Development and aging of cortical thickness correspond to genetic organization patterns

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There is a growing realization that early life influences have lasting impact on brain function and structure. Recent research has demonstrated that genetic relationships in adults can be used to parcellate the cortex into regions of maximal shared genetic influence, and a major hypothesis is that genetically programmed neurodevelopmental events cause a lasting impact on the organization of the cerebral cortex observable decades later. Here we tested how developmental and lifespan changes in cortical thickness fit the underlying genetic organizational principles of cortical thickness in a longitudinal sample of 974 participants between 4.1 and 88.5 y of age with a total of 1,633 scans, including 773 scans from children below 12 y. Genetic clustering of cortical thickness was based on an independent dataset of 406 adult twins. Developmental and adult age-related changes in cortical thickness followed closely the genetic organization of the cerebral cortex, with change rates varying as a function of genetic similarity between regions. Cortical regions with overlapping genetic architecture showed correlated developmental and adult age change trajectories and vice versa for regions with low genetic overlap. Thus, effects of genes on regional variations in cortical thickness in middle age can be traced to regional differences in neurodevelopmental change rates and extrapolated to further adult aging-related cortical thinning. This finding suggests that genetic factors contribute to cortical changes through life and calls for a lifespan perspective in research aimed at identifying the genetic and environmental determinants of cortical development and aging.

genetic | cerebral cortex | magnetic resonance imaging | aging | development

There is a growing realization that events during development impact brain and cognition throughout the entire lifespan (1). For instance, the major portion of the relationship between cortical thickness and IQ in old age can be explained by childhood IQ (2), and genotype may explain a substantial part of the lifetime stability in intelligence (3). Effects of genes on the organization of the cortex have been shown in adults (4–6), but it is unknown whether and how regional differences in cortical development correspond to these regional genetic subdivisions.

Although consensus has not been reached for the exact trajectories, cortical thickness as measured by MRI appears to decrease in childhood (7–12). The exact foundation for this thinning is not known, as MRI provides merely representations of the underlying neurobiology, and available histological data cannot with certainty be used to guide interpretations of MRI results. Although speculative, apparent thickness decrease may be grounded in factors such as synaptic pruning and intracortical myelination, although the link between established synaptic processes (13–15) and cortical thickness has not been empirically confirmed. After childhood, cortical thinning continues throughout the remainder of the lifespan, speculated to reflect neuronal shrinkage and reductions in number of spines and synapses (16), although similar to development, we lack data to support a direct connection between cortical thinning and specific neurobiological events.

It has been demonstrated that genetic correlations between thickness in different surface locations can be used to parcellate the adult cortex into regions of maximal shared genetic influence (4). This result can be interpreted according to the hypothesis that genetically programmed neurodevelopmental events cause lasting impact on the organization of the cerebral cortex detectable decades later (4–6). Here we tested how developmental and lifespan changes fit the genetic organization of cortical thickness in a large longitudinal sample with 1,633 scans from 974 participants between 4.1 and 88.5 y of age, including 773 scans from children below 12 y Genetically based subdivisions of cortical thickness from an independent dataset of 406 twins (4) were applied to the data, yielding 12 separate regions under maximum control of shared genetic

Significance

Here we show that developmental and adult aging-related changes in cortical thickness follow closely the genetic organization of the cerebral cortex. A total of 1,633 MRI scans from 974 participants from 4.1 to 88.5 y of age were used to measure longitudinal changes in cortical thickness, and the topographic pattern of change was compared with the genetic relationship between cortical subdivisions of maximal shared genetic influence, obtained from an independent sample of 406 middle-aged twins. Cortical changes due to maturation and adult age changes adhered to the genetic organization of the cortex, indicating that individual differences in cortical architecture in middle-aged adults have a neurodevelopmental origin and that genetic factors affect cortical changes through life.

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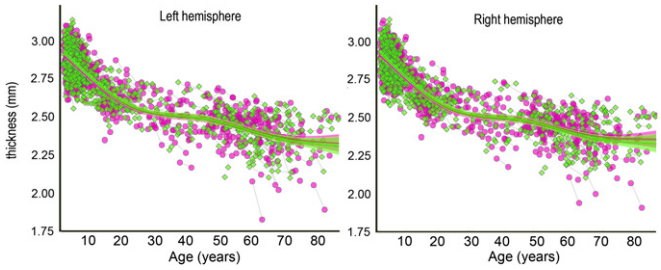

Fig. 1. Global change in cortical thickness. GAMM was used to estimate the lifespan trajectory of cortical thickness separately for each hemisphere, based on both the cross-sectional and the longitudinal information in the 1,633 observations in the total sample. The shaded area around the fit line represents the 95% CI. Green signifies female and pink signifies male.

influences. We hypothesized that thickness in cortical regions with overlapping genetic architecture would show similar developmental and adult age change trajectories and dissimilar trajectories for regions with low genetic overlap.

