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Development of the cerebral cortex across adolescence: A multisample study of interrelated longitudinal changes in cortical volume, surface area and thickness

Christian K. Tamnes[1], Megan M. Herting[2], Anne-Lise Goddings[3], Rosa Meuwese[4,5], Sarah-Jayne Blakemore[6], Ronald E. Dahl[7], Berna Güro#lu[4,5], Armin Raznahan[8], Elizabeth R. Sowell[9], Eveline A. Crone[4,5] and Kathryn L. Mills[10,11]

[1]*Department of Psychology, University of Oslo, Oslo, Norway*
[2]*Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA*
[3]*Institute of Child Health, University College London, London, UK*
[4]*Brain and Development Research Center, Institute of Psychology, Leiden University, Leiden, The Netherlands*
[5]*Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands*
[6]*Institute of Cognitive Neuroscience, University College London, London, UK*
[7]*Institute of Human Development, University of California Berkeley, Berkeley, CA, USA*
[8]*Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD, USA*
[9]*Children's Hospital of Los Angeles, Los Angeles, CA, USA*
[10]*Department of Psychology, University of Oregon, Eugene, OR, USA*
[11]*Center for Translational Neuroscience, University of Oregon, Eugene, OR, USA*

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Corresponding author: Christian K. Tamnes, Department of Psychology, University of Oslo, PO Box 1094 Blindern, 0317 Oslo, Norway; Email: c.k.tamnes@psykologi.uio.no

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Christian K. Tamnes[1], Megan M. Herting[2], Anne-Lise Goddings[3], Rosa Meuwese[4,5], Sarah-Jayne Blakemore[6], Ronald E. Dahl[7], Berna Güroğlu[4,5], Armin Raznahan[8], Elizabeth R. Sowell[9], Eveline A. Crone[4,5], and Kathryn L. Mills[10,11]

[1] Department of Psychology, University of Oslo, Oslo, Norway

[2] Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA

[3] Institute of Child Health, University College London, London, UK

[4] Brain and Development Research Center, Institute of Psychology, Leiden University, Leiden, The Netherlands

[5] Leiden Institute for Brain and Cognition, Leiden University, Leiden, The Netherlands

[6] Institute of Cognitive Neuroscience, University College London, London, UK

[7] Institute of Human Development, University of California Berkeley, Berkeley, CA, USA

[8] Child Psychiatry Branch, National Institute of Mental Health, Bethesda, MD, USA

[9] Children's Hospital of Los Angeles, Los Angeles, CA, USA

[10] Department of Psychology, University of Oregon, Eugene, OR, USA

[11] Center for Translational Neuroscience, University of Oregon, Eugene, OR, USA

Corresponding author: Christian K. Tamnes, Department of Psychology, University of Oslo, PO Box 1094 Blindern, 0317 Oslo, Norway; Email: c.k.tamnes@psykologi.uio.no

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Abstract

Accurate understanding of typical human brain development and how changes in different structural components relate to each other is critical before we can assess and interpret how they relate to cognition, affect and motivation, and how these processes are perturbed in clinical or at-risk populations. We conducted a multisample magnetic resonance imaging (MRI) study to investigate the development of cortical volume, surface area and thickness, as well as their interrelationships, from late childhood to early adulthood (7-29 years) using four separate longitudinal samples including 388 participants and 854 scans in total. These independent datasets were processed and quality-controlled using the same methods, but analyzed separately to study the replicability of the results across sample and image acquisition characteristics. The results consistently showed widespread and regionally variable non-linear decreases in cortical volume and thickness and comparably smaller steady decreases in surface area. Further, the dominant contributor to cortical volume reductions during adolescence was thinning. Finally, complex regional and topological patterns of associations between changes in surface area and thickness were observed. Positive relationships were seen in sulcal regions in prefrontal and temporal cortices, while negative relationships were seen mainly in gyral regions in more posterior cortices. Collectively, these results help to resolve previous inconsistencies regarding the structural development of the cerebral cortex from childhood to adulthood, and provide novel insight into how changes in the different dimensions of the cortex in this period of life are interrelated.

Keywords: brain development; gray matter; morphometry; MRI; replication

Significance Statement

Different measures of brain anatomy develop differently across adolescence. Their precise trajectories and how they relate to each other throughout development is not established, but important for our understanding of both typical development, as well as disorders involving aberrant brain development. To provide accurate characterizations of how different measures of cortical structure develop, we performed an MRI investigation across four independent datasets. The most profound anatomical change in the cortex during adolescence was thinning, with largest decreases observed in the parietal lobe. There were complex regional patterns of associations between changes in surface area and thickness, with positive relationships seen in sulcal regions in prefrontal and temporal cortices, and negative relationships seen mainly in gyral regions in more posterior cortices.

Introduction

Insight into postnatal human brain development has been greatly enhanced over the last two decades by the use of imaging methods, and particularly magnetic resonance imaging (MRI) (Blakemore, 2012; Giedd et al., 2015; Jernigan et al., 2011). There are however still fundamental disagreements across available studies regarding the developmental patterns and precise trajectories for cortical volume and its distinct components surface area and thickness (Mills & Tamnes, 2014). To try to resolve the inconsistencies and also provide clues about the processes driving the changes in the different dimensions of the cerebral cortex from childhood to adulthood, we investigated the development of cortical structure concurrently in four separate longitudinal samples, and directly assessed how changes in different cortical measures are interrelated.

