

Continuity and discontinuity in human cortical development and change from embryonic stages to old age

Running title: Coordinated cortical development

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Abstract

The human cerebral cortex is highly regionalized, and this feature emerges from morphometric gradients in the cerebral vesicles during embryonic development. We tested if this principle of regionalization could be traced from the embryonic development to the human lifespan. Data-driven fuzzy-clustering was used to identify regions of coordinated longitudinal development of cortical surface area (SA) and thickness (CT) (n = 301, 4-12 years). The principal divide for the developmental SA clusters extended from the inferior-posterior to the superior-anterior cortex, corresponding to the major embryonic morphometric anterior-posterior (AP) gradient. Embryonic factors showing a clear AP gradient were identified, and we found significant differences in gene expression of these factors between the anterior and posterior clusters. Further, each identified developmental SA and CT cluster showed distinguishable lifespan trajectories in a larger longitudinal dataset (4-88 years, 1633 observations), and the SA and CT clusters showed differential relationships to cognitive functions. This means that regions that developed together in childhood also changed together throughout life, demonstrating continuity in regionalization of cortical changes. The AP divide in SA development also characterized genetic patterning obtained in an adult twin sample. In conclusion, development of cortical regionalization is a continuous process from the embryonic stage throughout life.

Keywords: protomap theory, cortical development, aging, magnetic resonance imaging, cognition

Expansion of cortical surface area (SA) in human development is highly regionalized (Amlien et al. 2016). According to the protomap (Rakic 1988) and radial unit models (Rakic et al. 2009), the blueprint for this regional cortical expansion is established already in early embryonic development. Cortical neurons are not born within the cerebral cortex itself, but migrate from the ventricular zone to their final destination. The major morphometric gradient governing areal identity runs along the anterior-posterior axis (Rakic et al. 2009). However, it is not known if the governing principles of embryonic brain development apply to cortical expansion in children. In the present study, we tested this hypothesis, which would show a continuity of cortical expansion from the early fetal to the latest stages of development in the pre-teen years.

Moreover, the related tenet that late-life brain health and cognitive function have developmental origins is getting increasing support (Jagust 2016; Walhovd et al. 2016). Adult genetic SA topography – the delineation of regions influenced by the same genes - is characterized by an anterior-posterior gradient, likely due to prenatal factors (Rakic 2009; Walhovd et al. 2012), corresponding to our hypothesis for organization of SA development. Thus, an intriguing possibility is that the fundamental organizational principles for regional brain development in children, likely reflecting patterns from embryonic development, can be traceable also in higher age. This would mean that anatomical regions that develop together also show distinct lifespan trajectories of adult cortical change and decline in aging. We know that cortical maturation to some degree proceeds along functional and structural networks established in adults (Zielinski et al. 2010; Raznahan, Lerch, et al. 2011; Alexander-Bloch et al. 2013; Walhovd et al. 2015; Krongold et al. 2017; Sotiras et al. 2017), but not whether brain regions that develop together also change together through the rest of life. Testing this was the second main aim of the project.

These hypotheses were addressed through several steps. First, a data-driven fuzzy clustering approach was used to parcellate longitudinal change in SA and apparent thickness (CT) of the cerebral cortex into regions of coordinated development. CT and SA develop differently (Raznahan, Shaw, et al. 2011; Amlien et al. 2016; Walhovd et al. In press) and have different genetic and molecular foundations (Rakic 1988; Panizzon et al. 2009; Rakic et al. 2009). We selected an age-range when SA still expands and apparent CT is continuously declining, i.e. 4-12 years (n = 301). Clustering was based on 1.5 years longitudinal change to avoid confounds from cross-sectional differences. The principal axes of the developmental clusters were extracted and tested against the anterior-posterior morphometric gradient from gene expression patterns in embryonic development, identified in (Rakic et al. 2009).

