Title: Pregnancy and adolescence entail similar neuroanatomical adaptations: A comparative analysis of cerebral morphometric changes

Authors:

Susanna Carmona, Magdalena Martínez García, María Paternina Die, Erika Barba-Müller, Lara M. Wierenga, Yasser Aleman, Clara Pretus, Luis Marcos Vidal, Laura Beumala, Romina Cortizo, Cristina Pozzobon, Marisol Picado, Florencio Lucco, David García-García, Juan Carlos Soliva, Adolf Tobeña, Jiska S., Peper, Eveline A Crone, Agustín Ballesteros, Oscar Vilarroya, Manuel Desco & Elseline Hoekzema.

Academic/professional affiliations:

Centro de Investigación Biomédica en Red de Salud Mental, Madrid, Spain (SC, MMG, MD); Unidad de Medicina y Cirugía Experimental, Instituto de Investigación Sanitaria Gregorio Marañón, Madrid, Spain (SC, MMG, MPD, LMV, DGG, MD); Faculty of Health Sciences, Universitat Oberta de Catalunya, Barcelona, Spain (SC); Departamento de Bioingeniería e Ingeniería Aeroespacial, Universidad Carlos III de Madrid, Leganés, Spain (MPD, LMV, MD); University Institute of Mental Health Vidal i Barraquer, Ramon Llull University, Barcelona, Spain (EBM); Brain and Development Laboratory, Leiden University, Leiden, the Netherlands (LMW, JSP, EAC, EH); Leiden Institute for Brain and Cognition, Leiden University, Leiden, the Netherlands (LMW, JSP, EAC, EH); Center for Psychiatric Neuroscience, Department of Psychiatry, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland (YA); Department of Radiology, Centre Hospitalier Universitaire Vaudois and University of Lausanne, Lausanne, Switzerland (YA); Hospital del Mar Research Institute, Barcelona, Spain (CP, MP, OV); Unitat de Recerca en Neurociència Cognitiva, Department of Psychiatry and Forensic Medicine, Universitat Autònoma de Barcelona, Cerdanyola del Vallés, Spain (LB, RC, MP, JCS, AT, OV); IVI Barcelona, Assisted Medicine Reproduction, Barcelona, Spain (CP, FL, AB); Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III, Madrid, Spain (MD).

S.C and M.M.G. contributed equally to this work, and M.D and E.H equally supervised this work.

Address correspondence to Susanna Carmona, Hospital General Universitario Gregorio Marañón, Avenida Dr Esquerdo 46, 28007 Madrid, Spain (scarmona@hggm.es) and Oscar Vilarroya, Hospital del Mar Medical Research Institute (IMIM), 08003 Barcelona, Spain (oscar.vilarroya@gmail.com).

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Keywords: adolescence; neuroanatomy; cortex, pregnancy; MRI; hormones; plasticity.

ABSTRACT

Mapping the impact of pregnancy on the human brain is essential for understanding the neurobiology of maternal caregiving. Recently, we found that pregnancy leads to a long-lasting reduction in cerebral gray matter volume. However, the morphometric features behind the volumetric reductions remain unexplored. Furthermore, the similarity between these reductions and those occurring during adolescence, another hormonally similar transitional period of life, still needs to be investigated. Here, we used surface-based methods to analyze the longitudinal MRI data of a group of 25 first-time mothers (before and after pregnancy) and compare them to those of a group of 25 female adolescents (during two years of pubertal development). For both first-time mothers and adolescent girls, a monthly rate of volumetric reductions of 0.09 mm^3 was observed. In both cases, these reductions were accompanied by decreases in cortical thickness, surface area, local gyrification index, sulcal depth, and sulcal length, as well as by increases in sulcal width. In fact, the changes associated with pregnancy did not differ from those that characterize the transition during adolescence in any of these measures. Our findings are consistent with the notion that the brain morphometric changes associated with pregnancy and adolescence reflect similar hormonally primed biological processes.

INTRODUCTION

Motherhood and maternal caregiving are crucial for the survival of our species and accordingly imply dramatic adaptations from a psychological and physiological perspective. Efforts have been focused on determining how the body of a pregnant woman adapts at the cardiovascular, renal, metabolic, respiratory, muscular and endocrine level, and the consequences these adaptations might have on the health of the mother and the newborn [Brunton and Russell, 2014]. Surprisingly, little is known on how the human brain adapts to prepare for motherhood.

In mammalian species, the peripartum period is one of the most sensitive neuroplastic periods of a female's life. Converging evidence from non-human animal studies indicates that during this period, the interplay between pregnancy hormones and peripheral stimulation leads to multiple structural and functional adaptations in the mother's brain that are necessary for the onset, maintenance, and regulation of maternal behavior [Numan, 2007]. For instance, in rodents, it is well established that the unequal hormonal fluctuations during the peripartum period (mainly changes in sex steroid hormones, oxytocin, and prolactin levels) trigger the activation of the maternal circuit, which comprises mesolimbic, hypothalamic and cortical areas [Numan, 2012]. At this stage, pregnancy hormones modulate several forms of neuronal plasticity, including changes in glia, dendritic and synaptic remodeling and neurogenesis [Kinsley et al., 2006; Leuner et al., 2010; Salmaso et al., 2009]. Once this circuit is primed by the endocrine events associated with pregnancy and parturition, maternal behavior is maintained by environmental cues derived from the interaction with offspring [Numan, 2007].

In contrast to the vast amount of studies that approach the topic of maternal brain through non-human animal models [Numan, 2012], there have been few attempts exploring this topic in humans. There is evidence from longitudinal MRI studies of brain volumetric changes during human pregnancy [Hoekzema et al., 2017; Oatridge et al., 2002] and early postpartum periods [Kim et al., 2010; Kim et al., 2014; Oatridge et al., 2002], yet the specific morphometric features underlying these volumetric changes still remain to be resolved. Describing how the human brain changes during pregnancy is a first step towards investigating maternal caregiving behavior and the role that these neural changes might play in the highly prevalent postpartum mental disorders, which affect around 10-15% of the mothers in developed countries [Fisher et al., 2012].

