Sex differences in thickness, and folding developments throughout the cortex

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While significant differences in male and female brain structures have commonly been reported, only a few studies have focused on the sex differences in the way the cortex matures over time. Here, we investigated cortical thickness maturation between the age of 6 to 30 years, using 209 longitudinally-acquired brain MRI scans. Significant sex differences in the trajectories of cortical thickness change with age were evidenced using non-linear mixed effects models. Similar statistical analyses were computed to quantify the differences between cortical gyriﬁcation changes with age in males and females. During adolescence, we observed a statistically signiﬁcant higher rate of cortical thinning in females compared to males in the right temporal regions, the left temporoparietal junction and the left orbitofrontal cortex. This ﬁnding is interpreted as a faster maturation of the social brain areas in females. Concomitantly, statistically signiﬁcant sex differences in cortical folding changes with age were observed only in one cluster of the right prefrontal regions, suggesting that the mechanisms underlying cortical thickness and gyrification changes with age are quite distinct. Sexual dimorphism in the developmental course of the cortical maturation may be associated with the different age of onset and clinical presentation of many psychiatric disorders between males and females.

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Introduction

There is an increasing recognition of the importance of atypical brain development in the emergence of mental diseases (Insel and Wang, 2010). As nearly all mental disorders have different prevalence, age of onset, and symptomatology between males and females, an understanding of the sex differences in brain development is highly pertinent for the investigation of the pathological development in a mental disorder (Giedd and Rapoport, 2010). Given the central role played by the cerebral cortex with regard to typical and atypical cognition, it has naturally been considered as a determinant factor in the onset of psychopathology. Therefore, an understanding of the sex differences in cortical development is one of the first fundamental steps for biological psychiatry.

Although initial morphometric studies pointed to sex differences in cortical volumes across broad age ranges (Giedd et al., 1996; Reiss et al., 1996; Sowell et al., 2007), the most recent studies emphasize the importance of measuring differences in the trajectories of cortical development (Raznahan et al., 2011). Indeed, longitudinal studies using large samples observed that the volumetric developments of almost all brain structures, including the cerebral cortex, are sexually dimorphic (Giedd et al., 2012; Lenroot et al., 2007). Nowadays, advances in image processing techniques provide the possibility to measure distinct structural features of the cortex with a fine-grained resolution, such as cortical thickness (Fischl and Dale, 2000) or cortical folding (Schaer et al., 2008). As a result, determining age-related changes in cortical thickness and cortical folding provides a more comprehensive study of sexual dimorphism on cortical development than studying cortical volume alone.

Cortical thickness has been shown to be highly sensitive to age, with regional specificities in the cortical maturation process (Shaw et al., 2008). Given previous observations of different cortical thickness trajectories as a function of cognitive abilities (Shaw et al., 2006) or in psychiatric diseases (Shaw et al., 2010), one could expect some extent of sexual dimorphism in cortical thickness trajectories. However, to the best of our knowledge, only one study using a longitudinal sample of healthy individuals reported sex difference in cortical thickness maturation to date (Raznahan et al., 2010). In the age range of 9 to 22 years, Raznahan et al. found that the cortical thinning rate was significantly greater in males in left frontopolar regions, with greater initial thickness in males in those regions. They speculated that the frontal maturation delay in males may partially account for the fact that, during adolescence, males are much more prone to impulsive and risk-taking behaviors than females.

Contrary to cortical thickness, cortical folding (gyriﬁcation) is typically investigated to reveal information on the early brain development. Therefore, little is known on developmental changes in gyrification. However, Raznahan et al. (2011) recently provided some evidence that, at the global level, cortical surface area and gyrification index have nonlinear and sexually dimorphic developmental course. This interesting ﬁnding warrants further exploration of potential sex differences in the regional development of cortical folding. Indeed, a recent...
normative study revealed regional specificities in gyri
cation changes with age between 20 and 85 years old, with non-linear trajectories
being observed exclusively in the frontal lobe (Hogstrom et al., 2012).
This cross-sectional study, however, did not address the question of
sexual dimorphism in the regional trajectories of gyri
cation.
To address these key questions of the sexual dimorphism in the de-
velopment of the different cortical features, we studied the sex differ-
ences in cortical thickness and folding development at thousands of
points over the cortex. We employed a multilevel data analysis on a lon-\ngitudinal data comprising 209 brain MRI scans acquired from healthy
subjects.