The developmental clusters were further tested against genetic cortical topography established in an adult sample of twins (Chen et al. 2012; Chen et al. 2013). CT shows more age change and is more affected by later-life events than SA (Engvig et al. 2010; Wenger et al. 2012; Storsve et al. 2014), and the original genetic patterning work predicted that CT clusters, more than SA clusters, would show genetic relatedness with clusters of similar maturational timing (Chen et al. 2013). Thus, we hypothesized that developmental SA change would adhere more closely to prenatal gene expression gradients while CT change clusters would be more similar to genetic clusters obtained from adult twins (Fjell et al. 2015).

Next, we tested if the developmental clusters showed different age-trajectories in a longitudinal dataset covering more than eight decades (4.1-88.5 years, $n = 974$, 1633 scans). On the assumption of continuity between fetal and child development and lasting impacts of early-life factors on later brain changes, we hypothesized that the residual variance in each developmental cluster would be differentially related to age when the common variance shared among the clusters was accounted for. This means that we expected each developmental cluster to show different lifespan trajectories.

Finally, we tested whether the developmental clusters showed differential relationships to four empirically derived domains of cognitive function – episodic memory, executive-speed, working memory and general cognitive ability (GCA). These domains were identified from a principal component analysis (PCA) of multiple cognitive scores from an extended longitudinal dataset (4.1-93.4 years, 4065 observation). As SA and CT have different early determinants and show different developmental and lifespan trajectories, we hypothesized different relationships to cognition. We expected the SA clusters to relate to GCA, which is likely heavily influenced by early life factors and shows high life-span stability (Lyons et al. 2009; Deary et al. 2012; Vuoksimaa et al. 2015; Walhovd et al. 2016). The scores included in the GCA component (matrix reasoning and vocabulary) load strongly on the *g*-factor (Deary et al. 2010), and have previously been found to correlate more with SA than CT (Vuoksimaa et al. 2015; Walhovd et al. 2016). As likely more amendable to environmental influences through life, CT was hypothesized to correlate more strongly with more specific cognitive functions, indicated by lower loadings on the *g*-factor. These could include episodic memory and executive-speed, which show different change trajectories across people (Salthouse 2016) and are less strongly related to global cognitive change (Tucker-Drob 2011).

Materials and methods

Sample

A total of 1633 valid scans from 974 healthy participants (508 females/ 466 males), 4.1 to 88.5 years (mean visit age 25.8, SD 24.1), were drawn from three Norwegian studies coordinated by the Research Group for Lifespan Changes in Brain and Cognition; The Norwegian Mother and Child Cohort Neurocognitive Study (MoBa)/ Neurocognitive Development (ND)/ Cognition and Plasticity Through the Lifespan (CPLS)) (see SI for details). 635 participants had two scans and 24 had 3 (mean scan interval 2.3 years [0.2-6.6]). The sample is identical to (Fjell et al. 2015). All were screened for conditions assumed to affect CNS function. Number of observations in different age spans is provided in Table 1.

The cluster-forming sample consisted of all MoBa participants with two scans ($n = 301$, 602 scans in total, mean age 7.3 years [range 4.1-12.0], mean scan interval 1.5 years [1.0-2.2]). This is a population based sample, with participants recruited by the Norwegian Medical Birth Registry through the national Norwegian Mother and Child Cohort Study (82), see (8, 83) and Supplementak information for details. The age-range is well covered, with good sample density across.

The twin sample used to generate the genetic clusters consisted of 406 middle-aged men (55.8 years [51-59]), including 110 monozygotic and 93 dizygotic twin pairs, from the Vietnam Twin Study of Aging (see SI and (Kremen et al. 2013) for details).