In a previous study involving first-time parents, we found that women undergoing pregnancy exhibited pronounced and long-lasting (at least two years postpartum) reductions in cerebral gray matter volume [Hoekzema et al., 2017]. We suggested that the neural changes experienced during pregnancy might be similar to those consistently reported in the adolescence period, another stage of life that involves an increase in sex steroid hormone levels [Cameron, 2004] accompanied by reductions in gray matter volume [Mills et al., 2016], important behavioral changes [Yurgelun-Todd, 2007], and an increased risk for many psychiatric disorders [Paus et al., 2008]. In terms of MRI morphometrics, the reduction of gray matter volume during adolescence is associated with a decrease of cortical thickness but also with reductions in surface area and cortical gyrification, as sulci become wider and shallower [Aleman-Gomez et al., 2013]. Such volumetric reductions are thought to reflect processes of synaptic pruning, myelination and other glia associated adaptations, which are

involved in the development of mental processes [Mills and Tamnes, 2014]. Adolescence is also associated with increases in white matter thickness around the sulci, supposedly due to the myelination process that expands the walls of the sulci outward and reduces the overall sulcal depth [Paus, 2010].

As opposed to the large body of literature addressing the neural changes occurring during adolescence, the specific morphometric features behind the volumetric reductions associated with pregnancy remain unexplored. Thus, the main objectives of the current research were to decompose the volumetric reductions associated with pregnancy into their specific morphometric measures, and to determine whether the obtained profile of changes resembles that occurring during adolescence. As a secondary aim, we explored whether there is an association between the morphometric changes and the time exposed to environmental factors related to the postpartum period.

METHODS

Study participants

The present study analyzed the MRI prospective data of a group of 25 female adolescents who had never been pregnant, a group of 25 first-time adult mothers, and a group of 20 adult females who had never been pregnant. For simplicity, we will use the following abbreviations throughout the manuscript to refer to each of the groups: adolescents, mothers, and female controls. For each of the study subjects we analyzed two time points. For the adolescent sample, time point 1 was acquired during mid puberty and time point 2 approximately two years later. For the mothers, time point 1 was acquired before the conception of their first child and time point 2 during the early postpartum period. The two time points of the female control group were acquired at time intervals comparable to those of the mothers group. Table I provides a general description of the study participants.

The mothers and female controls samples were recruited throughout the *Instituto Valenciano de Infertilidad* (Barcelona, Spain), as well as by flyers and word of mouth. Pre-established exclusion criteria comprised neurological or psychiatric conditions and/or any history of substance use disorders as assessed by means of the MINI International Neuropsychiatric Interview applied by a clinical psychologist [Sheehan et al., 1998].

Nine mothers achieved pregnancy by natural conception and 16 women by means of fertility treatment. Of the fertility-assisted group, 12 women underwent in vitro fertilization (3 involving an egg donation, 5 involving intracytoplasmic sperm injection (ICSI) and 4 without egg donation or ICSI), three intrauterine insemination, and one a frozen embryo transfer. All

participants form the fertility group received progesterone until weeks 7 to 12 of gestation. Those that underwent egg donation or frozen embryo transfer also received estrogens until weeks 7 to 12 of gestation. Among the 25 participants, eight of the mothers gave birth by cesarean section and 17 by vaginal birth. Eighteen mothers practiced breastfeeding by the time of the Post scan (16 of them practiced exclusive breastfeeding and two supplemented breastfeeding with formula feedings) and seven were not breastfeeding by the time of the Post scan (two never started breastfeeding and five had stopped by the time of the Post scan). For a more comprehensive description of the adult participants see [Hoekzema et al., 2017].

The female adolescent sample of the current study was obtained from the *Brain and Development Lab* of *Leiden University Medical Center*, the Netherlands, as part of the *BrainTime project*. The *BrainTime project* is a large study on adolescent brain development [Koolschijn et al., 2014; Peper et al., 2013]. As part of this project, participants of varying ages spanning the complete range of adolescent development were investigated for an initial baseline session. They were subsequently examined two more times, with an interval of 2 years, in order to track changes in brain structure and function across the different phases of adolescence [Peters and Crone, 2017]. From the original sample of 299 participants scanned at baseline (age 8-25), we selected a random subsample of 25 girls on late adolescence with initial age between 14-18 years (Table I). We employed a minimum age of 14 years at baseline because pregnancy seems to primarily affect brain regions that mature relatively late in adolescence [Burnett et al., 2011; Hoekzema et al., 2017]. To confirm that all participants showed signs of physical pubertal development, only subjects whose pubertal development was examined by means of the Pubertal Development Scale (PDS) [Petersen et al., 1988] were included. The mean PDS score at baseline was 3.4 (std= 0.4). According to the

categorical classification seven adolescents were classified as mid pubertal, nine as late pubertal and nine as post pubertal. All participants were right-handed and reported an absence of neurological or psychiatric impairment. Further details about the adolescent sample can be found elsewhere [Peters et al., 2017].

The studies from which the data were obtained were approved by their corresponding local ethics committees, that is, the *Clinical Research Ethical Committee* of the *Hospital del Mar Research Institute* for the adults' samples, and the *Ethics Review Board* of the *Leiden University Medical Center* for the adolescent sample. Written informed consent was obtained from all subjects, or their legal representatives in the case of the adolescent sample, before their participation in the study.

Neuroimaging

The MR images of the adult participants were acquired in a Philips 3 Tesla scanner located at the *Hospital del Mar* in Barcelona. High-resolution anatomical MRI brain scans were acquired in the axial plane using a T1-weighted gradient echo pulse sequence (repetition time (TR) = 8.2 ms, echo time (TE) = 3.7 ms, voxel size = 0.9375 mm x 0.9375 mm x 1 mm, field of view (FOV) = 240 mm x 240 mm x180 mm, flip angle (FA)= 8°. The images for the adolescent sample were obtained in a Philips 3 Tesla scanner from the *Leiden University Medical Center*, the Netherlands. Acquisition parameters were as follows: TR= 9.751 ms, TE= 4.59 ms, voxel size= 0.875 mm x 0.875 mm x 1.2 mm, FOV= 224 mm x 177 mm x 168 mm, FA= 8 º.