Previous results are particularly contradictory with regard to the development of cortical thickness, with some studies reporting increases until late childhood, while others find continuous thinning from early- or mid-childhood (Walhovd et al., 2016). Inconsistencies across studies of development of cortical structure may have resulted from varying sample characteristics, image acquisition, image processing including quality control (QC) procedures and software used, and/or statistical analyses and curve fitting (see e.g. (Aubert-Broche et al., 2013; Ducharme et al., 2015b; Fjell et al., 2010; Mills et al., 2016; Sullivan et al., 2011)). One approach to try to clarify these inconsistencies is to conduct multisample studies following current standards and recommendations for processing and analysis. Here, we build upon a recent such study in which we reported replicable models for gross structural brain development between childhood and adulthood (Mills et al., 2016).

Cortical volume is determined by surface area and thickness, and these components are influenced by different evolutionary (Geschwind & Rakic, 2013), genetic (Chen et al., 2013; Kremen et al., 2013), and cellular (Chenn & Walsh, 2002) processes, and show unique changes across different stages of life (Amlien et al., 2016; Brown et al., 2012; Lyall et al., 2015; Storsve et al., 2014; Wierenga et al., 2014). Knowledge about the relative contributions of surface area and thickness to developmental cortical volume changes, and the relationship between changes in surface area and thickness during adolescence, may provide important, although indirect, clues for understanding the biological processes underlying development of cortical structure. In prenatal and perinatal life, the primary processes driving surface area expansion and thickening are cortical column generation and genesis of neurons within columns, respectively (Bhardwaj et al., 2006; Rakic, 1988). The processes underlying changes in cortical structure throughout childhood and adolescence are less well understood, although we know that the protracted human brain development involves increasing caliber and myelination of axons (Benes, 1989; Benes et al., 1994; Yakovlev & Lecours, 1967), and that early synaptogenesis is followed by pruning (Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011).

To increase our confidence in current interpretations about how the cerebral cortex grows and to yield novel knowledge that might help us understand the processes driving its development, the present study aimed to 1) Characterize the regional developmental trajectories of cortical volume, surface area and thickness across adolescence in four separate longitudinal samples and 2) Directly test how changes in the distinct cortical components are interrelated. Each independent dataset was analyzed separately to examine the consistency and replicability of the results across sample and image acquisition specifics.

Materials and Methods

Participants

This study utilized four separate datasets (*Child Psychiatry Branch (CPB), Pittsburgh (PIT), Neurocognitive Development (NCD), Braintime (BT)*), each including typically developing participants, collected at four separate sites (National Institutes of Health, University of Pittsburgh, University of Oslo, Leiden University) spanning three countries (US, Norway, Netherlands). All datasets were collected using accelerated longitudinal designs. Each separate study was approved by a local review board. For the CPB dataset, participants and scans were selected from a pool of over 1,000 scans for their quality and number of time points per individual. For the PIT, NCD and BT datasets, respectively, 126, 111 and 299 participants were recruited and scanned at baseline. Of these, 20, 26 and 45 dropped out at follow up, and an additional 33, 9 and 45 were excluded based on the QC of the MRI data (see below). The final CPB, PIT, NCD and BT datasets included 30, 73, 76 and 209 participants, respectively. In total the present study includes 388 participants (199 females) and 854 scans covering the age-range 7-29 years old (Table 1). Details regarding participant recruitment have been described previously for each sample separately (Braams et al., 2015; Herting et al., 2014; Mills et al., 2014a; Tamnes et al., 2013) and together (Mills et al., 2016).

Image acquisition and processing

T1-weighted anatomical scans were obtained at four different sites using different scanners and sequences. Only key parameters are summarized here (see Table 1), as details regarding image acquisition at each site are described in detail in a previous publication (Mills et al., 2016). At each site, a radiologist reviewed all scans for gross abnormalities. Image processing was performed with FreeSurfer 5.3 (RRID:SCR_001847), which is documented and freely available online (http://surfer.nmr.mgh.harvard.edu/). The technical details of the procedures

158 are described in detail elsewhere (Dale et al., 1999; Fischl et al., 2002; Fischl et al., 1999).
159 The processing stream includes motion correction (Reuter et al., 2010), removal of non-brain
160 tissue using a hybrid watershed/surface deformation procedure (Segonne et al., 2004),
161 automated Talairach transformation, non-parametric non-uniform intensity normalization
162 (Sled et al., 1998), tessellation of the grey/white matter boundary, automated topology
163 correction (Fischl et al., 2001; Segonne et al., 2007), and surface deformation following
164 intensity gradients to optimally place the grey/white and grey/cerebrospinal fluid borders at
165 the location where the greatest shift in intensity defines the transition to the other tissue class
166 (Dale et al., 1999; Dale & Sereno, 1993; Fischl & Dale, 2000). Each cortical model was
167 registered to a spherical atlas using individual cortical folding patterns to match cortical
168 geometry across participants (Dale et al., 1999).
169
170 Images were then processed using FreeSurfer 5.3's longitudinal stream (Reuter et al., 2012).
171 This process includes the creation of an unbiased within-subject template space and image
172 using robust, inverse consistent registration (Reuter et al., 2010). Several processing steps,
173 such as skull stripping, Talairach transforms, atlas registration as well as spherical surface
174 maps and parcellations are then initialized with common information from the within-subject
175 template, significantly increasing reliability and statistical power (Reuter et al., 2012). The
176 QC procedure was coordinated across sites so that all images were visually inspected post-
177 processing by trained operators for accuracy, but no editing was performed.
178
179 Surface maps for cortical volume, surface area (white surface) and thickness, as well as
180 symmetrized annual percentage change (APC, i.e., the linear annual rate of change with
181 respect to the average volume/area/thickness measure across all available time points) over all
182 available observations for each measure, were generated and smoothed with a Gaussian

Kernel of full-width at half-maximum of 15 mm. Additionally, we computed global total cortical volume, total surface area and weighted mean thickness (with each label contributing to the mean according to its area) for each time point for each subject across all labels in the Desikan-Killiany cortical parcellation (Desikan et al., 2006), and APC for each of the measures. Similar variables were calculated for the frontal (including anterior cingulate), temporal (including insula), parietal (including posterior and retrosplenial cingulate) and occipital lobes, and for each label across both hemispheres.