[Insert Table 1 about here]

Cognitive testing

All participants underwent extensive neuropsychological testing. Cognitive test scores were entered into a principal component analysis (PCA) with varimax rotation with Kaiser normalization. The following test scores were included in the analysis: verbal learning (California Verbal Learning Test[CVLT], sum of trials 1 to 5), 30 minutes recall and 30 min recognition (Delis et al. 2000), Stroop reading, Stroop color naming and Stroop incongruent color naming (MacLeod 1992), digit span forward and backward (Wechsler 2008), vocabulary and matrix reasoning (Wechsler 1999), see SI for details about the tests. In contrast to the measured scores, the PCA derived components are free of measurement errors. To obtain a stable and generalizable component solution, the PCA was run on a larger healthy sample from the same research center, screened with the same instruments as the MRI subsample, containing 4065 participant observations (age 4.1-93.4 years, 2285/ 1722 females/ males observations), inclusive of those used in the present study. In case of missing values, the 'mean

substitution' method was used. Inspection of the scree plot revealed that both three and four components were reasonable solutions. The four-component solution gave most sense from a neuropsychological perspective, and the four component solution was thus chosen for further analyses, yielding 81.53% explained variance. See Table 2 and SI for details.

[Insert Table 2 about here]

To ensure that the PCA from the larger samples was representative also for the subsample used in the present paper, Procrustes rotation was used to assess degree of dissimilarity. This procedure rotates a matrix to maximum similarity with a target matrix minimizing the sum of squared differences. 10,000 permutations were run, yielding a p-value of $9.999e^{-05}$, sum of squares of 0.099 and a correlation for a symmetric Procrustes rotation of 0.95, indicating excellent correspondence between the matrices. This was further confirmed by a Mantel permutation test for similarity of two matrices, yielding an observed r of .95 and a simulated p-value of $9.999e^{-05}$ for 10,000 permutations. Thus, applying the PCA solution from the larger sample to the MRI subsample was clearly a valid approach.

MRI data acquisition and analysis

Imaging data (except VETSA) were acquired using a 12-channel head coil on two 1.5-Tesla Siemens Avanto scanners (Siemens Medical Solutions, Erlangen, Germany), yielding 2 repeated 3D T1-weighted magnetization prepared rapid gradient echo (MPRAGE): TR/TE/TI = 2400 ms/ 3.61 ms/ 1000 ms, FA = 8°, acquisition matrix 192 × 192, FOV = 240 mm, 160 sagittal slices with voxel sizes 1.25 × 1.25 × 1.2 mm. For most children 4-9 years old, iPAT (integrated parallel imaging) was used, acquiring multiple T1 scans within a short scan time with the same parameters as above, enabling us to discard scans with residual movement and average the scans with sufficient quality. Previous studies have shown that accelerated imaging does not introduce significant measurement bias in surface-based measures when using FreeSurfer for image analysis, compared with a standard MPRAGE protocol with otherwise identical voxel dimensions and sequence parameters (97), which is in accordance with our own analyses.

MRI data (except VETSA) were processed and analyzed with FreeSurfer 5.3

(<http://surfer.nmr.mgh.harvard.edu/>) (Dale 1993; Dale et al. 1999) longitudinal stream (Fischl and Dale 2000; Reuter and Fischl 2011; Reuter et al. 2012). SA maps were smoothed using a circularly symmetric Gaussian kernel with a full width at half maximum (FWHM) of 26 mm and CT maps with a

kernel of 21 FWHM. Movement is a major concern (Reuter et al. 2015), so scans were manually rated 1-4, and only 1 or 2 (no visible or only very minor possible signs of movement) were included. Also, all reconstructed surfaces were inspected, and discarded if they did not pass internal quality control. This led to the exclusion of 46 participants from MoBa-Neurocog and 9 from ND, reducing the total sample to the reported 1633 scans.

For VETSA, images were acquired on two Siemens 1.5 Tesla scanners. Sagittal T1-weighted MPRAGE sequences were employed with a TI=1000ms, TE=3.31ms, TR=2730ms, flip angle=7 degrees, slice thickness=1.33mm, voxel size 1.3x1.0x1.3mm. Similar to the other data, the scans were run through FreeSurfer and manually inspected and quality checked, with minimal manual editing performed. Details about the VETSA MRI processing can be found here (Chen et al. 2013).

