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Accelerated longitudinal cortical thinning in adolescence

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ABSTRACT

It remains unclear if changes of the cerebral cortex occur gradually from childhood to adulthood, or if adolescence marks a differential period of cortical development. In the current study of 90 healthy volunteers aged 5–32 years (48 females, 85 right handed) with 180 scans (2 scans for each participant with ~4 year gaps), thinning of overall mean thickness and across the four major cortical lobes bilaterally was observed across this full age span. However, the thinning rate, calculated as Δcortical thickness / Δage (mm/year) between scans of each participant, revealed an accelerated cortical thinning during adolescence, which was preceded by less thinning in childhood and followed by decelerated thinning in young adulthood. Males and females showed similarly faster thinning rates during adolescence relative to young adults. The underlying basis and role of accelerated cortical thinning during adolescence for cognition, behaviour and disorders that appear at such a stage of development remains to be determined in future work.

Introduction

Adolescents encounter important changes in physical, behavioral and emotional development, which are accompanied and likely driven, at least in part, by structural reorganization of the cerebral cortex (Spear, 2013; Giedd, 2008; Paus, 2013). Further, this is a critical transitional period in the life span when psychopathology can emerge or intensify (Kessler et al., 2005; Paus et al., 2008). MRI can provide an in vivo proxy of cortical thickness as the measured distance from the pial/cortical border to the gray/white matter border (MacDonald et al., 2000; Fischl and Dale, 2000). Differences of cortical thickness alterations with age are associated with typical cognitive ability changes in adolescents (Burgaleta et al., 2014; Squeglia et al., 2013) and have been observed in atypical populations (Dennis and Thompson, 2013) during adolescence including, but not limited to, attention deficit and schizophrenia (Shaw et al., 2013; Thormodsen et al., 2013). However, it is not clear whether adolescence marks an accelerated period of cerebral cortex development, or if the cortical changes occur gradually from childhood into young adulthood.

In healthy development, longitudinal studies from the National Institutes of Health (NIH) with large populations have suggested that cortical thickness decreases linearly with age over 7 to 22 years (Raznahan et al., 2010; Mills et al., 2012; Shaw et al., 2013). Linear fits by necessity imply the same cortical thinning rate over this full age range. Recently, a longitudinal study of a different multi-site subject pool (Evans and Brain Development Cooperative Group, 2006) reported that much of the cortex showed linearly decreasing cortical thickness with age over 6–22 years (Burgaleta et al., 2014). However, other longitudinal studies from the same NIH group above that scanned to younger ages are not consistent with a linear age trajectory of cortical thickness and instead have fit with a cubic trajectory from ~3 to 30 years suggesting initial increases (albeit slight and nearly flat) of cortical thickness in early childhood that peaks at about 9–11 years depending on the region, and then decreases during adolescence which then levels off into young adulthood (Shaw et al., 2008; Raznahan et al., 2011). This initial increase does not fit with the aforementioned data sets (Raznahan et al., 2010; Mills et al., 2012; Shaw et al., 2013), granted their minimum age of 7–9 years is older than the 3 years in (Shaw et al., 2008; Raznahan et al., 2011). One recent longitudinal infant study showed that the cortical thickness increased rapidly from birth to 1 years and then leveled off at 1–2 years (Lyall et al., 2014). Together with a cross-sectional study that observed that the cortical thickness decreased with age already from 4 years and up (Brown et al., 2012; Brown and Jernigan, 2012), this suggests that the cortex may reach peak thickness values in early life. This is also supported by two other independent longitudinal studies that have reported pre-adolescence regional cortical

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thinning in healthy subjects over a 2 year gap covering 5 to 11 years (Sowell et al., 2004), and over a 3 year gap from 9 to 12 years (van Soelen et al., 2012) with no evidence of any thickness increases, but they do not inform about the adolescent period.

The transition of cortical thickness from childhood to adulthood requires further investigation to examine whether there are specific periods of greater change. To address this, the current study investigated longitudinal cortical thickness trajectories in 90 typically developing participants aged 5–32 years with 180 scans (2 scans each ~2–7 years apart).

Materials and methods

Subjects

Subjects were 90 healthy volunteers (48 females, 85 right handed) with no self-reported (or parent-reported) history of neurological or psychiatric disease or brain injury. The original recruitment pool included 103 participants, who were reported in a longitudinal DTI white matter analysis (Lebel and Beaulieu, 2011), but only participants with at least two high-quality MPRAGE scans (as determined by visual inspection and CIVET quality control) were included in the current study. For participants with more than two scans ($n = 7$), only the initial and latest scans were included thus yielding a total of 180 scans (Fig. 1). The age of the first scan for the youngest child was 5.6 years, and the age of the second scan of the oldest was 32.2 years. The mean age gap between the two scans was 4.1 ± 0.8 years with a gap range of 1.8–6.9 years. This study was approved by the Health Research Ethics Board of the University of Alberta. All subjects gave informed consent (or child assent and parent/guardian consent for volunteers under 18 years of age) prior to study participation.