Statistical analysis

First, spaghetti plots and longitudinal curve fitting was performed using the MMIL data portal (Bartsch et al., 2014; Vidal-Pineiro et al., 2016), which uses functions freely available through the statistical environment R (http://www.r-project.org/, RRID:SCR_001905). Cortical volume, surface area and thickness measures from each time point, adjusted for the effect of sex, were introduced as predicted variables in generalized additive mixed model (GAMM) analyses where the predictor was age, with k parameters specifying the stiffness of the model curves set to 5 (except for temporal lobe volume where 4 was used so the models would converge). The main effect of sex was adjusted for through linear mixed effect models. GAMM can be represented as the following formula: $G(y) = X^*\alpha + \sum_{j=1}^{p} f_j(x_j) + Zb + \varepsilon$ where G(·) is a monotonic differentiable link function; α the vector of regression coefficients for the fixed parameters; X^* the fixed effects matrix; f_j the smooth function of the covariate x_j; Z the random effects model matrix; b the vector of random effects coefficients and ε the residual error vector (Wood, 2006). GAMM fitting was visualized over its correspondent spaghetti plots. Estimated mean values across sex were used as display values. GAMM provides accurate delineations of developmental trajectories, as it avoids some of the inherent weaknesses of global polynomial models, e.g. quadratic and cubic models, where the timing

of peaks and the end-points of the trajectories may be substantially affected by irrelevant factors such as the age-range sampled (Fjell et al., 2010).

Second, as background analyses before testing for interrelationships between cortical volume, surface area and thickness, mean global and lobar APC values for each cortical measure for each sample were calculated, one-sample t-tests were used to test whether the APC values were significantly different from zero, and ANOVAs with Tukey HSD post-hoc comparisons were performed to test for sample differences. For each sample we then performed vertex-wise general linear models (GLMs) as implemented in FreeSurfer 5.3 testing whether APC for each of the measures were significantly different from zero, with sex, age (mean across time-points) and their interaction as covariates.

Third, regional relationships between changes in cortical volume, surface area and thickness were initially tested for by means of partial correlations between global and lobar APC in each measure, with sex and mean age as covariates. Then, a series of GLMs were performed in FreeSurfer to test for vertex-wise change-change relationships among the different measures across the cortical surface. APC maps for each measure were entered as per-vertex regressors of interest to the other measures, with sex, mean age and their interaction as covariates.

All regional (global and lobar) results were Bonferroni-corrected by a factor of 5 (reflecting the number of regions), corresponding to a corrected alpha of $p < .01$. For all vertex-wise analyses, the data were tested against an empirical null distribution of maximum cluster size across 10,000 iterations using Z Monte Carlo simulations as implemented in FreeSurfer (Hagler et al., 2006; Hayasaka & Nichols, 2003) synthesized with a cluster-forming threshold

of $p < 0.05$ (two-sided), yielding clusters fully corrected for multiple comparisons across the surfaces. Cluster-wise corrected $p < 0.05$ was regarded significant.

Results

Delineating cortical developmental trajectories

To accurately characterize longitudinal developmental trajectories, global (**Figure 1**) and lobar (**Figure 2**) cortical volume, surface area and thickness measures were visualized as spaghetti plots fitted with GAMM. Total cortical volume decreased across the whole age-range in all four samples, with slightly accelerated decreases in the adolescent period compared to late childhood and early adulthood. Total cortical surface area showed nearly linear decreases in all four samples, but appeared overall greater for the two European samples (NCD, BT) and also had a somewhat flatter slope for one of the US samples (CPB). Mean cortical thickness showed highly overlapping non-linear trajectories, with accelerated thinning in adolescence.

The lobar trajectories were overall similar to the global results, although some regional differences were also evident. For example, cortical volume showed a relatively stable trajectory in late childhood in the frontal lobe, and the accelerated thinning in adolescence was most clearly seen in the frontal lobe, while decelerating trajectories with increasing age were seen for thickness in the parietal and occipital lobes.

Mapping longitudinal cortical change

On average for each sample, and on both the global and lobar level, cortical volume, thickness and surface area all showed negative change rates, i.e. reductions with increasing age (**Table 2**, see **Table 3** for APC for all measures for all labels in the cortical parcellation). For the

global measures and within all four samples, cortical volume showed the largest decrease (APC from -1.10 to -1.87, sample mean = -1.43), followed by thickness (APC from -0.83 to -1.38, sample mean = -1.03), and lastly surface area (APC from -0.36 to -0.71, sample mean = -0.55). Although the ranking of APC in the different global measures was the same in all four samples, there were also significant sample differences in all three measures (see Table 2).

For the lobar measures, cortical volume consistently showed the same ranking of APC within all four samples, with largest decrease in the parietal lobe, followed by the frontal, the temporal and finally the occipital lobe. The parietal lobe also showed the largest decrease in both cortical surface area and thickness in all four samples, and the occipital lobe consistently showed the smallest decrease in cortical thickness. Except for frontal lobe volume and thickness and occipital lobe thickness, there were significant sample differences in the lobar APC values in all measures (see Table 2).