Image processing

In the present study, we used a pipeline analysis that combines FreeSurfer and BrainVISA image processing packages to compute a set of detailed neuroanatomical measures i.e., total brain volume (TBV), cortical volume (CV), cortical thickness (CT), pial surface area (SA), the exposed cortical hull surface area (HA), local gyrification index (LGI), sulcal CT (SCT), sulcal SA (SSA), sulcal depth (SD), sulcal length (SL), sulcal width (SW) and gyral white matter thickness (WMT). Figure 1 displays a schematic representation of the different morphological measures calculated in the study.

Images were processed with the standard FreeSurfer longitudinal stream (version 5.3) (http://surfer.nmr.mgh.harvard.edu/fswiki; [Reuter et al., 2012]). The longitudinal pipeline involves an individual processing of the images for each of the time points, to later generate baseline and follow-up inner (white) and outer (pial) surfaces, their voxel-based maps (ribbon mask, structures parcellation, etc) and vertex wise maps (cortical thickness, curvature, local gyrification index, etc). TBV and CV were computed as the number of voxels belonging to gray and white matter segmentations, and to the cortical gray matter segmentation, respectively, multiplied by voxel volume. CT was defined as the Euclidian distance between the inner and outer cortical surfaces). Pial SA was calculated as the sum of the areas of the triangles making up the outer surface. The hull surface was constructed as a mantle that envelops the pial surface but excluding sulcal regions and HA was computed as the sum of the areas of the triangles belonging to the hull surface. LGI represents the amount of cortex buried within the sulcal folds and was calculated at each pial vertex as the ratio between pial SA and HA (Figure 1) [Schaer et al., 2008].

FreeSurfer outputs were imported into the BrainVISA Morphologist 2012 stream (version 4.5.0) (http://www.brainvisa.info; [Cointepas et al., 2001]) to reuse the pre-computed segmentations. This step guarantees that the tissues segmentations as well as the cortical surfaces (pial and white surfaces) are the same across the whole processing stream. Thereafter, the cortical fold graphs, also called median meshes, were extracted and each cortical sulcus was automatically labeled using a neural network-based pattern classifier. The reconstruction and labeling of the cortical folds was visually inspected and manually corrected to avoid inaccuracies between time points.

SCT and SSA measures were computed taking into account only the sulcal regions and discarding gyral regions. SD was defined as the length of the geodesic curve that runs across the middle of the sulcal space joining the hull surface to the sulcal fundus. SL was computed as the length of the interception curve between the hull surface and the median meshes. SW was computed as the distance between each gyral bank averaged over all points along the median sulcal surface (Figure 1) [Kochunov et al., 2012].

In addition, we estimated WMT using a white matter skeleton constructed from the white matter segmentation image. White matter skeleton is the surface that transverses the white matter space parallel to the gray matter/white matter boundary and covers the entire gyral depth from crest to fundus (Figure 1). WMT was calculated as the Euclidean distance between two points residing on the opposing sides of the gyral white matter surface in the direction normal to the white matter skeleton averaged over the entire gyrus [Kochunov et al., 2012]. Both whole-brain and hemispheric measures were obtained by either summing (for CV, pial SA, SSA, HA, and SL) or averaging (for CT, SCT, GI, SD, SW and WMT) the

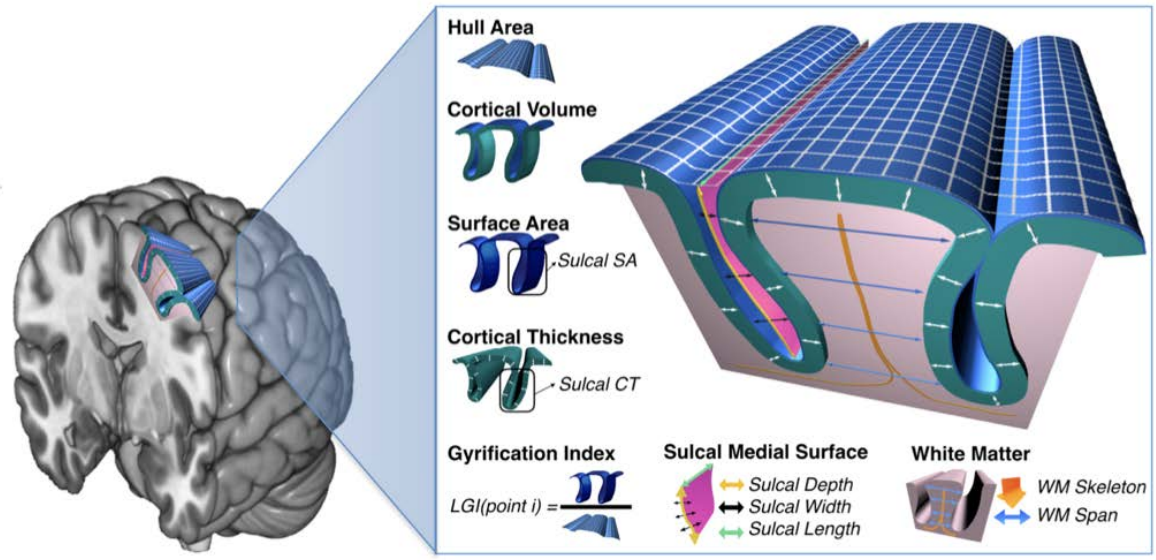
measures provided by Freesurfer and BrainVISA. Due to the high variability obtained when reconstructing the sulci of the insular cortex, this region was not taken into account when computing the morphological measures.

Statistical Analyses

For each subject, longitudinal change was calculated by means of the formula:

$$Percentage\ of\ change_{measure} = \frac{measure_{follow-up} - measure_{baseline}}{measure_{baseline}} \times 100$$

Since the interval between the two time points of the adolescents' group was longer than that of the mothers and female controls groups (all p-values<0.0001, Table I), percentage of change for each measure was divided by the number of months between the Pre and the Post MRI sessions at the individual level, thus obtaining an estimated monthly rate percentage of change.



$$Monthly\ rate\ percentage\ of\ change_{measure} = \frac{Percentage\ of\ change_{measure}}{Number\ of\ months_{subject}}$$

All the statistical analyses were performed using Matlab R2015b (MathWorks, Inc., Natick, MA). One-sample T-tests were used to assess if the groups' monthly rate percentage of change was significantly different from zero and Analysis of variance (ANOVA) F-tests to determine if the monthly rate percentage of change differed among the groups. The ANOVA tests were complemented by two sample T-test group comparisons: 1) mothers vs. female controls; 2) mothers vs. adolescents; and 3) adolescents vs. female controls.