Imaging and processing

All data were acquired on the same 1.5 T Siemens Sonata MRI with the same protocol. Head motion was minimized using ear pads. Total acquisition time was approximately 25 min and included DTI, T1-weighted MPRAGE, T2-weighted, and fluid-attenuated inversion recovery (FLAIR) imaging. High-resolution ($1 \times 1 \times 1$ mm^3) 3D MPRAGE T1-weighted axial images were used in the current study with TE = 4.38 ms, TI = 1,100 ms and 4:29 min scan time. Images were processed with the CIVET 1.1.11 pipeline online with CBrain (https://cbrain.mcgill.ca/) with normalization to the ICBM-152 template. Cortical thickness was measured as the distance between corresponding vertices of inner and outer surfaces of gray matter across 40,962 vertices in each hemisphere. Thickness data were blurred using a surface-based diffusion smoothing kernel of 20 mm FWHM that preserves cortical topology. Cortical surface area was measured at the middle of the inner and outer surfaces of the gray matter on each of the link lines that measured the cortical thickness, which can be summed to give the lobar surface areas.

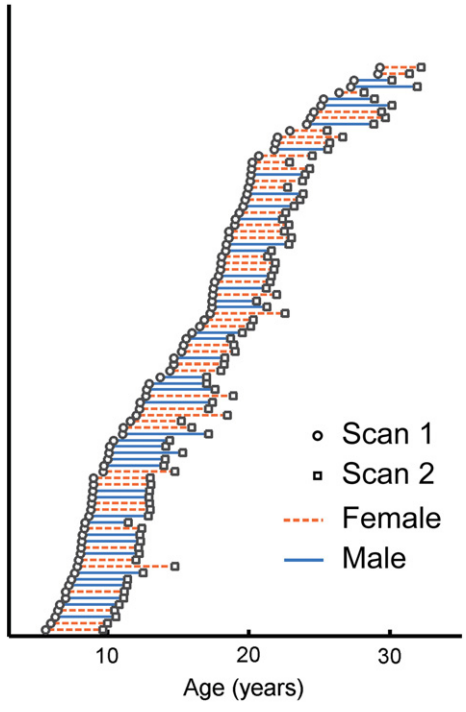

Fig. 1. Repeated scan timings for all 90 subjects with an inter-scan gap of ~4 years on average.

Statistics

The focus in this paper was on the overall mean cortical thickness averaged over all the vertices of the cortex and the four primary lobes of the brain (frontal, temporal, parietal and occipital as defined on the AAL template) in each hemisphere to streamline the analysis.

As the primary goal of the paper is to assess whether the cortical thickness changes might differ with age in the transition from children to adults, inter scan changes in cortical thickness were evaluated relative to a test of inter-scan reliability where 5 adults (21, 24, 27, 28 and 36 years) were scanned 10 times each within 5 days using the same imaging protocol as in the main study. Mean standard deviations of cortical thickness (SDs measured from consecutive scans of each subject, averaged across subjects) were used to provide estimates of inter-scan variability, independent of development. If the cortical thickness (or surface area) change between scans of a particular participant in our longitudinal development cohort was within ±1 SD of the inter-scan variability of these 5 reliability subjects, then it was attributed as no change, >1 SD as an increase and <−1 SD as a decrease. Accordingly, the SD in surface area was also used to measure the change of surface area in each participant.

Beyond the absolute changes in cortical thickness (or surface area) above, the relative change in the thinning (or thickening) rate (mm/year) was evaluated for each individual, which was defined as the cortical thickness difference between the second scan and the first scan (Δthickness = thickness2 − thickness1) divided by the age difference between scans (Δage = age2 − age1). Negative values of the rate would indicate cortical thinning while positive would reflect thickening with age. The age associated with each participant's rate was taken as the mean age of the two scans. Similarly, the expanding rate of the overall cortical surface area (Δsurface area/Δage) was evaluated where positive values indicate expansion and negative values contraction of surface area.

To better analyze the change of thinning rate in development, a 'moving average filter', which is usually used to smooth out fluctuations and highlight consistent trends, was applied on the individual thinning rates with a subgroup of 10 consecutively aged participants to generate a mean thinning rate for each of 81 subgroups. Group 1 contained the first 10 lowest mean scan ages, then Group 2 comprised those counted from the 2nd lowest mean scan age to the 11th participant, and so on for the 81 subgroups. The choice of 10 participants in each subgroup is arbitrary, but with this group size, the age of both scans in the first subgroup fell in childhood or right before adolescence (age range 5.6–12.5 years, mean 8.8 ± 0.7 years) in the current data set. Each subgroup age was calculated by averaging the mean scan ages of all 10 participants in that subgroup. Furthermore, the mean thinning rate in each subgroup was compared with either the youngest subgroup (listed above) or the oldest subgroup (age range 24.1–32.2 years, mean 28.2 ± 1.5 years) with the Student's t-test ($p < 0.05$).

Cortical thinning was further evaluated in three age subgroups, namely, children, adolescents and young adults based on their ages at the final scans. Children had all scans before age 12 years ($N = 10$ for 20 scans, 4 females), adolescents were aged 12–19 years at their last scan ($N = 28$ for 56 scans, 18 females) and adults were aged 20–32 years at their final scan ($N = 42$ for 84 scans, 26 females). The number of participants who had decreased (< -1 SD of reliability test), increased (>1 SD) or unchanged inter-scan thickness were counted and significant differences of their ratios were evaluated with a non-parametric Kruskal–Wallis test with a significant level of 0.05. Also, the differences of the cortical thinning rate between children, adolescents and young adults were tested with the Student's *t*-test with a significant level of 0.05. A similar three subgroup analysis was performed for changes in overall surface area of the brain.