Vertex-wise surface maps were then created to visualize the statistical significance (controlling for sex and mean age) and rate of APC in cortical volume (**Figure 3**), surface area (**Figure 4**) and thickness (**Figure 5**) for each of the samples separately. Corrected significant negative changes were seen for all three measures for extensive portions of the cerebral cortex in all four samples. Some exceptions or sample differences were noted. For volume, significant increases or no effects were seen around the central sulcus and in insular, medial temporal, and medial occipital cortices. For surface area compared to the other two measures, more regions did not show significant APC, especially gyral regions in the three smaller samples. And finally, for thickness, the rate decrease in most regions was larger for the sample with a narrower age-range in adolescence (PIT), than for the other three samples. Note that the scale for rate of APC varies across the different measures.

283

284 ***Testing for interrelated changes in different cortical components***

285 Relationships between global and lobar changes in surface area and volume, and thickness
286 and volume were first tested with partial correlations, controlling for sex and mean age (**Table**
287 **4**). All samples showed large positive associations between thickness APC and volume APC
288 (*pr* from .72 to .95) for both global and all lobar measures. For global measures, the
289 associations between surface area APC and volume APC varied from small to medium (*pr*
290 from .16 to .55), while for the lobar measures medium-to-large positive associations (*pr* from
291 .51 to .76) were seen in the frontal lobe in three of the samples (PIT, NCD, BT), in the
292 temporal lobe in two samples (NCD, BT) and in the parietal lobe in one sample (PIT).

293

294 The results from the per-vertex regression models (controlling for sex and mean age) of
295 surface area APC and volume APC and thickness APC and volume APC, respectively,
296 confirmed these general patterns (**Figure 6**). Highly significant positive associations between
297 thickness change and volume change were observed across nearly the entire cerebral cortex in
298 all four samples. In comparison, the associations between area change and volume change
299 were not as strong or widespread, and in several regions in two of the samples (NCD, BT)
300 even in the opposite direction (i.e. negative).

301

302 Interrelationships between APC in cortical surface area and APC in cortical thickness were
303 first tested on global and lobar measures with partial correlations, controlling for sex and
304 mean age (**Table 5**). For the global measures, a significant small positive association (*pr* =
305 .22) was seen in the largest sample (BT). For the lobar measures, significant small-to-medium
306 positive associations (*pr* from .21 to .52) were seen for the frontal lobe in three samples (PIT,
307 NCD, BT) and for the temporal lobe in two samples (NCD, BT), while significant medium

negative associations (*pr* from -.46 to -.48) were seen for the occipital lobe in two samples (PIT, BT). Inconsistent with the other samples, the CPB sample showed negative, although non-significant, associations for the frontal and temporal lobe measures, possibly related to the younger average baseline age of this sample.

To investigate these regional differences in more detail, per-vertex regression models (controlling for sex and mean age) of surface area APC and thickness APC were performed (**Figure 7**). In all four samples, positive associations were observed in lateral prefrontal and temporal cortices, while negative associations were seen around the central sulcus, and in paracentral, insular and both lateral and medial occipital cortices. Generally, the negative associations were more widespread than the positive. Importantly, the vertex-wise results also revealed a complex topographic pattern of positive and negative associations, with positive relations mainly seen in sulcal regions and negative relations seen in gyral and insular regions. The exact location of some of the relations between surface area APC and thickness APC did however vary across samples, e.g. three samples (CPB, NCD, BT) showed positive associations in the superior temporal sulcus, while one sample (PIT) showed positive associations in the middle and interior temporal cortices. Also, the extent of both the positive and negative associations appeared to be related to sample size, with the spatially most limited effects seen in the CPB sample and the most widespread effects, especially negative associations, seen in the BT sample. In the three smallest samples (CPB, PIT, NCD), the majority of vertices did not show significant associations.

Discussion

The current multisample neuroimaging study aimed to examine the development of the human cerebral cortex across adolescence in four independent longitudinal samples. The

results were generally consistent across samples and showed: 1) widespread and regionally variable non-linear decreases in cortical volume and thickness with increasing age, and comparatively smaller steady decreases in surface area; 2) that the dominant contributor to cortical volume reductions during adolescence is cortical thinning; and 3) complex regional and topological patterns of relationships between longitudinal changes in surface area and thickness. Together, the results increase confidence in conclusions about structural cortical development and provide novel insight into how changes in distinct cortical components are linked.

In the first two years of life, cortical volume, surface area and thickness all increase over time (Gilmore et al., 2012; Lyall et al., 2015). There is a near complete lack of data for the following years of early childhood due to head motion-related MRI artifacts, and there are inconsistencies across studies regarding developmental patterns and trajectories of different structural measures from mid-childhood to adulthood (Mills & Tamnes, 2014; Walhovd et al., 2016). Early longitudinal studies suggested continued increases in cortical volume until late childhood or early adolescence (Giedd et al., 1999; Lenroot et al., 2007; Raznahan et al., 2011), while later longitudinal studies (Aubert-Broche et al., 2013; Lebel & Beaulieu, 2011; Mills et al., 2016; Mills et al., 2014b; Tamnes et al., 2013; Wierenga et al., 2014), as well as the current results, indicate that cortical volume is at its highest earlier in childhood and decreases in late childhood and throughout adolescence.