Material and methods

Sample characteristics and image acquisition

The sample consisted of 137 healthy individuals of whom 68 are
males and 69 are females. The subjects were recruited through a news-
letter distributed in Geneva, Switzerland. A complete medical history
was used to screen the participants. Those with a history of past or
present neurological or mental disorders were excluded. In addition,
we collected parent report for children below the age of 11 (CBCL, Man-
ual for the child behavior checklist/4–18 and 1991 profile) and self-
report for older participants (YSR after the age of 11 years old, Manual
for the Youth Self-Report and 1991 profile; and ASR after the age of 18,
manual for the ASEBA adult forms and profiles) to quantify behavioral
problems. In average, the participants had the following T-score obtained
from the CBCL, YSR or ASR: 50.6 ± 9.3 for the internalized problems and
49.9 ± 9.4 for the externalized problems (data missing for 7 partici-
pants). Most of the participants scored below the clinical threshold for
externalized problems (14 had scores ranging from 64 to 74, six of which
were males) and externalized problems (14 had scores ranging from 64 to 72, nine of them were males). The detailed distribution of internal-
ized and externalized scores in each sex group is provided in Supplemen-
tary Table 1. Written informed consent was received from all of the
subjects, and the parents of the subjects younger than 18 years of age,
in accordance with protocols approved by the institutional review
board of the medical school of the University of Geneva.

We acquired 209 cranial MRI scans. Ninety-five of them were ac-
quired from males in the age range of 6.3 to 29.7 years, and 114 of
them were from females in the age range of 6 to 28.8 years. As depicted in Fig. 1, repeated MRI scans were available for a large pro-
portion of the participants, with up to 4 scans per subject. As shown
in Supplementary Table 1, there was no significant difference in the
distribution of age, socio-economic and cognitive variables between
sex groups.

The cerebral MRI were acquired using two different scanners: 90 of
the images were acquired using a T1-weighted 3D volumetric pulse se-
quency using a Philips Interia 1.5 T scanner as a series of 124 contiguous
coronal slices, with a voxel size of 0.9375 × 0.9375 × 1.5 mm (TR =
35 ms, TE = 6 ms, flip angle = 45, NEX = 1); and 119 of the images
were acquired using a Siemens Trio 3 T scanner as a series of 192 con-
tiguous coronal slices, with a voxel size of 0.86 × 0.86 × 1.1 mm
(TR = 2500 ms, TE = 3 ms, flip angle = 8). The gender distribution
was similar for the data collected on the 1.5 Tesla scanner (males: 41/
90 = 45.6%) and on the 3 Tesla scanner (males: 54/119 = 45.4%)
(Pearson’s Chi Square = 0.980). There was no significant difference be-
tween the ages corresponding to the 90 scanners acquired on the
1.5 Tesla machine (15.13 ± 6.45 years old, range: 6.03–29.67) and
the ages corresponding to the 119 scanners acquired on the 3 Tesla ma-
chine (16.25 ± 5.66 years old, range: 6.24–28.85, p = 0.186).

Image processing

The images were imported into the FreeSurfer software (http://
surfer.nmr.mgh.harvard.edu) for processing. Fully automated image
processing started by resampling into cubic voxels, intensity normaliza-
tion and skull stripping. Triangle meshes which represent the boundary
between the white and gray matter (hereafter, white surface), and the
boundary between the gray matter and cephalospinal fluid (hereafter,
pial surface) were generated using deformation algorithms based on
the local intensity value (Dale et al., 1999), and geometrical and topo-
logical constraints (Fischl et al., 2001).