Group difference on the overall mean thickness between males ($N = 42$, 6.3–31.9 years, 37 right handed, 84 scans) and females ($N = 48$, 5.6–32.2 years, 48 right handed, 96 scans) was tested with a mixed model controlling for age and handedness using the SurfStat toolbox (www.math.mcgill.ca/keith/surfstat) in MATLAB. Cortical thinning rates in each sex group were also calculated and binned over 10 age-consecutive participants. As before, within each sex, the thinning rates of each subgroup were compared to zero and to the thinning rate of the youngest and oldest subgroups. Also, cortical thinning was further evaluated in each sex for children, adolescents and young adults as before.

Results

Whole brain mean cortical thinning with age

The overall mean cortical thickness of all participants was within 2.9–3.9 mm (Fig. 2a). It is apparent that the thickness values were higher in the early years (<12 years) and then relatively lower but stable in later years (>20 years), and that there were many obvious decreases around adolescence. The mean SD for overall mean thickness in the inter-scan reliability study was ±0.055 mm. Many of the participants (65 of 90, 72%) decreased with a Δthickness < -1 SD, while only 5 increased (6%) and 20 were within ±1 SD (22%). The individual subject thinning rates showed that the 10 participants with the greatest thinning rates (i.e., below −0.07 mm/year) were all in the mean age of scanning range of 10–18 years (Fig. 2b). After smoothing over 10 adjacent participants to clearly identify trends with age, the cortical thickness change rate in most of the subgroups was negative indicating thinning over the full age span that was significantly different relative to 0 rate ($p < 0.05$, indicated by * at the top of Fig. 2c). There is an evident dip indicating accelerated cortical thinning during adolescence, then a decelerated but continuous thinning in young adulthood. The group differences (indicated by * at bottom of Fig. 2c) between each of the age subgroups and the oldest subgroup (~28 years) were significant from group 8 (mean age 10.1 ± 0.5 years, scan range 7.2 to 12.4 years) to group 46 (mean age 18.6 ± 1.0 years, scan range 15.3 to 18.9 years). While comparing with the youngest group, the first significantly decreased subgroup was group 10 (mean age 10.3 ± 0.4 years, scan range 7.7 to 12.5 years), and the last significantly decreased subgroup was group 41 (mean age 17.0 ± 1.0 years, scan range 13.7 to 17.0 years). The nadir of thinning rate (−0.054 mm/year) for whole brain cortical thickness was found in group 38 with mean age of 16.2 ± 0.8 years and scan range 12.7 to 18.9 years.

After dividing the cohort into 3 groups based on the ages of the last scans, it is clear that the most consistent decreases of overall mean thickness are in adolescents (Fig. 2d). Using the 5 subject reliability data, 35/38 (92%) of adolescents decreased by more than 1 SD with a mean thinning rate of these participants of −0.052 ± 0.022 mm/year (while −0.048 ± 0.025 mm/year in all adolescents), whereas 3 (8%)