Previous longitudinal studies are particularly conflicting with regard to cortical thickness, with some indicating inverted-U trajectories from childhood to adulthood, with estimates of peak thickness in late childhood (Raznahan et al., 2011; Shaw et al., 2007; Shaw et al., 2008), while others show widespread monotonic decreases during childhood and adolescence

(Alexander-Bloch et al., 2014; Ducharme et al., 2015b; Fjell et al., 2015; Mills et al., 2014b; Mutlu et al., 2013; Shaw et al., 2006; Sowell et al., 2004; van Soelen et al., 2012; Vijayakumar et al., 2016; Wierenga et al., 2014; Zhou et al., 2015; Zielinski et al., 2014). Our results support the conclusion of decreasing cortical thickness with increasing age during late childhood and across adolescence. Fewer longitudinal studies have investigated cortical surface area, but with the exception of one recent paper showing increases in adolescence (Vijayakumar et al., 2016), these (Ducharme et al., 2015a; Mills et al., 2014b; Raznahan et al., 2011; Wierenga et al., 2014) and the present results together support the conclusion of childhood increases followed by subtle decreases during adolescence.

After applying similar processing and analytic techniques, the results of the present multisample study showed consistent developmental patterns and trajectories for cortical structure across four longitudinal datasets with varying sample and image acquisition characteristics. We did not observe any global increase or "peak" for cortical volume, surface area or thickness from ages 7 to 29 in any of the four samples. The same was true for the lobar measures, except for a small early increase in frontal lobe volume in two of the samples. Our results suggest that previous inconsistencies have not primarily resulted from sample or image acquisition differences. Rather, we speculate that they stem from the combined effects of differences in image processing, including QC procedures, and/or statistical analyses and curve fitting. All datasets in the present study were processed with an extensively used and well validated open source software suite (Fischl, 2012), underwent post-processing QC, and curve-fitting was performed with models that avoid some of the weaknesses of global polynomial models.

In both adult and developmental samples, head motion has a negative effect on estimates of cortical volume and thickness, even after excluding low-quality scans (Alexander-Bloch et al., 2016; Reuter et al., 2015). As younger participants generally move more during acquisition, motion is often confounded with age or time-point (Satterthwaite et al., 2012). The importance of post-processing QC was demonstrated by Ducharme et al. (2015b), who showed that exclusion of scans defined as QC failures had a large impact on identified patterns for cortical thickness development, with a shift towards more complex trajectories when scans of lower quality were included. While we attempted to limit the impact of motion by visually inspecting all reconstructed images and only included scans judged to be of adequate quality, future studies might benefit from further efforts to limit motion during data acquisition, for example by further development of on-line motion correction procedures and quantitative motion assessment within popular software packages (Greene et al., 2016; Reuter et al., 2015; Tisdall et al., 2015). Additionally, it is likely that differences in statistical analyses may have contributed to the inconsistencies, as we recently showed that whether and how one controls for intracranial volume or total brain size influences developmental models of brain volumes (Mills et al., 2016). Related to this, future studies are needed to investigate the consistency of reported sex differences in brain structure and development (e.g. (Lenroot et al., 2007; Mutlu et al., 2013; Vijayakumar et al., 2016), using both raw and corrected measures (see e.g. (Marwha et al., 2017)).

In addition to providing detailed descriptions of developmental patterns and trajectories of cortical structure, our results also showed consistent and very strong positive relationships between cortical thickness change and volume change across nearly the entire cortex, such that relatively large reductions in thickness were associated with relatively large reductions in volume. In comparison, the relationships between surface area change and volume change

were not as strong or widespread, and for most of the occipital lobe either non-significant or negative. Thus, although most of the individual variation in adult cortical volume is due to variation in surface area and not thickness (Im et al., 2008), our results show that the greatest contributor to volume decrease from 7 to 29 years is thinning, as previously also shown to be the case across the adult lifespan (23-87 years) (Storsve et al., 2014).

Finally, complex regional and topological patterns in the relationships between surface area change and thickness change were observed. Across samples, both positive and negative associations were found, with positive relationships mainly seen in sulcal regions in prefrontal and temporal cortices, and negative relationships mainly seen in gyral regions in occipital cortices, paracentral cortex and insula, and around the central sulcus. Our results mainly showed decreases with increasing age for both surface area and thickness. Thus, positive relationships indicate that relatively large reductions in surface area are associated with relatively large reductions in thickness, while negative relationships indicate that relatively large reductions in surface area are associated with relatively small reductions in thickness, and vice versa. The importance of local topology for cortical development was demonstrated in a recent large cross-sectional study finding that age-related decreases in thickness were most pronounced in the sulci (Vandekar et al., 2015), but no previous study has examined the relationships between longitudinal change in different cortical metrics on a vertex-wise level in children and adolescents (but see (Storsve et al., 2014) for a study on adults and (Aleman-Gomez et al., 2013) for lobar analyses in adolescents).

The cellular and molecular changes underlying observed developmental changes in the different dimensions of the cerebral cortex and their interrelationships remain unknown. They likely include multiple interacting processes that vary in their relative importance across

regions and age (Mills & Tamnes, 2014). A recent imaging study suggests that increasing intra-cortical myelination is a significant driver of cortical changes in adolescence (Whitaker et al., 2016). A hypothesis for the relationships between area change and thickness change in development is that white matter growth in the form of increasing myelination and axon caliber (Benes, 1989; Benes et al., 1994; Yakovlev & Lecours, 1967) causes the cerebral cortex to stretch tangentially to the surface, expanding its area and becoming thinner, as well as improving its ability to differentiate incoming signals (Seldon, 2005, 2007). However, this does not fully explain the surface area decease seen in many regions in adolescence. A second hypothesis is that synaptic pruning and dendritic arborization (Bourgeois & Rakic, 1993; Huttenlocher & Dabholkar, 1997; Petanjek et al., 2011) results in decreasing gyrification and flattening of the cortex during adolescence (Aleman-Gomez et al., 2013; Klein et al., 2014; Raznahan et al., 2011) due to release of axonal tension (White et al., 2010). It is likely that a combination of these hypotheses might explain the observed complex patterns in the relationships between surface area change and thickness change.