The cortical thickness was estimated at each vertex as the shortest
distance between the meshes representing the white and pial surfaces
(Fischl and Dale, 2000). As a result, cortical thickness values with a sub-
millimeter accuracy were available at about 150,000 vertices on each
mesh representing the surface of a cerebral hemisphere. The algorithms
used to estimate the cortical thickness were previously validated
against manual delineation on MRI sections (Kuperberg et al., 2003)
and postmortem brains (Rosas et al., 2002). Moreover, the cortical
thickness estimations have been proven reliable, independent of the
scanner manufacturer or the field strength (Han et al., 2006). We quan-
tified the cortical folding at each cortical vertex using the local
gyration index (IGI), a validated method embedded in FreeSurfer
(Schaer et al., 2008).

Fig. 1. Distribution of the brain MRI scans across the subjects. The data points from a single subject are connected by a dotted line. The data from the males, and females are colored blue, and red, respectively.
Once the meshes were prepared for all the subjects, they were registered to the spherical atlas from FreeSurfer, which utilized the individual cortical folding patterns to match the cortical geometry across the subjects (Fischl et al., 1999).

To increase the signal to noise ratio, the cortical thickness, and gyriﬁcation index were smoothed on the cortical surface using a full width at half maximum (FWHM) kernel of 30 mm for the cortical thickness and 10 mm for the gyriﬁcation index. The relatively large FWHM for cortical thickness was chosen in order to increase the reliability between the two different scanners used in this study.

We conducted a reliability analysis for 20 subjects who underwent cerebral MRI acquisitions with both the 1.5 T and the 3 T scanner on the same day. The images were processed using the pipeline for within-subject template estimation (Reuter et al., 2012). A high cross-scanner vertex-wise consistency in cortical thickness estimation was conﬁrmed using the Cronbach’s alpha score (alpha > 0.9 for 89% of the vertices of the left hemisphere, and 90% of the vertices of the right hemisphere). Similarly high consistency was observed for the local gyriﬁcation index (alpha > 0.8 for 89.1% of the vertices of the left hemisphere, and 87.4% of the right hemisphere). The vertex-wise values of the Cronbach’s alpha, detailing the regions of higher and lower consistency for both the cortical thickness and the IGI, are depicted in the Supplementary Fig. 1.

Data analysis

Our longitudinal study produced multilevel data as the subjects were nested within the sample. The ideal method to analyze the statistical relationships among the variables, in such a data set is multilevel modeling (Dedrick et al., 2009). Therefore, we developed multilevel models for the relationships among cortical thickness, sex, and age; and gyriﬁcation index, sex, and age throughout the cortex. We proposed constant, linear, quadratic and cubic random intercept models for the relationships. The linear model is given by Eq. (1):

\[ y_{ijk} = \beta_0 + u_{ik} + \beta_1 x_i + \beta_2 x_j + \beta_3 x_k + \varepsilon_{ijk}. \]  

\( y: \) cortical thickness or gyriﬁcation index
\( i,j,k: \) [subject, scan, vertex] index
\( \beta_{0-3}: \) ﬁxed effects
\( u: \) normally distributed random effect
\( s: \) dummy variable encoding the sex
\( x: \) age
\( \varepsilon: \) normally distributed error term.

For each vertex on the mesh for a cerebral hemisphere, we ﬁtted the constant, linear, quadratic and cubic models to the data using the nlmefit function in MATLAB R2012a (MathWorks). We used a Bayesian information criterion (BIC)-based model selection method, as the BIC-based methods are one of the most powerful model selection methods for the mixed models (Peng and Lu, 2012). The BICs for the ﬁtted models were also computed by the nlmefit function. Even though the best model solely according to the BICs is the one with the minimum BIC, evidence to favor that model over a model whose BIC difference with that model is less than 2, is not worth more than a bare mention (Neath and Cavanaugh, 2012). Since Occam’s razor is followed in statistical modeling (Lazar, 2010), we selected the simplest model among the models whose BIC difference with the model with the minimum BIC was less than 2.

We investigated sex differences in thickness, and folding developments at each vertex by testing the statistical signiﬁcances of the sex-age interaction effect on the cortical thickness, and the local gyriﬁcation index, using likelihood-ratio test. In other words, we tested if the models we developed ﬁt to the data signiﬁcantly better than the null models which exclude the sex-age interaction terms. Then, we performed correction for multiple comparisons using the Monte Carlo method based technique embedded in FreeSurfer.