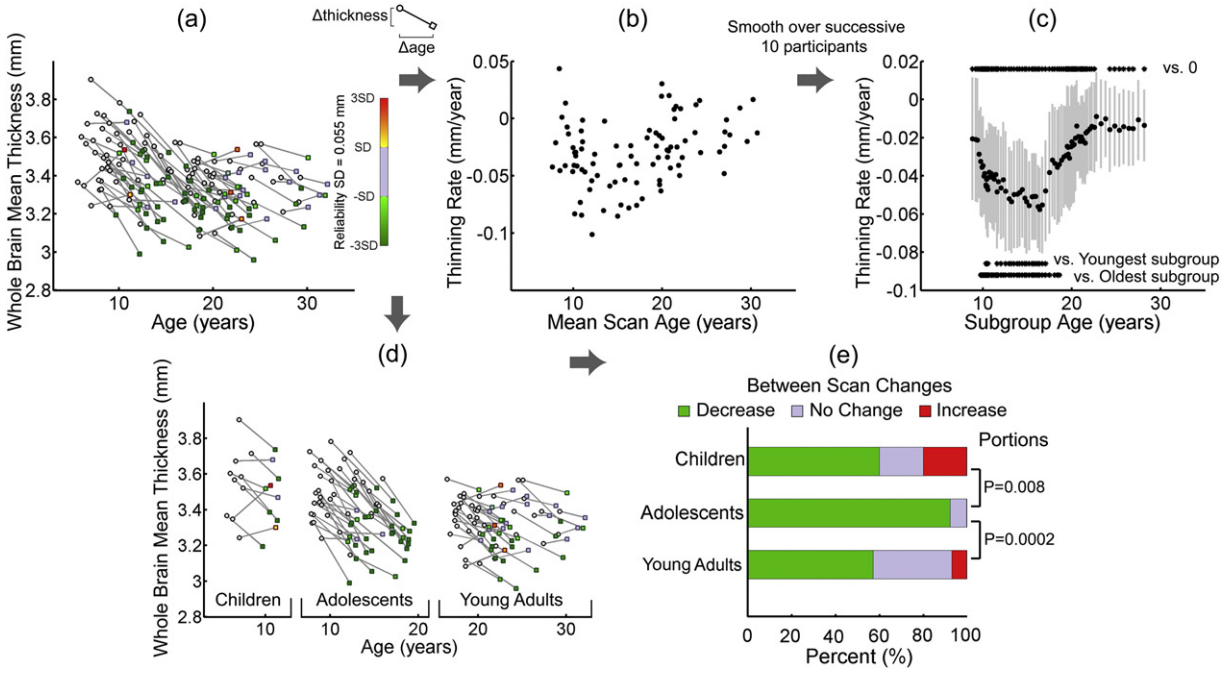

Fig. 2. (a) Whole brain overall mean cortical thickness for both scans is shown for 90 participants. The second scan symbols are filled in gray if thickness changes from the first scan were within ± 1 SD for inter-scan reliability, in light/dark green when thickness decreased by more than 1 SD and in yellow/red if thickness increased by more than 1 SD. Cortical thickness decreased between scans (in green) in most participants (71%). (b) The rate of change of cortical thickness between scans (Δthickness/Δage, mm/year) suggests that thinning is observed over the full age range but that there is a faster thinning rate (i.e., more negative) during adolescence. (c) This is better appreciated in the thinning rate curves versus age that are smoothed into different bins over 10 adjacent subjects to yield 81 age subgroups (mean ± standard deviation per bin). Significant differences in each bin of thinning rate versus 0, youngest subgroup (mean 8.8 years) and oldest subgroup (mean 28.2 years) are shown, the latter two showing greater thinning in the adolescent range. (d) An alternative strategy of grouping the participants into children ($N = 10$), adolescents ($N = 38$), and young adults ($N = 42$) showed that adolescents had more consistent reductions of cortical thickness. (e) Relative number (in percentage) of subjects whose overall mean cortical thickness either increased (red), did not change (gray) or decreased (green) between the first and second scans showed that most of the adolescents had decreases of cortical thickness (92%) as opposed to 60% of children and 57% of young adults (non-parametric Kruskal–Wallis test).

had no change and nobody increased in the final scans compared to their first scans (Fig. 2e). This is in contrast to the smaller proportion of subjects who underwent cortical thinning and at lower rates in children (6/10 for 60%; −0.042 ± 0.012 mm/year for those who decreased, and −0.021 ± 0.032 mm/year in all children) or in young adults (24/42 for 57%; −0.033 ± 0.014 mm/year for those who decreased, and −0.017 ± 0.023 mm/year in all adults).

Regional cortical thinning with age

The mean regional cortical thickness variation over the brain in all participants was similar to previous studies with greater thickness observed in bilateral insula, temporal lobe, temporal pole and medial frontal lobe and thinner cortex in the bilateral parietal and occipital lobes. Example maps of regional cortical thickness from different age groups are presented in our earlier cross-sectional aging paper over the life span (Zhou et al., 2013).

All of the frontal, parietal, temporal and occipital regions showed similar thinning patterns: thicker cortex in younger ages, fast drops during adolescence and then leveling off in young adulthood (Fig. 3, left panels). The smoothed subgroup analysis of thinning rate in each of the regional clusters (right panels in Fig. 3) showed similar patterns to that of overall mean thickness in Fig. 2c: a few relatively less thinning subgroups before 10 years (~−0.01 to −0.03 mm/year in all cases), an accelerated phase at ~10 years sustained until ~18 years (~−0.05 to −0.08 mm/year) and then decelerating to a lower but stable thinning rate during young adulthood (~−0.01 to −0.03 mm/year, again similar to childhood). As for mean overall cortical thinning rate, nearly all subgroups showed a cortical thickness change rate below zero indicating significant thinning over the full age span, and that the subgroups that differed significantly in thinning rate from either the youngest or

