explaining the different results reported in the literature. It is interesting to note that many of the presented results in our cross-sectional study are in accordance with previous longitudinal studies. First, for childhood, maturation peak between 8-10y for absolute cortical GM volume and earlier peak for females have been reported using longitudinal data (Giedd, Blumenthal et al. 1999, Raznahan, Shaw et al. 2011). Moreover, for adolescence, an increase of the absolute WM volume and a decrease of absolute GM volume between 10y and 20y have been observed in previous longitudinal studies (Giedd, Blumenthal et al. 1999, Aubert-Broche, Fonov et al. 2013, Mills, Goddings et al. 2016). Finally, for adulthood, our results on normalized subcortical structures volume are highly consistent with results presented in the longitudinal study published by Pfefferbaum et al. (2013). Nevertheless, we think that in a further work, a mixed cross-sectional / longitudinal study (Giedd, Blumenthal et al. 1999) could be done since some of the used datasets contain longitudinal data.

Conclusion

We have presented an MRI volumetric brain analysis study covering the entire lifespan based on a very large number of subjects. In this study we have dealt with main limitations of previous studies to offer a comprehensive analysis of maturation and aging effects at different brain tissues and structures. Absolute and relative measurements have been used to get a complete picture of the brain state at different development stages for both genders. Moreover, optimized models have been used to robustly characterize volume evolution of the different tissues and structures. The analysis of the results of this study has been very helpful to integrate several previous studies covering partial age ranges into a common framework, allowing a better understanding of the observed phenomena. Moreover, the use of these models as normative values can be of inestimable help when analyzing the state of new subjects. Furthermore, disease specific estimated models can be directly compared to the normal models estimated in this study without needing to acquire and analyze a control group. We will include these models in our open access web platform volBrain to provide normality bounds based on the appropriate sex and age for the analysis of new cases. We hope that the online availability of the volBrain online service in combination with the presented models will help our understanding of both normal and pathological human brain.

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