Results

We produced brain maps showing the development types of cortical thickness, and cortical folding; and the sex differences in cortical thickness development, and cortical folding development.

Fig. 2a shows the cortical thickness development types across the cortex. The development types were almost symmetric between the hemispheres. Constant cortical thickness development (i.e. no signiﬁcant change in cortical thickness with age) was found mostly in the temporal pole, and the occipital pole. The development was linear in large regions, mostly in the posterior frontal regions, the superior frontal regions, the temporal regions, and the orbitofrontal areas. A quadratic development was mostly found in the lateral prefrontal regions, the medial prefrontal regions, and the parieto-temporo-occipital junction; and medially around the precuneus. A cubic development was observed only in a small region in the right pregenual cingulate cortex.

As shown in Fig. 2b, cortical folding development types were also almost symmetric between the hemispheres. Curves of cortical folding changes with age were linear in most of the cortical regions. Nevertheless, we observed a constant development (i.e. no change with age) in the medial prefrontal regions, the occipital lobe, and some regions in the temporal lobe. A quadratic development was observed in small regions in the frontal lobe, and the parietal lobe. Cubic cortical folding development was found only in a tiny region in the left inferior parietal lobe.

Fig. 3 shows the differences in cortical thickness development across the cortex. In the right hemisphere, the differences were statistically signiﬁcant mostly in the temporal regions where the average cortical thinning rate was greater in females, and the occipital lobe where the rate was greater in males. In the left hemisphere, the differences was statistically signiﬁcant mostly in the anterior temporal regions, the temporoparietal junction, the superior frontal regions, and the orbitofrontal regions. In those regions, the thinning rate was greater in females. Fig. 3b shows the differences in cortical folding development across the cortex. We found statistically signiﬁcant sex differences in cortical folding development mostly in the right prefrontal regions where the average unfolding rate (the rate of IGI decrease with age) was mostly greater in males.

For visualization purposes, the curves with the most statistically signiﬁcant sex differences in cortical thickness and folding changes with age are plotted in Fig. 4.

Finally, we recorded video clips to show the sex differences in cortical thickness at each age (Supplementary movie 1 for the right hemisphere, Supplementary movie 2 for the left hemisphere). Similar video clips were created for the sex differences in local gyriﬁcation index at each age (Supplementary movies 5 and 6, for the right and respectively left hemispheres).

Discussion

We investigated the sex differences in cortical thickness development, and cortical folding development throughout the cortex, in the age range of 6 to 30 years. Four main observations emerged from our longitudinal analysis, which will be sequentially discussed: a) in the entire sample, we observed that the more complex trajectories of cortical thickness were symmetrically localized in cerebral regions sustaining higher order cognition, such as the prefrontal region, the temporoparietal junction and the precuneus; b) in further statistical group comparisons, we evidenced signiﬁcant sex differences in cortical thickness development, most prominent in the right temporal regions but also in the left anterior temporal, left orbitofrontal and left medial superior frontal regions; c) in contrast to cortical thickness,
Gyri
cification in most of the cortical regions was shown to be either
contant or linearly decreasing with age, pointing to a process less af-
fected by age-related maturational changes; d) statistically signi
cificant sex differences in cortical folding development were found in
the right prefrontal region.

Complexity of cortical thickness trajectories

The regions in which we observed the more complex trajectories of
cortical thickness changes with age, namely a quadratic function, strik-
ningly correspond to cerebral areas responsible for higher order cogni-
tive functions. Indeed, the prefrontal region, the temporoparietal
junction and the precuneus are cortical regions known to be key in
the integration of the information stemming from different areas. The
prefrontal cortex is a large region thought to be responsible for many
of the high order cognitive processes, such as socio-emotional and ex-
cutive functioning. For instance, the medial prefrontal cortex plays a role
in cognitive empathy (Shamay-Tsoory, 2011) and the dorsolateral pre-
frontal region is crucial for planning and decision making. The prefron-
tal region is typically known to mature later than the other cortical
regions (Teffer and Semendeferi, 2012). Aside from the prefrontal re-

dion, quadratic growth of cortical trajectories was also observed in the
left superior temporal sulcus, responsible for biological motion processing
and interpretation of other’s actions (Thompson and Parasuraman,
2012), in the temporoparietal junction (theory of mind and representa-
tion of other’s mental states (Samson et al., 2004; Saxe and Wexler,
2005)), and in the precuneus (self-consciousness and self-related men-
tal imagery (Cavanna and Trimble, 2006)).