Results

Across the full age range of 4.1–88.5 y, taking advantage of all longitudinal and cross-sectional observations, generalized additive mixed models (GAMMs) were used to fit mean thickness in each hemisphere to age, revealing a high rate of decrease for the first 20 y of life, followed by a more or less steady rate of thinning ($P < 0.001$ for the smooth effect of age; Fig. 1). A linear function yielded a much poorer fit, as evidenced by increases in Akaike's information criterion (AIC) and Bayesian IC (BIC) > 10. Sex did not contribute significantly to the model and was therefore not included in further analyses.

The sample was then divided into three age groups: <20 y (1,021 scans of 644 participants, mean age at baseline 9.18 y), 20–50 y (234 scans, 136 participants, mean age 35.16 y), and >50 y (378 scans of 194 participants, mean age 64.75 y). Within each group, all available scans were used, and a linear mixed effect model (LME) (17) was fitted to the data, revealing highly significant thinning over time in each group, controlled for multiple comparisons (Fig. 2). A smoothing spline approach was used to estimate annual percent change (APC) in thickness (Fig. 3), which exceeded −1.0% for the youngest participants, whereas APC during the remainder of the lifespan typically was between −0.1 and −0.5 depending on region.

GAMM was then used to fit thickness to age in each of the 12 genetically defined cortical clusters (Fig. 4). All clusters showed monotonic thickness reductions throughout the age span. To test the extent to which regional variations in longitudinal changes in cortical thickness in development and adulthood resembled the genetic architecture of regional cortical thickness, the mean APC in thickness was calculated for each cluster for the children (<20 y) and the adults (≥20 y) separately and was correlated across all clusters with mean APC across all clusters regressed out. Correlations maps for cortical thickness development and adult age changes were highly similar to the genetic correlations between clusters, i.e., reflecting the genetic relationships among them. The Mantel test confirmed that the relationships between the genetic correlation matrix and the developmental change matrix (observed $r^2 = 0.80$, $P < 10e^{-5}$) and the adult age change matrix (observed $r^2 = 0.82$, $P < 10e^{-5}$) were indeed highly significant. The Louvain algorithm for detecting communities in networks was applied to further investigate the similarities between the correlation matrices. The algorithm finds the optimal community structure in each correlation matrix separately. Four identical regions were identified for development and genetic organization. The first four clusters, motor/premotor/supplementary motor area, superior and inferior parietal, and perisylvian cortex, were grouped together in a superior structure around the central sulcus; the occipital and the ventromedial clusters were grouped together in a posterior structure; and the dorsolateral and medial prefrontal cortex were grouped in a frontal structure. Interestingly, the ventral frontal cortex was grouped together with the three temporal clusters. For adult changes, the Louvain algorithm suggested a slightly different organization (*SI Text*). Inspection of the correlation matrices revealed that also in adulthood and aging, all of the same clusters were correlated, indicating that were no qualitative differences between development, adult age changes, and genetic organization with regard to the structure of the correlation matrix. One possible exception was that, in contrast to development and genetic organization, the ventral frontal cortex did not correlate with the medial temporal cortex in adults. We also ran the adult analyses restricted to those participants above 50 y to obtain a more typical aging sample and found that the resulting matrix was very similar to the one obtained with the full adult sample ($r^2 = 0.99$, $P < 10e^{-5}$; *SI Text*). The analyses were also run without mean APC regressed out, again yielding correlation matrices highly similar to the genetic clustering ($Ps < 10e^{-5}$).

Discussion

We found monotonic thinning of the cerebral cortex from 4.1 y throughout the lifespan up to 88.5 y. Neurodevelopmental and adult aging-related changes in cortical thickness followed closely the genetic organization of the cortex, with change rates varying as a function of genetic similarity. This result indicates early impact of genes on brain development and age-related changes later in life. The findings are discussed in detail below.