Pearson correlations were calculated to determine if the percentages of change in the mothers

groups were associated with the time exposed to environmental postpartum factors, that is the days between the parturition date and the Post MRI scanning date.

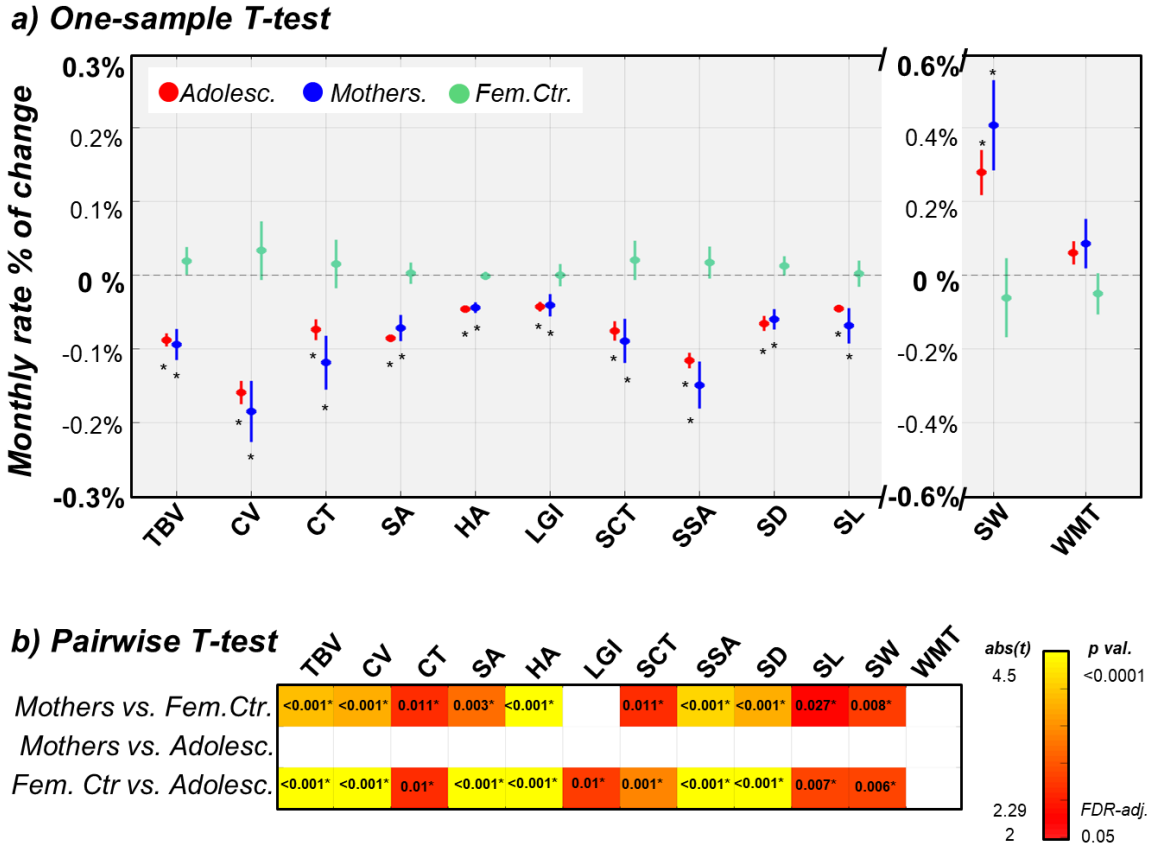
For all the inferential tests, we considered as significant results with an associated p-value<0.05 after controlling for multiple comparisons using the false discovery rate (FDR) adjusted value of q= 0.05 [Benjamini et al., 2001]. FDR adjustment was calculated via the matlab function *fdr (*Anderson M.Winkler; https://brainder.org/2011/09/05/fdr-corrected-fdr-adjusted-p-values/; Downloaded on December, 2017).