Fuzzy clustering

The fuzzy clustering procedure was performed using the ‘cluster’ package implemented in R (www.r-project.org/). The individual de-meant annualized symmetrized percentage change (APC) maps were fed into the cluster algorithm. The APC maps were computed by calculating the difference in thickness/ area for each vertex between timepoints, divide by the mean thickness/ area across time points for that vertex, and multiply by 100. Clustering methods partition the dataset into clusters based on the chosen proximity relations. We calculated pair-wise correlations of thickness and area change between every two vertices on the cortex for the left and right hemispheres separately. To reduce computation time, we subsampled the standardized cortical-surface tessellation from the original 163.842 to 2.562 vertices per hemisphere. We then transformed the change correlation matrix into the distance matrix by subtracting each correlation from 1. In fuzzy clustering, objects can belong to more than one cluster and with different degrees of membership to the different clusters, between 0 and 1. Thus, the memberships of objects at the overlapping boundaries will typically express the ambiguity of the cluster assignment. Fuzzy clustering aims to minimize the objective function

$$\sum_{v=1}^k \frac{\sum_{i=1}^n \sum_{j=1}^n u_{iv}^r u_{jv}^r d(i, j)}{2 \sum_{j=1}^n u_{jv}^r},$$

where n is the number of observations, k is the number of clusters, r is the membership exponent, u is the cluster membership, and d(i, j) is the dissimilarity between observations i and j (Kaufman and Rousseeuw 1990). The cluster memberships u are nonnegative and sum to one for a given data point.

To investigate the stability of the clustering in relation to initialization, we randomly initialized the algorithm for 100 runs and picked the cluster solution that maximized the likelihood function.

In addition, we generated random clusters to compare with the power of the real clusters. The performance of the developmental clusters was compared to randomly generated clusters for a three-cluster solution, since the three-cluster solution was used for the lifespan analyses (see below). The random clusters were generated using k-means algorithm implemented in MATLAB (R2015b). The spatial locations of the cerebral cortex mesh were partitioned into 15 clusters using the squared Euclidean distance metric and k-means++ algorithm for cluster center initialization. One of the clusters resulted in capturing the whole temporal lobe, therefore, it was further sub-divided into 4 clusters using the same procedure. The final 18 clusters were merged into 3 clusters of similar size to the empirically derived clusters.

Genetic clustering

The developmental clusters were compared to previously published genetic clusters (Chen et al. 2013), made accessible for formal comparisons to the present study. The genetic clusters were derived using a similar Fuzzy clustering approach to the one described above. The clustering was performed on genetic correlation maps for cortical thickness and area based on the VETSA sample. The resulting clusters represent boundaries of cortical divisions that are maximally under control of shared genetic influences. The present two- and three-cluster solutions for cortical thickness and area development were compared to the genetic two- and three-cluster thickness and area solutions by use of the Rand Index (see below).

Gene expression analyses

Cortical gene expression data were obtained from the BrainSpan Atlas of the Developing Human Brain (2010) (www.brainspan.org) (Miller et al. 2014), which provides a transcriptome of the developing human brain. We rated 31 transcription factors assumed responsible for shaping the partitioned neocortex (Rakic et al. 2009) according to how well their expression patterns were aligned to the AP axis. 18 factors showed a clear and four a partial AP gradient, yielding evidence that the AP axis constitutes a major regionalization gradient in early cortical development. To test whether this cluster gradient could be detected in later human gene expression patterns, we selected the candidate with the most established anterior-posterior expression pattern, *PAX6* (Bishop et al. 2000), and the candidate with the most pronounced posterior-anterior expression pattern, *P75* (Rakic et al. 2009). Thirty-four out of the forty-two donor brains in the BrainSpan Atlas

had valid probe data from at least one cortical region within each of the empirically derived developmental clusters (see below). Mean expression values for cortical regions falling within the developmental clusters were extracted for the 34 participants from the BrainSpan Atlas. For each donor, the average *PAX6/P75* expression was estimated through mean averaging of normalized expression values (Reads Per Kilobyte Million; RPKM) from cortical samples overlapping with the developmental clusters.