Cortical Thinning Throughout the Lifespan. We observed thinning across the entire cortex throughout the age range from 4.1 to 88.5 y. This finding is in contrast to earlier findings of regional developmental increases through preschool and early school years before later thinning (10–12, 18–22). However, the results are in line with other recent studies, suggesting monotonic cortical thinning from an early age (7–9, 23–28) and also in agreement with recently published studies of infants observing that cortical thickness in many regions may peak before 1 or at least 2 y of age (29, 30). The present findings may indicate that individual differences in offset and/or rate of thinning would be more relevant measures of cortical development than timing of peak cortical thickness. Several recent studies have found thinner cortex to be predictive of favorable cognitive development in school age years in a variety of cognitive domains (31–37), as well as in neurodevelopmental conditions such as schizophrenia (28, 38). However, it is important to note that also positive associations between cognitive function and cortical thickness have been found in childhood and adolescence (39, 40) and that symptoms of neurodevelopmental conditions and risk factors have been associated with thinner cortex as well (41–44), even in age-varying ways (45, 46) [see Vuoksimaa et al. for a more in-depth discussion on the relationship between cortical thickness and general cognitive abilities (47)]. These different effects may be due to offset differences between groups and/or differences in change rates and indicate a complex relationship between symptoms and cortical developmental markers (48, 49) that likely depends on the condition in question, cortical region, and age.

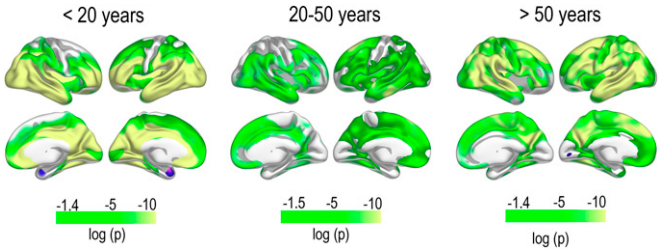

Fig. 2. Regional change in cortical thickness. Thinning of the cerebral cortex as tested LME using all cross-sectional and longitudinal data. Results are thresholded at false discovery rate <0.05 to control for familywise errors; thus, the left end of the *P* value scale will vary slightly between age groups and hemispheres.

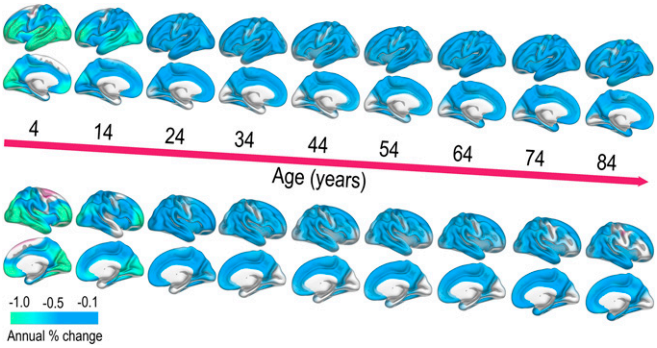

Fig. 3. Annual percent thickness decrease across the lifespan. APC in cortical thickness was estimated from a surface-based smoothing spline function, yielding APC estimates at each decade from 4 y. (*Upper*) Left hemisphere. (*Lower*) Right hemisphere. Blue-cyan colors indicate thinning.

The underlying neurobiological mechanisms of developmental changes in apparent cortical thickness are complex and involve processes that could lead to early postnatal thickness increase, such as proliferation of dendrites, dendritic spines, axonal sprouting, and vascular development, and also processes that would lead to apparent thinning, such as synaptic pruning and intracortical myelination (13–15, 50, 51). The latter could move the boundary detected in MRI between the gray and the white matter outward to the brain surface, thereby causing apparent thinning of the MRI-reconstructed cortex.

With increasing age, other processes come into play causing further thinning (16). Although neuronal number is likely not reduced at any age presently studied, reductions in the number of synaptic spines and synapses may be ongoing in older age at a level where functional consequences are not positive, and shrinkage of cell bodies is another candidate factor underlying cortical thinning in aging (52–54). We have previously reported a mixture of overlapping and spatially distinct patterns of change in maturation and older age (55) and identified a structural brain network sensitive to both (56). Importantly, however, the cognitive correlates of cortical changes are often different in development and aging, as cortical thickness has been more positively associated with cognitive function in older age (57–60). The impact on cognitive function of the observed cortical thinning seems at least partly different across aging and development, suggesting that either different neurobiological processes are at play or that the same processes have different consequences in opposite ends of the lifespan. Despite these likely partially differing mechanisms, we see that the regional variations in cortical thinning in development and adulthood correspond to patterns that vary as a function of shared genetic influence.