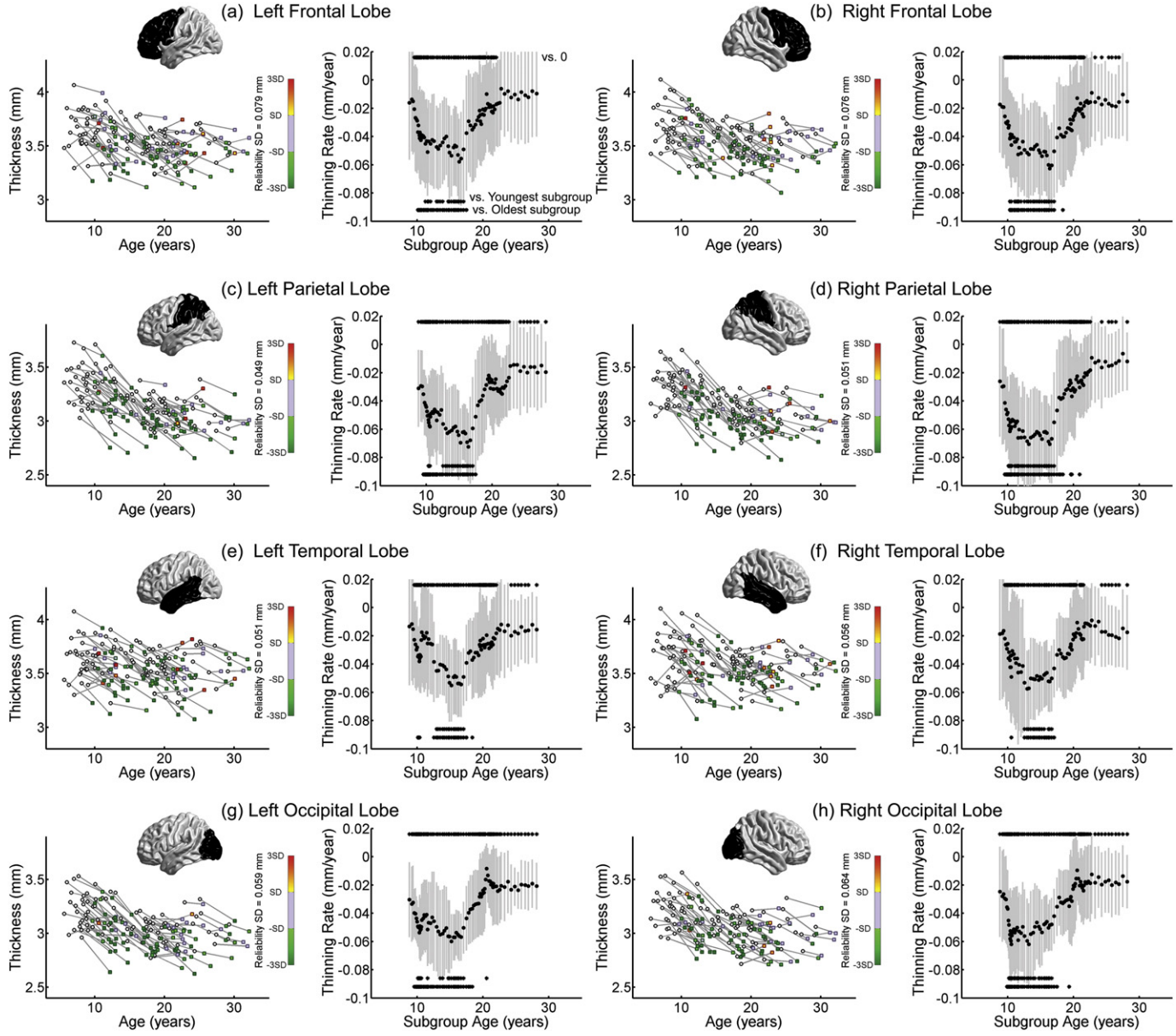

Fig. 3. Scatter plots of individual data (left panels) showed that many subjects had reduced cortical thickness between scans (indicated by green at second scan) and age subgroup analysis showed a common pattern of greater thinning around adolescence (right panels) for all lobes (a, b—frontal; c, d—parietal; e, f—temporal; and g, h—occipital). Asterisks indicate significant differences ($p < 0.05$) of the thinning rate for each subgroup compared to 0 (top *), or the youngest (middle *) or oldest (bottom *) subgroups.

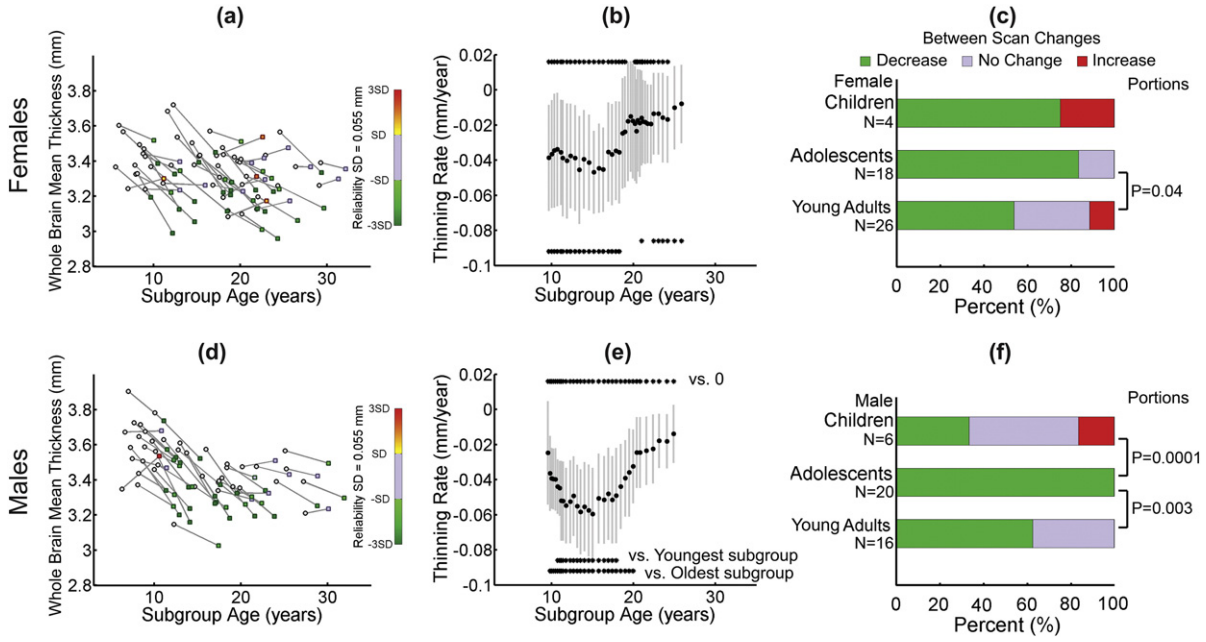

Fig. 4. (a, d) Whole brain mean cortical thickness was reduced between scans for 67% of females ($N = 48$) and 76% of males ($N = 42$). (b, e) The thinning rate was significantly below 0 over the full age span for both females and males (top row of *). Both the children and adolescent bins had significantly greater cortical thinning rates than the young adults in females and males (bottom row of *). Male adolescents showed significantly greater thinning than their youngest subgroup, whereas females did not (middle row of *), although the very small sample sizes in the children make this observation preliminary. (c) Most of the female adolescents (83%) decreased in cortical thickness in contrast to 53% of female young adults (non-parametric Kruskal–Wallis test). (f) All male adolescents decreased in cortical thickness as opposed to 33% in male children and 63% in male young adults.

oldest subgroups were in the 10–18 year range varying a bit by lobe (right panels in Fig. 3).