Sex differences in cortical thickness maturation

Along with providing a description of regional specificities in the
type of developmental trajectories, we also demonstrated the ability

Fig. 2. Development types of cortical thickness, and cortical folding. Red, green, blue, and orange represent constant, linear, quadratic, and cubic developments, respectively. The result is based on the entire sample. Noncortical regions are blacked out. a, Cortical thickness development types throughout the cortex. b, Cortical folding development types throughout the cortex.
Sex differences in cortical thickness development

Sex differences in cortical folding development

Fig. 3. Sex differences in cortical thickness development, and cortical folding development. a, Sex differences in cortical thickness development throughout the cortex. The p-value of the sex-age interaction effect on the cortical thickness was coded in the regions where the effect was statistically significant, by the blue–cyan color bar if the average thinning rate was greater in males (M) than in females (F), or by the red–yellow color bar if vice versa. Noncortical regions are blacked out. b, Sex differences in cortical folding development throughout the cortex. The p-value of the sex-age interaction effect on gyrification index was coded in the region where the effect was statistically significant by the blue–cyan color bar. The average unfolding rate was greater in males in that region. Noncortical regions are blacked out.

of our method to evidence statistically significant group differences in the shape of these trajectories. Over the last decade, an increasing interest has emerged for the quantification of between groups developmental differences using large-sized longitudinal samples. Previous studies have shown that differences in the maturation are associated with IQ level (Shaw et al., 2006), attention-deficit hyperactivity disorder (Shaw et al., 2007), childhood onset schizophrenia (Sporn et al., 2003) or pediatric bipolar disorders (Gogtay et al., 2007). Related to sexual dimorphism, many studies pointed global and regional differences in volume, cortical thickness or shape (see (Luders and Toga, 2003) for a review). However, there is far less data on the sexual dimorphism in the development of these morphometric features over childhood, adolescence and adulthood. Measuring cortical volume, Lenroot et al. (2007) observed an earlier peak of cortical volume in females compared to males in all lobes except the occipital lobe. They discussed this robust sex-related statistical significance in the trajectories of global and lobar cortical volume in light of the earlier puberty in females.

Focusing on cortical thickness, Sowell et al. (2007) investigated the statistical significance of the age-by-sex interaction in a large cross-sectional sample aged from 7 to 87 years. They identified a statistically significant interaction effect in bilateral dorsal frontal and right inferior temporal regions, and thus suggested that sex differences in cortical thickness were not stable over the life span. However, it is only recently that studies using longitudinal dataset started addressing the question of sexual dimorphism in the development of cortical thickness. Indeed, only two studies to date used mixed models with a consequent sample of repeated measurements to examine sexual dimorphism in the trajectories of cortical thickness changes. Raznahan et al. (2011) examined 1274 scans and have shown that, at the global level, cortical thickness development was not significantly different between males and females, although cortical volume trajectories were sexually dimorphic. This absence of effect may rely on the averaging of cortical thickness over the whole brain. Indeed, when measuring the development at the local level, the same authors (Raznahan et al., 2010) observed faster cortical thinning in males than females in almost the entire frontal lobe, but reaching statistical significance only in the left frontopolar region. They also observed a faster cortical thinning in females than males in non-frontal region, but not reaching significance. The authors related the opposite pattern of frontal vs parietal cortical thinning rate to an advantage for females in “prefrontally dependent domains of cognition and behavior and male advantage in parietally dependent visuospatial task”.