Regional Differences in Cortical Development and Aging Correspond to Genetic Influences on Cortical Thickness. As seen in Fig. 4, developmental and aging-related cortical thickness change varied as a function of shared genetic influence, so that genetically close clusters showed more similar rates of maturation and adult changes. The clusters were based on genetic correlations and represent shared genetic influences on cortical structure between different points on the surface (4). Although some regions corresponded to more traditionally defined anatomical regions based, e.g., on cytoarchitectural information or cortical gyrification, the genetic divisions were not identical to traditional regions defined on the basis of structure or function, implying that there is additional information to be obtained by this alternative parcellation of the cortex (4). For the main part, clusters anatomically close to each other are genetically closely related and change in coordinated ways during development and aging. However, not all anatomically close clusters showed converging development and adult change trajectories. For instance, the inferior and superior parietal clusters showed little such convergence with the occipital clusters despite close anatomical localization, and the same was true for the medial and the ventral frontal cortex. Furthermore, there were also instances of clusters involving anatomically more diverse regions that were genetically closely related and showing converging neurodevelopmental and aging relationships. This feature was seen for the ventral frontal cortex and the anterior ("temporal pole") temporal cluster. These regions showed high genetic correlations with each other and correlated change rates both in development and adulthood. Although having a common border, the clusters covered anatomically widespread areas. Direct connections from the ventrolateral prefrontal cortex to the temporal cortex exist (61, 62), possibly yielding a structural substrate for the observed relationship. This observation has interesting implications, because contrary to genetic covariance of importance for local arealization, effects of genetic variance on regional differences in cortical thickness have been argued to partly correspond to functional specializations rather that anatomical localization only (4). Applying this reasoning to the current results implies that functionally related regions could show more similar structural cortical developmental and adult age change trajectories than functionally less related regions, as has been observed for cortico-subcortical functionally related regions (63).

There were also exceptions to the observed relationship between genetic similarity and synchrony of developmental and adult age-related cortical changes. Change rate in ventromedial occipital cortex during development correlated with middle temporal cortex while being genetically less related. Thus, although a clear pattern of convergence was seen, correlated developmental or aging-related change did not necessitate genetic convergence.

Importantly, the subdivision of the cortex based on maximal independent genetic influence was performed in a completely independent, cross-sectional sample of middle-aged adult twins (4), but still revealed the same cortical organization that was found to characterize the current developmental and adult age-related cortical changes. This possible genetic influence on neurodevelopmental and adult age trajectories implies either that the effects of genes through early development have life-long impact on cortical thickness or that the influence of these genes is continuous through life and thereby can be detected at widely different ages. It can be questioned whether a sample of middle-aged males is representative for a mixed-sex developmental sample. We believe that the high degree of overlap between the correlation matrices for development vs. the genetic sample indicates that the genetic impact on the adult cerebral cortex (4–6, 64) partly has a neurodevelopmental origin and that the genetic organization of the cerebral cortex based on the Vietnam Era Twin Study of Aging (VETSA) sample likely is valid for the developmental and adult samples in the present study. This pattern adheres to a lifespan view on neurocognitive changes, where continuous influences of both genetic makeup and early events can be seen through life. For example, *APOE* (apolipoprotein E), an important risk factor for sporadic Alzheimer's disease (AD), has been shown to affect brain structure in neonates (65), and variants of the Fat mass and Obesity associated (*FTO*) gene, being associated with smaller brain volume (66) and increased AD risk (67) in aging, have been related to smaller brain volumes in adolescence (68).

Conclusion

Here we showed continuous thinning of the cerebral cortex from 4.1 to 88.5 y, with both developmental and adult age-related changes in cortical thickness following closely to cortical subdivisions based on common genetic influence. This finding suggests that genetic factors contribute to cortical changes through life and calls for a lifespan perspective in research aimed at identifying the genetic and environmental determinants of cortical development and aging.

Materials and Methods

Sample. A total of 1,633 valid scans from 974 healthy participants (508 females/466 males), 4.1–88.5 y of age (mean visit age, 25.8 y; SD = 24.1 y), were drawn from three Norwegian studies coordinated by the Research Group for Lifespan Changes in Brain and Cognition (LCBC), Department of Psychology, University of Oslo, Oslo, Norway [The Norwegian Mother and Child Cohort Neurocognitive Study (MoBa-Neurocog)/Neurocognitive Development (ND)/Cognition and