Cortical thinning in males and females

The whole brain mean thickness over all participants was significantly thicker in males (3.43 ± 0.17 mm) than that in females (3.32 ± 0.15 mm, $P = 4 \times 10^{-6}$). Both males and females showed a significant thinning rate across the full age range (Figs. 4a, d and * at top of Figs. 4b, e). Compared to the oldest subgroup, most of the subgroups under 20 years had a significantly faster thinning rate (* at bottom of Figs. 4b, e). However, it appears that the patterns of binned thinning rates differed between the males and females. Compared to the youngest subgroup, only the subgroups over 20 years in the females had smaller (but still negative) thinning rates, suggesting similar thinning rates in childhood and adolescence for females, whereas the males showed greater thinning rates during adolescence than that in childhood (* just below data in Figs. 4b, e). Using the 5 subject reliability data, 83% (15/18) of female adolescents decreased by more than 1 SD, which was similar to the 75% of female children (3/4) and greater than the 54% (14/26) in female young adults (Fig. 4c). All of the 20 male adolescents had cortical thickness decreases of more than 1 SD, in contrast to only 33% (2/6) in male children and 63% (10/16) in male young adults (Fig. 4f).

Cortical surface area

The whole brain overall surface area of all participants ranged from 146,605 to 227,079 mm^2. Many of the participants increased their surface area by more than 1 SD between scans (53 of 90 participants, 59%), while only 14 (16%) participants decreased (Fig. 5a). The increase in surface area was present similarly over the full age range (Fig. 5b). After being split into 3 age groups, there were 7 children (70% of 10 participants), 27 adolescents (71% of 38) and 19 young adults (45% of 42) that increased in surface area (defined as greater than 1 SD, +1381 mm^2, based on the 5 person reliability study), while only 1 child (10%), 3 adolescents (8%) and 10 young adults (24%) decreased in surface area (Fig. 5c). In the participants with increased surface area

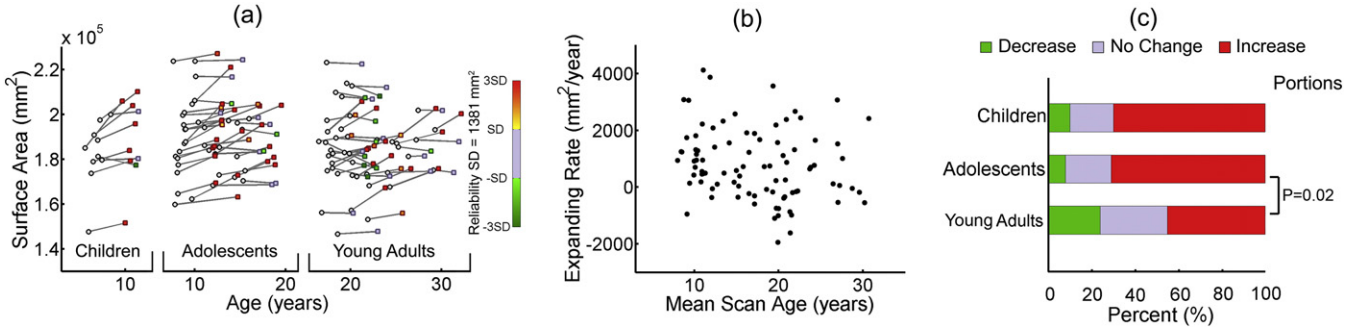

Fig. 5. (a) The overall cortical surface area in children, adolescents and young adults showed surface expansion in 59% of participants over the full age span. (b) The rate of change between scans (Δsurface area/Δage, mm^2/year) did not show any apparent relationship with age. (c) The surface area expanded in the majority of the children (70% of 10 participants) and adolescents (71% of 38), but less so in young adults (45% of 42) as supported by Kruskal–Wallis test.

only, the average expanding rates did not differ significantly between groups: 2343 ± 1489 mm^2/year in children (1602 ± 1736 mm^2/year in all children), 1474 ± 959 mm^2/year in adolescents (1021 ± 1090 mm^2/year in all adolescents) and 1654 ± 899 mm^2/year in young adults (485 ± 1299 mm^2/year in all adults) (Fig. 5c). While the majority of subjects showed increases of surface area and decreases of cortical thickness, overall surface area (Fig. 5b) did not show any age related differences such as whole brain mean cortical thickness (Figs. 2b, c). There was no obvious relationship between expanding rate in surface area and thinning rate in cortical thickness (data not shown). The surface area of the various lobes was not analyzed further given the lack of age effect in the overall cortical surface area.

Discussion

The current study demonstrates accelerated thinning of the cortex in adolescence compared to childhood and young adulthood, suggesting that adolescence marks a unique period of cortical development. This pattern of cortical change is coincident with sharp transitions in physical, behavioral, emotional and social development during adolescence (Spear, 2000; Ernst and Korelitz, 2009), albeit these were not measured in the cohort of our current study. Widespread cortical thinning likely stems from ongoing myelination (Benes et al., 1994; Paus, 2010), synaptic pruning (Rakic et al., 1994; Huttenlocher and Dabholkar, 1997) or likely a combination of both effects in the adolescent brain, which are thought to be integral for the functional neural networks to improve efficiency of information processing (Brown et al., 2005; Durston et al., 2006; Luna et al., 2010). Myelination may alter the T1-weighted gray-white matter contrast (Walters et al., 2003), leading to a change in classification of the gray/white border, thereby altering the measured "cortical thickness" in adolescents (Tamnes et al., 2010). However, a recent study observed the lack of a tight coupling of cortical thinning and white matter maturation patterns (measured with diffusion tensor imaging) and thus proposed that the cause of cortical thinning in adolescence is not explained by encroachment of subcortical white matter (Wu et al., 2014).