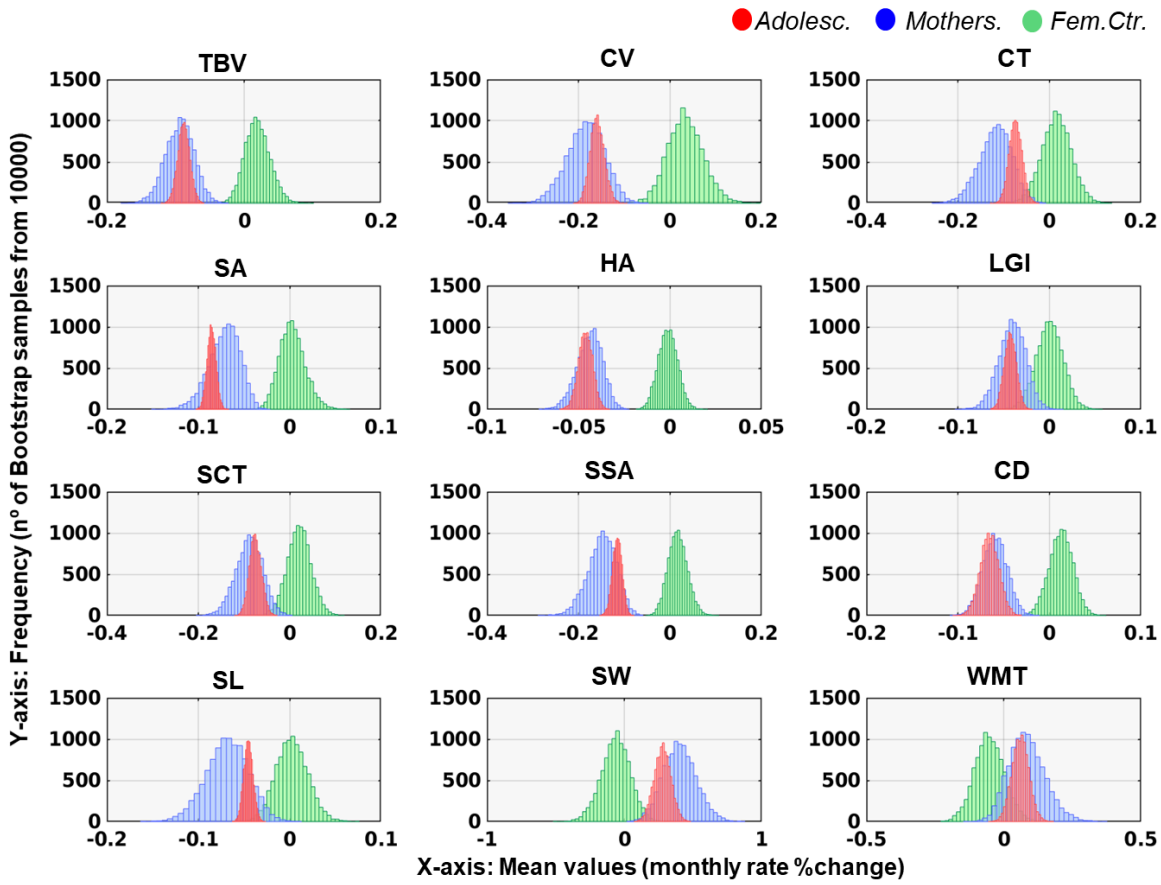
In addition to the above-described tests, we used the Matlab's functions *bootstrap* and *bootci* to draw 10000 random samples with replacement and re-estimate the descriptive statistics (mean, standard error and confidence interval) of the bootstrapped distributions and obtain a more accurate estimation of the morphometric changes in our sample populations.

Finally, we performed a series of supplementary analyses to further examine our findings and check their robustness. First, we examined if the monthly rate percentage of change differed in mothers as a function of: 1) means of conception (natural conception or fertility treatment); 2) type of parturition (vaginal delivery or elective cesarean section); and 3) type of lactation at Post MRI scanning (breastfeeding or formula). Second, we tested whether both hemispheres showed a similar pattern of morphometric changes. Third, we checked if the main findings persist after excluding the potential variability induced by age (within-group variability), radiofrequency head coil and scanner site.

RESULTS

Figure 2a and Supplementary Table I display the groups monthly rate percentage of change for each of the brain metrics. Across pregnancy, first-time mothers exhibited an estimated reduction in total brain volume (TBV) of 0.09% mm^3 per month (FDR-adjusted p-value=0.0004). The volumetric reduction is decomposed into significant decrease in cortical volume (CV), cortical thickness (CT) and surface area (SA) (all FDR-adjusted p-values<0.007). There was also a reduction in hull area (HA) that resulted in a reduced local gyrification index (LGI) (all FDR-adjusted p-values<0.02). Pregnancy also rendered significant changes in sulci morphology, specifically decreases in whole-brain sulcal CT (SCT), sulcal SA (SSA), sulcal depth (SD) and sulcal length (SL), and increases in sulcal width (SW) (all FDR-adjusted p-values<0.01).

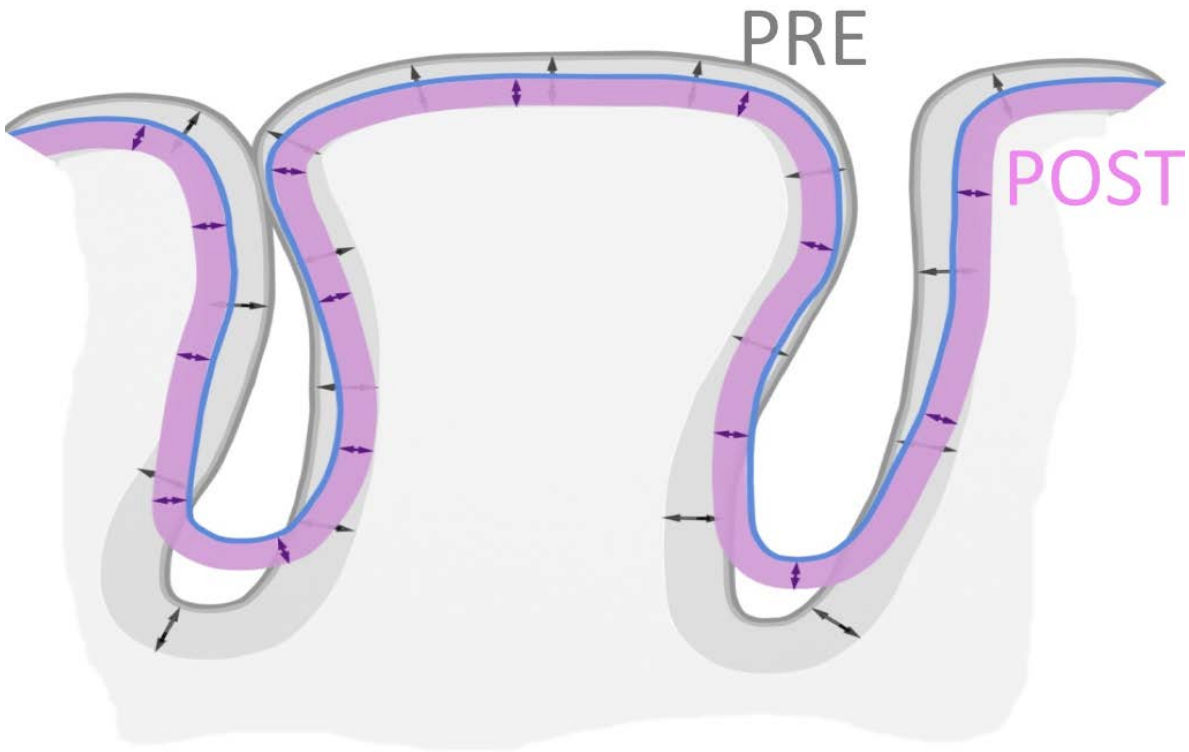




As indicated in Figure 2a and Supplementary Table I, the brain of the adolescent subjects underwent a highly similar pattern of changes as that detected in the mothers group. The TBV of the adolescents' sample exhibited an estimated volumetric reduction identical to that of the first-time mothers (0.09% per month, FDR-adjusted p-value<0.0001). As was the case in the mothers group, this reduction was accompanied by significant decreases in CV, CT, SA, HA, LGI, SCT, SSA, SD, SL and increases in SW (all FDR-adjusted p-values<0.004). Non-significant changes in WMT were found neither in the mothers (FDR-adjusted p-value= 0.33) nor in the adolescents (FDR-adjusted p-value= 0.10). Supplementary Table II shows the percentage of change in the mothers and female adolescents without the monthly rate adjustment.