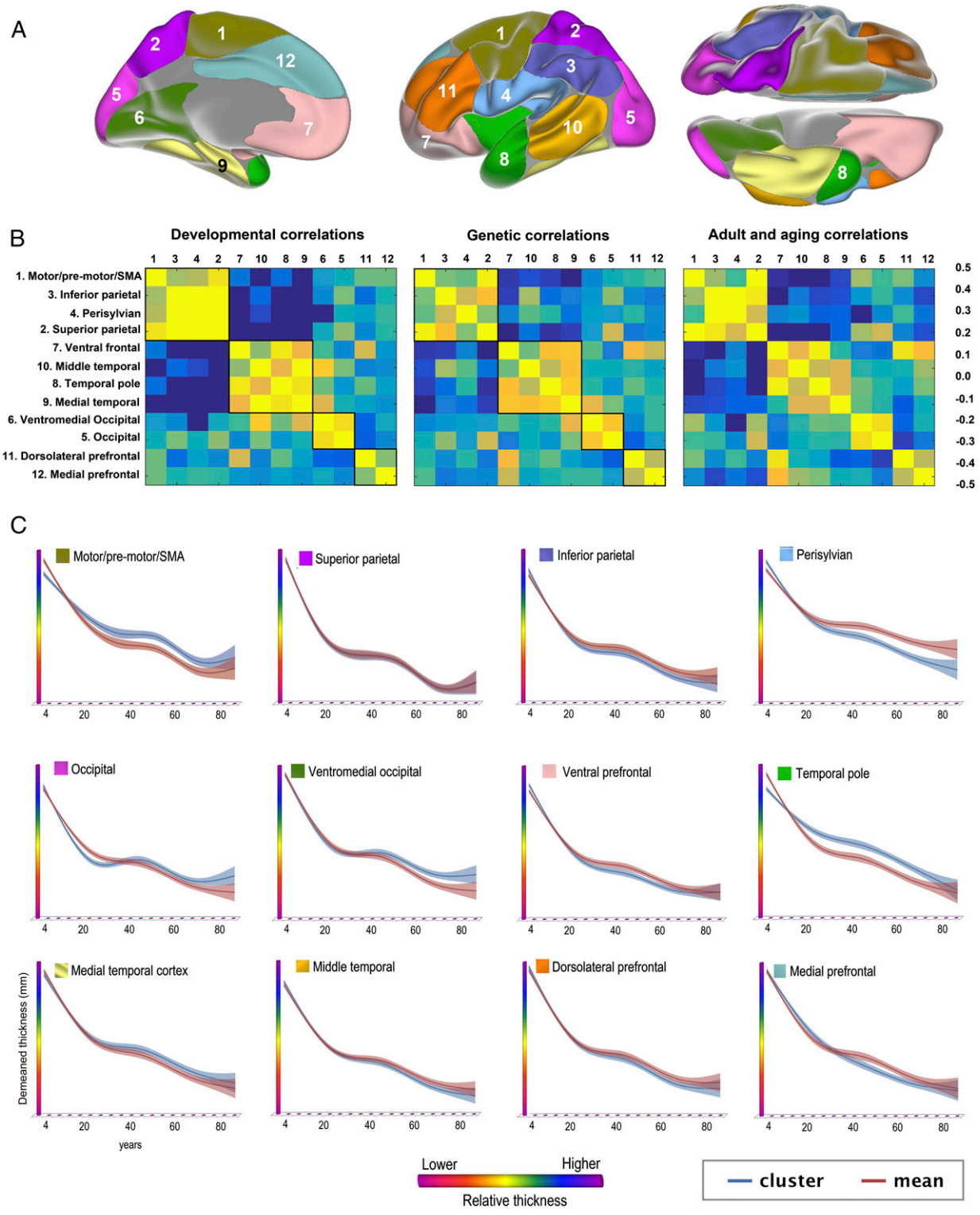

Fig. 4. Overlap between genetic organization of cortical thickness and developmental and aging-related change. (*A*) The cortex was parcellated into 12 regions (clusters) of maximal shared genetic influence, based on an independent sample of 406 middle aged twins (4). The fuzzy clusters as shown were thresholded at 0.5. (*B*) (*Center*) Genetic correlations between the clusters. The genetic correlation matrix was compared with the correlations matrices for representing the relationships between cortical thickness change in the same clusters in development (<20 y; *Left*) and aging (≥20 y; *Right*). The Louvain algorithm was run to find the optimal community structure in each correlation matrix separately, illustrated by the black lines within the color charts, and the development and genetic clusters were ordered according to this algorithm. For aging, the Louvain algorithm suggested a slightly different organization (*SI Text*), and to allow comparisons with the two matrices, the same cluster ordering is used, without the community structure shown. (*C*) Thickness in each genetically defined cluster was demeaned and fitted to age by use of GAMM and plotted together with the mean of all clusters for comparison purposes. The width of the fit line represents the 95% CI. The *y* axes are optimized for the data range for each cluster. The blue lines represent the demeaned trajectory for each cluster, whereas the red lines represent the mean of all clusters.