An alternative explanation might be the macro-structure morphology in the developing brain where the ongoing maturation in white matter during adolescence could flatten the cerebral cortex (Alemán-Gómez et al., 2013), thus stretching out the outer cortical surface like a balloon causing it to thin (Seldon, 2005; Hogstrom et al., 2013). In our study, the overall surface area increased with age in the majority of children and adolescents by a similar degree, but the cortical thinning was greater in adolescents. Therefore, surface area expansion does not appear to be a major factor for the accelerated cortical thinning in adolescents. This lack of synchrony has also been observed in a large cross-sectional, multi-site development study (Brown et al., 2012). Three independent longitudinal studies have shown increases of surface area in children before age 10 years (Wierenga et al., 2014), 11 years (Shaw et al., 2012) or by 13–16.5 years depending on IQ (Schnack et al., 2014), followed by decreases of surface area to older ages up to 23, 17 and 60 years, respectively. However, other longitudinal studies with a ~2 year scan gap either show decreases of surface area over all four lobes in the 11–17 year range (Alemán-Gómez et al., 2013) or that most of the brain regions show no change in surface area over 6–20 years (Burgaleta et al., 2014). Thus, there is a fair amount of inconsistency on the reports of surface area with development.

In contrast, cortical thinning during development is a robust observation over the ages of 7–22 years, but the use of a linear fit in most studies leads to the conclusion of similar rates of thinning in children and adolescents by necessity (Raznahan et al., 2010; Mills et al., 2012; Shaw et al., 2013; Burgaleta et al., 2014; Wierenga et al., 2014). However, by the addition of younger subjects down to 3 years and the use of cubic fits, some of the same groups show that cortical thickness changes with age are non-linear with slight increases in early childhood till around 9–11 years of age depending on the brain region and then greater decreases during adolescence (Shaw et al., 2008; Raznahan et al., 2011). In our study, very few children (only 3 of 26 whose mean scan age was less than 12 years) showed increases between scans for overall mean thickness (individual subject data in Fig. 2b), and the youngest subgroups had negative cortical thickness change rates for all four cerebral lobes, indicating widespread cortical thinning even in childhood (Fig. 3a–h). Our data suggest that after childhood, there is accelerated cortical thinning during adolescence, in keeping with the large changes identified by the cubic trajectories during this phase, which then levels off subsequently. Another large-scale longitudinal study has reported that cortical thickness drops rapidly around 10 years of age, which is in excellent agreement with our binned plots (Fig. 2c, right panels of Fig. 3), and then slows down to plateau around age 30 years (Schnack et al., 2014). However, our data suggests a more prolonged period of accelerated thinning till about 16–18 years that slows down, but still thins, into young adulthood. It should be noted that all of the plots of cortical thickness versus age (Fig. 2a, left panels of Fig. 3) can be fit significantly with linear regression ($p < 0.001$, plots not shown) because of the overall reduction from childhood to adulthood, but that this type of analysis masks the underlying variability with age, which has been highlighted by our focus on individual thinning rates of change with age rather than curve fitting the cortical thickness versus age. Early increases of cortical thickness are also not reported by others who found thinning in frontal and parietal-occipital regions in 7- to 11-year-old children compared to their previous scans 2 years earlier (Sowell et al., 2004), as well as in frontal, paracentral and occipital cortices in 12-year-olds compared to their first scans at 9 years (van Soelen et al., 2012). One alternative reason that we did not observe an obvious increase of cortical thickness in the children of our cohort is that the youngest was 5.6 years of age, and we may have missed the peak ages. However, one longitudinal study in infants found cortical thickness roughly reached adult values by age of 2 years after a rapid increase from birth to 1 years (Lyall et al., 2014), and another cross-sectional study suggested that the thickness might peak before 4 years as it continuously decreases from that age onwards till 20 years (Brown et al., 2012; Brown and Jernigan, 2012).

Longitudinal studies in children and/or adolescents report widespread areas of cortical thinning encompassing all the lobes (Sowell et al., 2004; Raznahan et al., 2010; van Soelen et al., 2012; Alemán-Gómez et al., 2013; Shaw et al., 2013; Burgaleta et al., 2014). Cortical thinning rates were faster in all four lobes during adolescence with similar rates of ~0.05–0.07 mm/year with the central portion of the thinning rate dip occurring rather uniformly around 15 years of age. Anecdotal observations suggest that the youngest age-group in children may undergo more rapid thinning early on in the parietal and occipital lobes (~0.02–0.03 mm/year) than that in the frontal and temporal lobes (~0.01–0.02 mm/year) (right panels of Fig. 3). In young adults, the thinning rate falls back to very similar rates of ~0.01–0.02 mm/year, which matches the children rate for the frontal and temporal lobes, but is slower than that of the children for the parietal and occipital lobes. The cortical thickness as measured on T1-weighted images is not uniform in the brain and this heterogeneity remains across the life span (Zhou et al., 2013). Notably, the parietal and occipital lobes start off with smaller cortical thickness (~3.3–3.4 mm on average), whereas the frontal and temporal lobes begin higher at ~3.7 mm on average (left panels of Fig. 3); therefore, the similar absolute decreases over the age span studied of 6–32 years leads to proportional greater decreases in the former two structures. Diffusion tensor imaging (DTI) tractography studies of the white matter tracts suggest that the fronto-temporal tracts have a protracted development (Lebel et al., 2008), and assuming that some of these changes are due to myelination, this may influence the differential rates of apparent cortical thinning for the frontal and temporal lobes in the youngest children. In 11- to 17-year-olds, the longitudinal rate of cortical thickness decrease between scans did not differ much (1.1–1.7%) among the four lobes