Conclusion

The present results from four independent longitudinal datasets showed consistent developmental trajectories and patterns of change in cortical volume, surface area and thickness across adolescence. Regionally variable non-linear decreases in cortical volume and thickness, and relatively smaller steady decreases in surface area, were observed from ages 7 to 29. Further, analyses of the interrelationships between changes in these different dimensions of the cortex revealed tight links between volume reductions and thinning, as well as regional and topological patterns in the relationships between surface area change and thickness change.

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688 **Figure Legends**

689 Figure 1. Developmental trajectories for global cortical measures. Spaghetti plots of mean
690 cortical thickness, total cortical surface area and total cortical volume, controlling for sex. The
691 colored lines represent the GAMM fitting while the lighter colored areas correspond to the
692 95% confidence intervals. Pink: CPB (Child Psychiatry Branch, National Institutes of Health);
693 Purple: PIT (Pittsburgh, University of Pittsburgh); Blue: NCD (Neurocognitive Development,
694 University of Oslo); Green: BT (Braintime, Leiden University).
695
696 Figure 2. Developmental trajectories for lobar cortical measures. Spaghetti plots of lobar
697 cortical thickness, surface area and volume, controlling for sex. The colored lines represent
698 the GAMM fitting while the lighter colored areas correspond to the 95% confidence intervals.
699 Pink: CPB (Child Psychiatry Branch, National Institutes of Health); Purple: PIT (Pittsburgh,
700 University of Pittsburgh); Blue: NCD (Neurocognitive Development, University of Oslo);
701 Green: BT (Braintime, Leiden University).
702
703 Figure 3. Longitudinal change in cortical volume. General linear models were used to test the
704 statistical significance of annual percentage change (APC) in volume across the brain surface
705 in each sample, with sex and mean age included as covariates. The results were corrected for
706 multiple comparisons using cluster size inference. Uncorrected p values within the corrected
707 significant clusters are shown in the left panel, and rates of change are shown in the right
708 panel. Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh,
709 University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT:
710 Braintime, Leiden University.
711

Figure 4. Longitudinal change in cortical surface area. General linear models were used to test the statistical significance of annual percentage change (APC) in area across the brain surface in each sample, with sex and mean age included as covariates. The results were corrected for multiple comparisons using cluster size inference. Uncorrected p values within the corrected significant clusters are shown in the left panel, and rates of change are shown in the right panel. Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT: Braintime, Leiden University.

Figure 5. Longitudinal change in cortical thickness. General linear models were used to test the statistical significance of annual percentage change (APC) in thickness across the brain surface in each sample, with sex and mean age included as covariates. The results were corrected for multiple comparisons using cluster size inference. Uncorrected p values within the corrected significant clusters are shown in the left panel, and rates of change are shown in the right panel. Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT: Braintime, Leiden University.

Figure 6. Relationships between change in surface area and thickness and change in volume. Vertex-wise p-value maps from general linear models testing the relationships between symmetrized annual percentage change (APC) in different cortical measures, with sex and mean age included as covariates. The results were corrected for multiple comparisons using cluster size inference. Uncorrected p values within the corrected significant clusters are shown. Red-yellow reflects a positive relationship, where a relatively large decrease in one measure is associated with a relatively large decrease in the other measure. Blue-cyan reflects

a negative relationship, in which a relatively large decrease on one measure is associated with a relatively small decrease or increase on the other measure. Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT: Braintime, Leiden University.

Figure 7. Relationships between change in surface area and change in thickness. Vertex-wise p-value maps from general linear models testing the relationships between symmetrized annual percentage change (APC) in different cortical measures, with sex and mean age included as covariates. The results were corrected for multiple comparisons using cluster size inference. Uncorrected p values within the corrected significant clusters are shown. Red-yellow reflects a positive relationship, where a relatively large decrease in one measure is associated with a relatively large decrease in the other measure. Blue-cyan reflects a negative relationship, in which a relatively large decrease on one measure is associated with a relatively small decrease or increase on the other measure. Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT: Braintime, Leiden University.

Tables

Table 1. Participant demographics and MRI acquisition parameters for each sample

	CPB	PIT	NCD	BT
N participants (females)	30 (9)	73 (41)	76 (37)	209 (112)
Age mean (SD)[a]	15.6 (1.7)	13.4 (0.9)	15.2 (3.3)	15.7 (3.6)
Age range	7.0 – 29.9	10.1 – 16.2	8.2 – 21.9	8.0 – 26.6
N scans (individual range)	138 (3 – 6)	146 (2)	152 (2)	418 (2)
Scan interval mean (SD)	3.7 (2.2)	2.2 (0.4)	2.6 (0.2)	2.0 (0.1)
Scan interval range	1.1 – 14.0	1.5 – 3.7	2.4 – 3.2	1.6 – 2.5
Scanner	GE Signa 1.5T	Siemens Allegra 3T	Siemens Avanto 1.5T	Philips Achieva 3T
Repetition time (TR), ms	2400	1540	2400	9.76
Echo time (TE), ms	5.00	3.04	3.61	4.59
Voxel-size, mm	.938 × .938 × 1.5	1.0 × 1.0 × 1.0	1.25 × 1.25 × 1.20	.875 × .875 × 1.2

Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT: Braintime, Leiden University. [a] mean across available time-points

Table 2. Global and lobar change in cortical volume, surface area and thickness for each sample