Statistical analyses

Analyses were run in R (<https://www.r-project.org>) using Rstudio (www.rstudio.com) IDE, except the PCA (SPSS v25). The Rand index (RI) and Silhouette plots (Rand 1971), in combination with visual inspections, were used to inform the choice of specific cluster solutions. RI is a number between 0 and 1 that quantifies the degree of similarity between two cluster solutions by computing the proportion of vertices that are given the same cluster label in both solutions. It is possible for some vertices to have the same cluster label by chance, and this is accounted for in the adjusted RI. Adjusted RI was used to compare area to thickness clusters, and the developmental clusters to the genetic clusters.

To characterize each two-cluster cluster solution according to the main axes (anterior-posterior [AP], inferior-superior [IS], lateral-medial [LM]), the cortical surface was divided in 20 bins along each axis. The mean probability of all the vertices within each bin along the AP axis to belong to a given cluster was calculated, and the same for the IS and LM axes. These values were then correlated with the axis bin numbers (from 1 to 20), yielding an objective measure of how much of the variance of the different cluster solutions that could be explained by each of the three principal axes.

Generalized Additive Mixed Models (GAMM) implemented in R (www.r-project.org) using the package “mgcv” (Wood 2006, 2011) were used to derive age-functions for morphometric and cognitive variables. Akaike Information Criterion (AIC) (Akaike 1974) and the Bayesian Information Criterion (BIC) was used to guide model selection and help guard against over-fitting. The smoothness of the age-curve is estimated as part of the model fit, and the resulting effective degrees of freedom (edf) was taken as a measure of deviation from linearity. The p-values associated with the smooth terms are only approximate, as they are based on the assumption that a penalized fit is equal to an unpenalized fit with the same edf, and do not take into account uncertainty associated with the smoothing parameter estimation. The major advantage of GAMM in the present setting is that relationships of any degree of complexity can be modelled without specification of the basic shape of

the relationship, and GAMM is thus especially well-suited to map life-span trajectories of neurocognitive variables which can be assumed to be non-linear and where the basic form of the curve is not known (Fjell et al. 2010). Sex was used as covariate in the area analyses, as sex is related to area but less to thickness (Fjell et al. 2009).

Results

Clusters of cortical change in development 4-12 years

Clusters are presented in Figure 1 (SA) and Figure 2 (CT). The two-cluster SA solution followed a clear anterior-posterior (AP, correlation with the AP axis $r = .91$) and inferior-superior (IS, $r = .97$) gradient, with less influence from the lateral-medial (LM, $r = .19$) axis. The AP division was tilted 19° from the base plane, causing the strong IS correlation. The posterior cluster covered the central sulcus and the adjacent anterior regions of the frontal cortex (premotor cortex), extending back to encapsulate the dorsolateral occipital cortex, and inferiorly down to the cingulum. For the three-cluster solution, an occipital-limbic cluster emerged. In the four-cluster solution, a new cluster appeared inferior to the first posterior cluster, distinguishing this cluster from the rest of the clusters both medially and laterally.

The two-cluster CT solution showed a very strong IS gradient ($r = .97$), with less AP (.39) and LM (.46) influence. With three clusters, an occipital-limbic cluster emerged. In the four-cluster solution, the superior cluster was split in two clusters. For both CT and SA, the silhouette values flattened after 4 clusters, suggesting that 5 clusters were too many (see SI). The adjusted Rand Index (adj RI) showed substantial overlap between the 2-cluster SA and CT solutions (adj RI = .88), with less similarity for three (adj RI = .27) and four (adj RI = .22) clusters. Still, the medial limbic cluster and the prefrontal – anterior-temporal relationship was similar between SA and for CT across the 3- and 4- cluster solutions.