(Alemán-Gómez et al., 2013). However, the largest longitudinal cortical thickness reductions have been observed in the occipital lobe for younger subjects covering 5–11 years (Sowell et al., 2004) and 9–12 years (van Soelen et al., 2012). A cross-sectional study from 8 to 30 years showed the greatest cortical thickness reductions with age and quadratic age effects (steeper declines that level off) in the parietal and occipital lobes (Tamnes et al., 2010) in agreement with Figs. 3c, d, g, h. At even earlier ages, 4- to 6-year-olds had the largest cortical thickness reductions in the occipital, parietal and prefrontal regions (Brown and Jernigan, 2012); the two first regions matching up with our observations in children.

Males at younger ages have larger brain size and gray matter volumes than females (Giedd et al., 2012), as well as thicker cortex (Sowell et al., 2007). The thicker cortical thickness in boys and male adolescents is observed in overall and regional cortical thickness trajectories (Raznahan et al., 2010, 2011; Mills et al., 2012). Our current study also showed that males had a thicker overall cortical thickness than females (Figs. 4a, d), but that there was a greater sex difference in children (0.22 ± 0.15 mm in first subgroup) than that in young adults (0.08 ± 0.14 mm in last subgroup). The majority of females (67%) and males (76%) show cortical thinning between scans (Fig. 4) that is present across the full age span, as seen in the comparison of the cortical thickness rate change versus zero (top line of stat symbols in Figs. 4b, e). There is accelerated cortical thinning in adolescence versus the oldest bin (bottom line of stat symbols in Figs. 4b, e) for both genders, but there is a notable difference in childhood. While the males in the 12- to 18-year-old age span show significantly greater cortical thinning than the youngest age bin, this is not the case for the females who show comparable accelerated thinning rates throughout childhood and adolescence (middle line of stat symbols in Figs. 4b, e). A larger portion of female children (75%, 3 of 4) showed a decrease in cortical thickness, which was comparable to the portion in female adolescents (83%, 15 of 18) (Fig. 4c), while only a much smaller portion of male children (33%, 2 of 6) showed decreases of cortical thickness, which was far less than the portion in male adolescents (100%, 20 of 20) in male children (Fig. 4f). This suggests there might be an earlier trajectory of overall thinning in the females in childhood. However, the sex differences in the children should be considered preliminary given the very small sample sizes of only 4 females and 6 males in the children group. Others have found only scattered regions of sex differences for cortical thickness development in a large-scale combined cross-sectional/longitudinal study over the ages of 6–30 years (Mutlu et al., 2013).

Adolescence marks a time when major psychopathology typically emerges or intensifies (Kessler et al., 2005; Paus et al., 2008). Changes of cortical thickness are often credited to normal cognitive development during adolescence such as shifts in intelligence quotient (IQ) over 6–22 years, which were related to rates of cortical thinning mainly in frontal regions (Burgaleta et al., 2014), and thinner parietal cortex, which predicted better neuropsychological performance in early adolescents at 12–14 years (Squeglia et al., 2013). Longitudinal cortical thickness trajectories have differed during adolescence with pathology where less thinning has been observed in cortical regions of early onset schizophrenia (Bakalar et al., 2009), fetal alcohol spectrum disorders (Treit et al., 2014) and attention deficit hyperactivity disorder (Shaw et al., 2013), while greater thinning has been reported in autism (Hardan et al., 2009) and 22q11.2 deletion syndrome (Schaer et al., 2009). Cortical development during childhood and adolescence may reflect genetic and/or early environment influences (Yoon et al., 2010; van Soelen et al., 2012; Yang et al., 2012; Paus, 2013).

There were some limitations in the current study. The number of young children was low and this could limit the analysis where participants were separated into three groups: children, adolescents and young adults. This limitation was most evident in the sex analysis particularly for the children. However, the smoothed age subgroup binned analysis showed a consistent effect of accelerated cortical thinning in the adolescent age range. Another limitation is that although this is a longitudinal study, the age range (5–32 years) was much larger than the follow-up intervals with a mean value of 4 years; therefore, cohort effects are still possible. The age gaps between scans in the current study were mostly between 3 and 5 years, but there were 17 participants outside this scan interval. A reanalysis of 73 participants with a 3–5 year age gap between scans showed a similar statistically significant finding of accelerated cortical thinning during adolescence (data not shown).

In summary, this longitudinal brain imaging study of a healthy population showed that cortical thickness across most of the brain decreases with age over 5 to 32 years with greatest reductions during adolescence. This accelerated cortical development may play a role in the typical physical, behavioral, cognitive and emotional evolution as well as its derailment in various disorders that appear at this time.

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Conflict of interest

None.

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