The ANOVA revealed a significant effect of group in the monthly rate percentage of change in all the metrics except in WMT (FDR-adjusted p-value= 0.19) (Supplementary Table I). Results from the *a priori* defined pairwise two-sample T-tests indicated that the above-mentioned group differences are mainly driven by differences between the mothers and the female control groups (Figure 2b). Remarkably, the comparisons between the mothers and the adolescents rendered no significant results for any of these morphological measures. Furthermore, even at the more lenient threshold of uncorrected p-value of 0.05, no differences were detected in any morphometric changes between women going through pregnancy and girls going through adolescence.

As displayed in Figure 3 and Supplementary Table III, the bootstrap distributions of mothers and adolescents majorly overlapped across the different metrics while differing from those of the female control group, thus validating the results of the parametric analyses.



Regarding the correlation analyses we did not detect significant associations between the percentages of change and the time exposed to environmental postpartum factors (time in days between the parturition date and the Post MRI scanning date) (all p-values>0.54 uncorrected).

Results from the supplementary analyses are summarized below and explained in detail in supplementary information. First, no significant differences were detected in the mothers group as a function of the means of conception, the type of parturition or the type of lactation (Supplementary Information I). Second, a very similar pattern of results was obtained when analyzing the morphometric changes for the left and right hemispheres separately (Supplementary Information II). Third, the resulting p-values after controlling for the effects of age and radiofrequency head coil were comparable to those obtained with the most

parsimonious one-sample and ANOVA models (Supplementary Information III and IV respectively). Finally, results from an additional general lineal model indicated that scanner site does not have a significant effect on any of the measures of monthly rate percentage of change (Supplementary Information V).

DISCUSSION

The neural bases underlying human pregnancy are barely explored. We recently found that pregnancy leads to consistent gray matter volumetric reductions in the human brain [Hoekzema et al., 2017]. Here we used a surface-based method to quantify the change over time in a detailed set of metrics that fully characterize the brain's anatomy. Extending the initial research [Hoekzema et al., 2017], we characterized for the first time the morphometric changes in the cortical mantle and sulcal anatomy that occur during pregnancy, and demonstrated that these changes highly resemble those occurring during adolescence. In fact, pairwise comparisons revealed that the profile of changes associated with pregnancy did not differ from that characterizing the adolescence period on any of the morphological measures, not even at the more lenient threshold of p-value of 0.05 uncorrected.

Adolescence and pregnancy are two life-changing events across a woman's lifespan that involve dramatic adaptations at the physical, psychosocial and behavioral level. There are several remarkable similarities between the adaptations characterizing these two stages of life. Both adolescence and pregnancy represent stages where coordinated fluctuations of sex steroid hormones exert important physiological modifications [Sisk and Zehr, 2005; Soma-Pillay et al., 2016]. Periods of acute hormonal fluctuations, while generally considered to be beneficial for confronting the challenges ahead, also increase the vulnerability of the brain to pathological alterations [Seeman, 1997]. Accordingly, both adolescence and pregnancy are transitions associated with an increased risk for the emergence of psychopathology [Kim et al., 2016; Paus et al., 2008]. Finally, neuroimaging studies have shown that both stages are

accompanied by reductions in gray matter volume that persist beyond the period of hormonal exposure [Hoekzema et al., 2017; Sisk and Foster, 2004; Sisk and Zehr, 2005].

Human and non-human studies consistently show, using a variety of techniques, that the transition from childhood to adulthood is characterized by an intense reshaping of brain structure [Mills et al., 2016; Sisk and Foster, 2004]. In particular, MRI studies in human adolescence show reductions in cortical volume, surface area, cortical thickness [Giorgio et al., 2010; Tamnes et al., 2017; Vijayakumar et al., 2016; Wierenga et al., 2014], a concurrent increase in white matter thickness of the adjacent gyri [Aleman-Gomez et al., 2013; Giorgio et al., 2010], and a global flattening of the cortex, that is, a sulcal widening and a decrease in sulcal depth and length [Aleman-Gomez et al., 2013]. We replicated this profile of cortical and sulcal changes in our sample of female adolescents, except for the increase in WMT that did not reach statistical significance. Extending the above-mentioned similarities between the adolescent and pregnant brains, the present study demonstrated that the pregnancy period is characterized by the same pattern of morphometric changes, that is, reductions in surface area and cortical thickness and an overall flattening of the cerebral cortex (see Figure 4 for a schematic representation of the described flattening process).

The pattern of morphometric changes obtained in the mothers sample could reflect various cellular mechanisms. However, on the basis of our MRI results, it is not possible to infer the specific cellular processes behind these changes. Taking as a reference the adolescent brain, literature has suggested that changes in cortical volume and thickness are likely triggered by two simultaneous cellular processes: a glial-dependent selective elimination of redundant synapses (i.e. synaptic pruning) and a concurrent gaining in myelinated white matter. On the

one hand, reductions in neuropil, glial cells and vasculature elements surrounding the pruned synapses are considered to be the main factors contributing to the reduction in cortical volume and cortical thickness seen in adolescence [Mills and Tamnes, 2014]. On the other hand, increased myelination in the periphery of the neuropil can lead to voxels at the white and gray matter interface being classified as gray matter, thus inducing an apparent decrease in cortical thickness that likely contributes to the overall cortical thinning [Paus, 2010]. Regarding sulcal morphometry, the overall sulcal flattening described in adolescence likely results from a combination of increases in intracortical myelination that expand the sulcal walls outwards reducing their overall depth, and the process of synaptic pruning producing a release in tensile forces that create the gyral and sulcal regions [White et al., 2010]. This sulcal flattening is accompanied by decreases in surface-related measures such as surface and hull area [Aleman-Gomez et al., 2013]. According to the radial unit hypothesis, surface area is dependent on the number of ontogenic columns perpendicular to the surface, whereas cortical thickness depends on the number of cells within these columns [Rakic, 1988]. This suggests that changes in surface-related measures could reflect changes in the number of cells located between radial columns (e.g. vertical glia, astrocytes or vasculature) or in the number of radial columns themselves.