	CPB	PIT	NCD	BT	Sample differences
Cortical volume	-1.10	-1.87	-1.15	-1.60	CPB-PIT, PIT-NCD, NCD-BT
Frontal lobe	-1.04	-1.67	-1.08	-1.60	
Temporal lobe	-0.88	-1.65	-0.99	-1.32	CPB-PIT, PIT-NCD
Parietal lobe	-1.54	-2.53	-1.49	-1.98	CPB-PIT, PIT-NCD, PIT-BT, NCD-BT
Occipital lobe	-0.61	-1.31	-0.84	-1.28	CPB-PIT, CPB-BT, NCD-BT
Cortical surface area	-0.36	-0.61	-0.53	-0.71	CPB-PIT, CPB-BT, NCD-BT
Frontal lobe	-0.29	-0.48	-0.47	-0.61	CPB-BT
Temporal lobe	-0.31	-0.52	-0.43	-0.59	CPB-BT
Parietal lobe	-0.50	-0.90	-0.71	-0.87	CPB-PIT, CPB-BT
Occipital lobe	-0.34	-0.46	-0.47	-0.85	CPB-BT, PII-BT NCD-BT
Cortical thickness	-0.93	-1.38	-0.83	-0.98	PIT-NCD, PIT-BT
Frontal lobe	-0.93	-1.29	-0.83	-0.99	
Temporal lobe	-0.89	-1.43	-0.82	-0.90	PIT-NCD, PIT-BT
Parietal lobe	-1.15	-1.63	-0.94	-1.17	PIT-NCD, PIT-BT
Occipital lobe	-0.45	-0.90	-0.58	-0.66	

Values displayed are mean symmetrized annual percentage change (APC) for each measure. Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT: Braintime, Leiden University. All APC values were significantly different from zero ($p < .001$). Differences among the samples were tested with ANOVAs ($p < .05$, Bonferroni-corrected, factor of 5) with Tukey HSD post-hoc comparisons ($p < .05$) and those showing significant differences are listed in the far right column.

767 Table 3. Regional change in cortical volume, surface area and thickness for each sample

	Cortical volume				Cortical surface area				Cortical thickness			
	CPB	PIT	NCD	BT	CPB	PIT	NCD	BT	CPB	PIT	NCD	BT
Frontal, superior	-1.04	-1.63	-0.99	-1.66	-0.21	-0.33	-0.36	-0.50	-0.92	-1.36	-0.80	-1.09
Frontal, rostral middle	-1.27	-2.14	-1.42	-2.12	-0.52	-0.74	-0.64	-0.79	-1.25	-1.73	-1.26	-1.34
Frontal, caudal middle	-1.38	-2.09	-1.55	-1.90	-0.54	-0.79	-0.83	-0.80	-0.94	-1.24	-0.87	-1.02
Frontal, lateral orbital	-1.02	-1.78	-1.14	-1.29	-0.14	-0.62	-0.38	-0.34	-0.93	-1.27	-0.78	-0.91
Frontal, pars orbitalis	-1.06	-1.67	-1.12	-1.65	-0.26	-0.45	-0.47	-0.95	-0.93	-1.19	-0.71	-0.87
Frontal, pars triangularis	-0.96	-1.74	-0.99	-1.70	-0.06	-0.26	-0.24	-0.62	-1.02	-1.49	-0.96	-1.15
Frontal, pars opercularis	-1.02	-1.66	-1.15	-1.51	-0.28	-0.46	-0.47	-0.50	-0.95	-1.28	-0.86	-1.00
Frontal, precentral	-0.55	-1.24	-0.57	-1.07	-0.20	-0.36	-0.42	-0.50	-0.41	-0.78	-0.28	-0.55
Frontal, pole	-0.42	-0.95	0.17	-2.38	-0.32	-0.58	0.31	-1.52	-0.54	-0.77	-0.45	-0.89
Frontal, medial orbital	-1.12	-1.26	-1.46	-1.33	-0.18	-0.29	-0.55	-0.62	-1.08	-1.01	-1.06	-0.79
Frontal, rostral anterior cingulate	-1.07	-0.40	-0.44	-0.82	-0.22	-0.02	-0.15	-0.40	-1.14	-1.08	-0.68	-0.49
Frontal, caudal anterior cingulate	-1.11	-1.06	-1.08	-1.26	-0.29	-0.08	-0.26	-0.31	-1.05	-1.08	-1.03	-1.05
Frontal, paracentral	-1.33	-2.15	-1.36	-1.62	-0.41	-0.70	-0.62	-0.92	-1.01	-1.69	-0.95	-1.07
Temporal, superior	-0.73	-1.59	-0.80	-1.28	-0.22	-0.37	-0.26	-0.56	-0.79	-1.35	-0.76	-0.82
Temporal, middle	-0.74	-1.50	-0.92	-1.42	-0.19	-0.34	-0.26	-0.52	-1.07	-1.64	-1.06	-1.06
Temporal, inferior	-0.98	-1.90	-1.31	-1.52	-0.38	-0.66	-0.51	-0.65	-1.02	-1.69	-1.06	-1.01
Temporal, banks sup. temp. sulcus	-2.06	-3.12	-1.91	-2.06	-0.76	-1.23	-1.02	-0.84	-1.91	-2.45	-1.32	-1.57
Temporal, transverse	-1.27	-1.91	-1.36	-1.47	-0.45	-1.08	-0.95	-1.21	-0.71	-0.75	-0.51	-0.49
Temporal, pole	0.28	-0.85	0.59	0.01	0.02	-0.28	0.27	-0.07	0.14	-0.66	0.13	0.09
Temporal, entorhinal	-0.43	-0.45	-0.56	-0.25	-0.36	-0.22	-0.40	-0.34	0.07	-0.13	0.08	0.11
Temporal, parahippocampal	-1.32	-1.77	-0.83	-1.20	-0.29	-0.51	-0.27	-0.52	-1.03	-1.49	-0.62	-0.81
Temporal, fusiform	-1.28	-2.02	-1.19	-1.50	-0.23	-0.43	-0.38	-0.64	-1.04	-1.53	-0.82	-0.95
Temporal, insula	-0.58	-0.94	-0.85	-1.12	-0.46	-0.62	-0.76	-0.54	-0.54	-0.95	-0.53	-0.92
Parietal, superior	-1.64	-2.58	-1.45	-2.02	-0.55	-0.83	-0.80	-0.93	-1.18	-1.66	-0.83	-1.08
Parietal, inferior	-1.65	-2.58	-1.67	-2.15	-0.53	-1.01	-0.82	-0.88	-1.34	-1.72	-1.05	-1.32
Parietal, supramarginal	-1.48	-2.71	-1.53	-2.01	-0.51	-1.01	-0.71	-0.86	-1.07	-1.64	-0.93	-1.14