Whereas Raznahan and colleagues modeled only linear effects of age in their study, we reconstructed curvilinear developmental trajectories in a longitudinal sample of healthy participants. We observed that the temporal and superior frontal regions mature more rapidly in females than males, and that the right occipital pole matures more rapidly in males than females. It is striking to note that most of the regions with more rapid cortical maturation in females encompass cortical areas of the social brain (Frith, 2007): the anterior temporal regions are thought to encode knowledge about social concepts and rules (Wong and Gallate, 2012), the superior temporal
sulcus may play a role in the interpretation of other’s actions (Thompson and Parasuraman, 2012), and the orbitofrontal region implicated in decision-making based on expected reward (Rolls and Grabenhorst, 2008), but also more specifically in social decision-making (Seo and Lee, 2012). It has to be noted that we did not identify any significant sex difference in the maturation of the ventromedial prefrontal region, a region commonly identified as belonging to the “social brain” and consistently activated when thinking about self or about close-others. However, we observed sexual dimorphism in the maturation of the dorsomedial prefrontal region, a region which has been related to similar processes but with lower degree of self-relatedness (i.e. thinking to non-close others) (Murray et al., 2012). From a global perspective, the ensemble of these regions leads us to speculate that faster cortical maturation of the social brain in females could be related to their relative advantage in empathizing (reviewed in (Baron-Cohen, 2002)), with better rational of the social brain in females could be related to their relative advantage in empathizing (reviewed in (Baron-Cohen, 2002)), with better ability to infer what other people have in mind, more efficient decoding of non-verbal communication and more comforting responses to the distress of someone else. Contrarily, males tend to show advantage in systematizing, with better skills in maths, better constructional abilities, and more efficient spatial orientation (Baron-Cohen, 2002), which are all skills that are more likely encoded in the parieto-occipital region. In the present study, we didn’t observe any sex difference in the maturation of the parietal lobe, but we found one region with faster rate of cortical thinning in males compared to females in the right occipital pole. This region is thought to encode primary and secondary visual processing. Strikingly, important sex differences in basic visual functions are described (Abramov et al., 2012), with greater sensitivity for fine details and for rapidly moving stimuli in males compared to females. Differences in the density of testosterone receptors in the cortical areas (DonCarlos et al., 2006) may explain both the sex differences in visual performances reported by Abramov et al. (2012), and the current observation of sex differences in the trajectories of the occipital lobe maturation. Developmental changes in local gyrification & sex differences

Aside from measuring cortical thickness trajectories, we also examined the changes in local gyrification index with age. Traditionally, the gyrification index (GI) was thought to be a stable feature, unchanged from the first months of postnatal life until elderliness (Armstrong et al., 1995). This lifetime stability has led to the idea that cortical folding or GI alterations convey information on pre- or perinatal disruption in the brain development (Gimenez et al., 2006; Kesler et al., 2006). However, more recent tools for measuring gyrification, such as the IGI, were shown to significantly decrease with age (Schaer et al., 2008). In the absence of significant age-by-diagnosis interaction, the IGI was still most commonly interpreted as an index of early brain development, as it successfully discriminates between population with early insults compared to controls (Haukvik et al., 2012; Schaer et al., 2009). Recently, a cross-sectional study including healthy adults from 20 to 85 years old has however observed that IGI follows a quadratic development in the superior and medial frontal regions (Hogstrom et al., 2012), with larger rates of IGI decrease with age in individuals older than 60 than in young adults. The observation of a quadratic trajectory of IGI with age provides a first evidence that IGI is not only affected by a linear, unmodulated process, and leads to the idea that IGI could also be used to measure neurodegenerative changes. The higher rate of IGI decrease in older individuals could rely on the previously observed decreased sulcal depth with increasing age (Kochunov et al., 2005). In this study, we detailed the regional specificities in the IGI trajectories using sophisticated model selection and a longitudinal design. In the period of 6 to 30 years old, we observed that IGI in most of the regions showed either no change at all with age, or decreased linearly with age. The relative absence of quadratic trajectories as observed by Hogstrom et al. (2012) could be attributed to the younger age span of our sample. Indeed, the relatively simple trajectories of IGI changes with age over the 6 to 30 years period, as compared with the more complex cortical thickness trajectories at the same age, strengthen the view that IGI...
References