Synaptic pruning and myelination are generally considered indicators of a process of neurocognitive adaptations, the former by fine-tuning the functional networks and the latter by increasing conducting velocity and the synchronization of information transmission [Stiles and Jernigan, 2010]. Postnatal brain development involves an overproduction of neural cells and synaptic connections [Stiles and Jernigan, 2010] . This exuberance of connectivity and neural processes is progressively pruned during adolescence through

activity-dependent mechanisms mediated by hormonal factors [Arain et al., 2013; Riccomagno and Kolodkin, 2015]. Accompanying the synaptic pruning, adolescence is also characterized by an ongoing growth of the myelin processes surrounding axons, resulting in accelerated axonal transmission and optimal neural communication [Ladouceur et al., 2012; O'Rourke et al., 2014]. These two biological processes follow a pattern that parallels cognitive development, such that regions involved in more sophisticated functions are those in which synaptic pruning and myelination occurs latter in time [Gogtay et al., 2004].

Interestingly, recent data have established that synaptic pruning and myelination in humans do not cease in adolescence but continue into early adulthood [O'Rourke et al., 2014; Petanjek et al., 2011], indicating that neural plasticity is rather a lifelong process that permits the brain to adapt to the changing internal and external conditions. We suspect that, as in adolescence, brain changes associated with pregnancy reflect a fine-tuning of the brain into a more specialized and efficient system for the pending change. We also suspect that the cellular mechanisms underlying this neural remodeling are similar to those occurring in the adolescent period. Future studies involving diffusion-based MRI techniques and histology will help to determine the exact cellular mechanisms behind the observed macroscopic neural changes in women having undergone pregnancy.

It would be audacious to consider the profile of morphometric changes obtained in the mothers sample as a fingerprint of neurodevelopment. Studies that test the similarities between pregnancy-related brain changes and those related to neurodegenerative disorders would be necessary to complement our current findings. Yet, we believe it is unlikely that the changes in gray and white matter that occur during pregnancy reflect a neurodegenerative

process rather than a neurodevelopmental one for several reasons. First, pregnancy, like adolescence, is associated with cognitive and behavioral changes that improve the subjects' ability to deal with the challenges ahead [Brunton and Russell, 2014; Nelson et al., 2005], whereas the cognitive and behavioral changes observed in neurodegenerative processes worsen their ability to autonomously face future challenges. Second, unlike pregnancy and adolescence, neurodegenerative processes are not characterized by unparalleled increases in sex steroid hormones, which are more commonly associated with neuroprotective effects than with neurodegenerative ones [Garcia-Segura and Balthazart, 2009; Villa et al., 2016]. Third, studies examining surface-based and sulcal morphology in normal aging and in patients that suffer a neurodegenerative disease suggest a distinct pattern of morphometric changes, characterized by a large reduction in cortical thickness with minimal additional effect on surface area [Dickerson et al., 2009; Gerrits et al., 2016; Storsve et al., 2014]. Therefore, although it is prompt to conclude that the profile of changes obtained in the current investigation is a hallmark of biological adaptation, there are indications that support this notion.

The marked physiological changes during pregnancy, parturition and postpartum period are orchestrated by multiple neuroendocrine mechanisms. Human pregnancy is characterized by unparalleled increases in sex steroid hormone levels (progesterone and estradiol) that exceed the exposure levels of a woman's entire non-pregnant life [Soma-Pillay et al., 2016]. Progesterone and estradiol increase steadily across the three trimesters and then return rapidly to baseline following parturition. We know from non-human animal studies that hormonal events during gestation and parturition remodel neural circuits such that maternal behavior is induced [Numan, 2012]. Ex-vivo and in-vitro experiments have shown that sex steroid

hormones regulate different aspects of neural plasticity such as changes in dendrite morphology, synaptic connectivity and glia cells [Garcia-Segura and Melcangi, 2006; Hansberg-Pastor et al., 2015]. Progesterone, for instance, is known to enhance the number of oligodendrocytes (the myelinating glial cells of the central nervous system), the formation of myelin sheath and synthesis of myelin proteins; directly affecting the process of white matter myelination [Baulieu and Schumacher, 1997]. Regarding humans, MRI data indicate that hormonal fluctuations render structural and functional modifications in the brain (see [Barth et al., 2015] for a review). For instance, circulating levels in sex steroid hormones contribute to the brain structural reorganization taking place during adolescence [Herting and Sowell, 2017; Peper et al., 2011]. Likewise, the effect of sex steroid hormones on brain structure has also been documented in studies tracking menstrual cycles [Protopopescu et al., 2008] and menopause [Eberling et al., 2003], as well as in studies analyzing the effect of hormonal treatment in transgender subjects [Zubiaurre-Elorza et al., 2014]. Overall, studies suggest that exposure to female sex steroid hormones leads to a similar pattern of decreases in gray matter volumes, cortical thickness and surface area [Koolschijn et al., 2014; Peper et al., 2011; Zubiaurre-Elorza et al., 2014].

The integration of our findings with the above literature leads us to consider that sex steroid hormones are the main mediators of the observed morphometric changes. Nonetheless, brain plasticity can be also induced by environmental signals that alter the body homeodynamics [Mandolesi et al., 2017]. Indeed, in rodent and primate species, the emergence of maternal behavior is stimulated not only by the array of endocrine changes accompanying gestation, but also by environmental cues coming from the offspring [Numan, 2007; Numan and Woodside, 2010]. Therefore, it is also possible that experience-dependent changes associated

with approaching parenthood --which include, but are not restricted to, the interaction with the baby-- might account for the pattern of neural changes observed in our sample of mothers.