Parietal, postcentral	-1.23	-2.26	-1.27	-1.64	-0.42	-0.73	-0.57	-0.96	-0.77	-1.22	-0.74	-0.74
Parietal, precuneus	-1.60	-2.65	-1.44	-1.99	-0.46	-0.90	-0.64	-0.78	-1.26	-1.92	-0.99	-1.42
Parietal, posterior cingulate	-1.52	-2.17	-1.45	-1.78	-0.57	-0.90	-0.57	-0.59	-1.18	-1.54	-1.05	-1.34
Parietal, retrosplenial cingulate	-1.46	-2.37	-1.64	-2.08	-0.44	-0.98	-0.54	-0.73	-1.07	-1.45	-1.16	-1.41
Occipital, lateral	-0.48	-1.38	-0.97	-1.43	-0.55	-0.36	-0.51	-1.03	-0.30	-1.12	-0.81	-0.72
Occipital, cuneus	-0.94	-1.36	-0.90	-1.36	-0.37	-0.58	-0.54	-0.80	-0.72	-0.94	-0.53	-0.84
Occipital, pericalcarine	0.05	0.35	0.37	0.11	0.17	-0.08	-0.23	-0.33	-0.21	0.21	0.25	0.17
Occipital, lingual	-0.89	-1.69	-0.99	-1.39	-0.20	-0.72	-0.48	-0.84	-0.62	-0.91	-0.50	-0.67

Values displayed are mean symmetrized annual percentage change (APC) for each measure. Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT: Braintime, Leiden University.

Table 4. Relationships between changes in a) surface area and volume and b) thickness and volume, for each sample

a) Surface area change – Volume change

	CPB	PIT	NCD	BT
Global cortex	.16 (.427)	**.47** (<.001)	**.55** (<.001)	**.51** (<.001)
Frontal lobe	.26 (.179)	**.68** (<.001)	**.69** (<.001)	**.51** (<.001)
Temporal lobe	.04 (.827)	**.37** (.002)	**.69** (<.001)	**.52** (<.001)
Parietal lobe	.00 (.985)	**.76** (<.001)	**.33** (.005)	**.29** (<.001)
Occipital lobe	.37 (.056)	.07 (.543)	.01 (.922)	-.07 (.304)

b) Thickness change – Volume change

	CPB	PIT	NCD	BT
Global cortex	**.87** (<.001)	**.85** (<.001)	**.93** (<.001)	**.93** (<.001)
Frontal lobe	**.86** (<.001)	**.87** (<.001)	**.94** (<.001)	**.93** (<.001)
Temporal lobe	**.90** (<.001)	**.95** (<.001)	**.95** (<.001)	**.92** (<.001)
Parietal lobe	**.90** (<.001)	**.72** (<.001)	**.91** (<.001)	**.93** (<.001)
Occipital lobe	**.82** (<.001)	**.79** (<.001)	**.94** (<.001)	**.89** (<.001)

Values displayed are partial correlations between symmetrized annual percentage change (APC) in different cortical measures, controlling for sex and age, with p-values in parentheses. Bold: $p < .05$ (Bonferroni-corrected, factor of 5). Samples: CPB: Child Psychiatry Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT: Braintime, Leiden University.

778 Table 5. Global and lobar relationships between changes in cortical surface area and thickness for each sample

Surface area change – Thickness change				
	CPB	PIT	NCD	BT
Global cortex	-.23 (.231)	.03 (.827)	.30 (.011)	**.22** (.001)
Frontal lobe	-.13 (.524)	**.38** (.001)	**.49** (<.001)	**.21** (.002)
Temporal lobe	-.21 (.278)	.15 (.219)	**.52** (<.001)	**.23** (.001)
Parietal lobe	-.32 (.098)	.18 (.143)	-.01 (.940)	-.03 (.656)
Occipital lobe	-.18 (.374)	**-.46** (<.001)	-.28 (.014)	**-.48** (<.001)

779 Values displayed are partial correlations between symmetrized annual percentage change (APC) in cortical surface area and thickness,
780 controlling for sex and age, with p-values in parentheses. Bold: $p < .05$ (Bonferroni-corrected, factor of 5). Samples: CPB: Child Psychiatry
781 Branch, National Institutes of Health; PIT: Pittsburgh, University of Pittsburgh; NCD: Neurocognitive Development, University of Oslo; BT:
782 Braintime, Leiden University.
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