Plasticity Through the Lifespan (CPLS)]. For 635 participants, one follow-up scan was available, whereas 24 of these had two follow-ups. Mean follow-up interval was 2.30 y (range, 0.15–6.63 y; SD = 1.19 y). A total of 472 participants were from MoBa-Neurocog (508 girls/466 boys; 773 observations; mean age at testing, 7.3 y; range, 4.1–12.0 y; 301 with two tests; mean follow-up interval, 1.5 y; range, 1.0–2.2 y), and 502 were from ND/CPLS (277 girls, 225 boys; 860 observations; mean age at testing, 42.4 y; range, 8.2–88.5 y; 334 with two tests and 24 with three tests; mean follow-up interval, 3.1 y; range, 0.2–6.6 y). Sample density was higher in childhood/adolescence than adulthood, because we expected more rapid changes during that age period (731 observations < 10 y; 275 observations ≥ 10 and < 20 y; 165 observations ≥ 20 and < 40 y; 213 observations ≥ 40 and < 60 y; and 249 observations 60–88.5 y). The studies were approved by a Norwegian Regional Committee for Medical and Health Research Ethics. The twin sample consisted of 406 men, including 110 monozygotic and 93 dizygotic twin pairs, 51–59 y of age (mean age, 55.8 y; SD = 2.6 y). Written informed consent was obtained from all participants older than 12 y of age and from a parent/guardian of volunteers under 16 y of age. Oral informed consent was obtained from all participants under 12 y of age. See *SI Text* for details on samples.

MRI Data Acquisition and Analysis. Imaging data were acquired using a 12-channel head coil on a 1.5-T Siemens Avanto scanner (Siemens Medical Solutions) at Oslo University Hospital Rikshospitalet and St. Olav's University Hospital in Trondheim, yielding two repeated 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE): TR/TE/TI = 2,400 ms/3.61 ms/1,000 ms, FA = 8°, acquisition matrix = 192 × 192, FOV = 192, 160 sagittal slices with voxel sizes 1.25 × 1.25 × 1.2 mm. For most children 4–9 y old, integrated parallel acquisition techniques (iPAT) was used, acquiring multiple T1 scans within a short scan time.

MRI data were processed and analyzed with the longitudinal stream (69, 70) in FreeSurfer 5.3 (surfer.nmr.mgh.harvard.edu/) (71, 72). For the children, the issue of movement is especially important, as it could potentially induce bias in the analyses (73). All scans were manually rated for movement on a 1–4 scale, and only scans rated 1 and 2 (no visible or only very minor possible signs of movement) were included. For details on MRI analyses, see *SI Text*.

After surface reconstruction, the cortex was parcellated in 12 separate genetic clusters of cortical thickness, each under maximal control of shared genetic influences. This was based on fuzzy cluster analyses of apparent cortical thickness in an independent sample of 406 twins from the VETSA (74). In brief, cluster analyses were used to identify the boundaries of cortical divisions that were maximally genetically correlated, i.e., under control of shared genetic influences on cortical thickness. The procedures are described in detail elsewhere (4).

Statistical Analyses. First, GAMM implemented in R (www.r-project.org) using the package "mgcv" (75) was used to derive age functions for mean thickness in each hemisphere based on all 1,633 longitudinal and cross-sectional observations, run through the PING data portal (76). AIC (77) and BIC were used to guide model selection and help guard against overfitting. Next, thickness change was tested in the age groups by LME implemented in FreeSurfer (17). Multiple comparisons were controlled by a false discovery rate threshold of 0.05. A nonparametric local smoothing model implemented in Matlab (78) was used to estimate APC across the brain surface. APC in each genetic cluster was then correlated separately for the child (age < 20 y) and adult (age ≥ 20 y) age span, with mean change across all clusters regressed out. This was compared with the correlation map of the genetic correlations between each of the 12 clusters by use of the Mantel test (79), as implemented in R using the *ade4* package. The community structure or modules in each matrix were obtained using the Louvain algorithm (80), part of the Brain Connectivity Toolbox (www.brain-connectivity-toolbox.net) (81).

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