To determine the impact of environmental factors associated to motherhood in the observed morphometric changes, we tested whether the time exposed to experiential postpartum variables (time between the delivery and the Post scan) was significantly associated with the variability in morphometric changes in the mother's brain. We did not find any significant correlation between the duration of the postpartum period and the brain morphometric changes. Together, these results suggest that the brain changes observed in our study are not primarily mediated by the experience-dependent adaptations associated with approaching parenthood, thus reinforcing the possible implication of gestational biological factors as regulators of the observed neural plasticity. However, future studies collecting more direct and specific measures of environmental and lifestyle changes associated with parenthood, as well as detailed information about hormonal fluctuations during the pregnancy and postpartum periods, are required to further discern the mediators contributing to the observed neural changes.

The main limitation of the current study is that we cannot disentangle with certainty whether changes occurred during pregnancy, labor or postpartum, neither if they reflect separate or cumulative effects. Future studies that analyze the brain at different time-points during pregnancy and postpartum periods, and collect information about the co-occurring hormonal and lifestyle changes, are necessary to clarify the developmental pattern and the neurobiological mediators of the human maternal brain. Regarding methodological limitation, we acknowledge that the use of different sites for data acquisition can be

worrisome. However, this should not be a major concern for our data since our analysis largely run in parallel and group comparisons were performed over a percentage of change. Furthermore, supplementary analyses demonstrated that, indeed, scanner site does not have a significant effect in the monthly rate percentage of change of any of the metrics.

CONCLUSION

In the present study, a detailed morphometric analyses unveiled, for the first time, the effects of pregnancy on the distinct features of the human cerebral mantle. Moreover, comparisons with a group of adolescents indicated similar morphometric changes in both phases of life. In fact, no differences were observed between women going through pregnancy and girls going through adolescence in any of the features of morphometric change, suggesting that pregnancy and adolescence exert the same morphometric effects on the cortical mantle of the human brain. These data provide preliminary indications that pregnancy, like adolescence, represents a sensitive period during which hormonal priming triggers an augmented state of neuroplasticity that might serve an adaptive purpose for pending environmental demands. The possibility of shared neurobiological mechanisms in pregnancy and adolescence is especially relevant considering the increased prevalence of mental disorders in both these transitional stages of life.

FUNDING

This work was supported by a Miguel Servet Type I Grant (CP16/00096) of the Spanish Instituto de Salud Carlos III. S.C. was supported by a Miguel Servet Typpe I Contract (CP16/00096) of the Spanish Instituto de Salud Carlos III and E.H. was supported by an Innovational Research Incentives Scheme grant (Veni, 451-14-036) of the Netherlands Organization for Scientific Research. Fundación Centro Nacional de Investigaciones Cardiovasculares Carlos III (CNIC) is supported by Ministerio de Economía, Industria y Competitividad and the Pro CNIC Foundation and is a Severo Ochoa Center of Excellence (SEV-2015-0505).

ACKNOWLEDGMENTS

We acknowledge the participants for their contribution to this study. In addition, we thank A. Fernández-Pena for advice on the image processing. Conflict of Interest: None declared.

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FIGURE LEGENDS

Figure 1. Brain morphological measures.

Figure 1 legend. Schematic representation of a gyrus and sulci displaying the different cortical morphological measures used in the current study, i.e. gray matter cortical volume (CV), cortical thickness (CT), surface area (SA), sulcal CT (SCT), sulcal SA (SSA), the exposed cortical convex hull area (HA), local gyrification index (LGI), gyral white matter thickness (WMT) and sulcal depth (SD), length (SL) and width (SW). Figure adapted from [Aleman-Gomez et al., 2013].

Figure 2. Whole-brain longitudinal changes for each morphological measure.

Figure 2 legend. a) One-sample T-test analysis of the monthly rate percentage of change (y-axis) for each metric. Results have different colors for each sample group (adolescents, mothers and female controls). Circles indicate the means and dispersion bars indicate the standard errors of the means. Asterisks indicate the one-sample T-test comparisons that survive the FDR-adjusted threshold of a $q<0.05$, which corresponds to an uncorrected p-value of 0.0122 and an absolute t-value (abs(t)) of 2.71. **b)** Two-sample T-test analyses pairwise comparisons: 1) mothers vs. female controls; 2) mothers vs. adolescents; and 3) adolescents vs. female controls. Reported p-values refer to the uncorrected p-values. Results have different colors for different thresholds, with p-value<0.05 uncorrected as the most lenient threshold. Asterisk indicate the two-sample T-test comparisons that survive the FDR adjusted threshold of $q<0.05$, which corresponds to an uncorrected p-value of 0.027 and an absolute t-value (abs(t)) of 2.29. Abbreviations: Adolesc: Female adolescent sample, Fem.

Ctr: Female control sample, TBV: total brain volume, CV: gray matter cortical volume, CT: cortical thickness, SA: surface area, HA: hull area, LGI: local gyrification index, SCT: sulcal CT, SSA: sulcal SA, SD: sulcal depth, SL: sulcal length, SW: sulcal width, and WMT: gyral white matter thickness.

Figure 3. Bootstrap distributions of female adolescents, mothers and female control groups.

Figure 3 legend. Histograms of the bootstrap distribution of the mean for 10000 resamples. In the twelve histograms (one for each metric), the Y-axis indicates the frequency of bootstrapped samples out of 10000 random samples with replacement, and the X-axis indicates the mean values of monthly rate percentage of change. Abbreviations: Adolesc: Female adolescent sample, Fem. Ctr: Female control sample, TBV: total brain volume, CV: gray matter cortical volume, CT: cortical thickness, SA: surface area, HA: hull area, LGI: local gyrification index, SCT: sulcal CT, SSA: sulcal SA, SD: sulcal depth, SL: sulcal length, SW: sulcal width, and WMT: gyral white matter thickness.

Figure 4. Schematic representation of the flattening of the cortex during pregnancy and during adolescence.