[Insert Figure 1 and 2 about here]

To validate the Fuzzy clustering results, we ran seed point analyses from 360 seeds based on a multi-modal parcellation scheme (Glasser et al. 2016). The critical features of the cluster results were confirmed, including the AP axis for SA, the IS axis for CT, and the prefrontal-temporal relationship and delineation of the limbic clusters for both SA and CT (see SI).

Adherence of SA development to early morphometric gradients

Mean expression values for *PAX6*/*P75* in cortical regions falling within the anterior and the posterior developmental clusters were extracted for 34 participants from the BrainSpan Atlas (www.brainspan.org). Five samples from the atlas fell within the superior-anterior cluster: samples from dorsolateral prefrontal cortex, ventrolateral prefrontal cortex, orbital frontal cortex, inferolateral temporal cortex, and anterior cingulate cortex. Four samples fell within the inferior-posterior cluster: primary motor cortex, primary somatosensory cortex, posteroventral parietal cortex, and primary auditory cortex. Difference in expression between the superior-anterior cluster and the inferior-posterior cluster was assessed for *PAX6* and *P75(NGFR)* separately using paired-samples t-tests. Expression values of *PAX6* were significantly higher ($t = 4.24$, $df = 33$, $p < .0002$) in the anterior than the posterior development cluster, while the opposite was found for *P75* ($t = -3.03$, $df = 33$, $p < .005$) (Figure 3). Put together, this shows that traces of the major expression patterns in embryonic development can be recovered in later childhood, and that the gene expression patterns in humans follow cortical change in ways predicted from early embryonic development. It was not given that genes with strong AP gradients during embryonic brain development would also adhere to an empirically derived AP cluster solution based on cortical changes during childhood development.

[Insert Figure 3 about here]

Resemblance to cortical genetic patterning

After having established that SA development follows the main AP gradient identified in embryonic development, we tested how similar the developmental SA and CT clusters were to mid-life genetic cortical topography (Chen et al. 2013) (Figure 4). Genetic topography represents the delineation of regions influenced by the same genes. Rand Index suggested low overlap (adj RI < .10 for 2 and 3 cluster solutions) between genetic topography and the developmental clusters. The AP division was seen for both, but the boundary between the clusters was shifted from inferior-posterior to anterior-superior for the development clusters (-71° from the perpendicular axis) compared to inferior-anterior to superior-posterior ($+38^\circ$) for the genetic clusters. Adherence to the AP axis was slightly higher for the genetic ($r = .96$) vs. the developmental ($r = .91$) clusters, and slightly lower for the IS axis ($r = .82$ for genetics vs. $r = .91$ for development).

Comparing the developmental and the genetic CT clusters, the same IS division was seen for the 2-cluster solution ($r = .96$ for genetics vs. $.93$ for development, $RI = .69$, $adj RI = .39$). The genetic clusters also followed the AP ($r = .90$) and to a lesser extent the medial-lateral ($r = .25$) gradient. For the 3-cluster solution, the medial delineation of the limbic developmental cluster included the medial

temporal lobe and the cingulum as well as the occipital cortex, while the genetic homologue cluster did not include the occipital lobe but more of the prefrontal cortex laterally and medially. RI indicated similar genetic-developmental overlap (RI = .68) for the three-cluster solutions, but adj RI dropped to .31, with a further drop to the 4-clusters solution (RI = .70, adj RI = .23). Thus, the overlap between CT development and genetic topography dropped with higher number of clusters.

[Insert Figure 4 about here]

Lifespan-trajectories of developmental clusters

Mean CT and SA values in each cluster from the 3-cluster solutions were extracted for each participant and time point in the full MRI sample from 4.1 to 88.5 years, yielding 1633 observations. Generalized Additive Mixed Models (GAMM) with cluster as dependent variable, age as predictor and a random effect for intercept, showed that all clusters showed highly non-linear relationships to age (all p 's $< 2e^{-16}$, effective degrees of freedom [edf] for all > 5). SA differs as a function of sex (Amlien et al. 2016), and was included as a nuisance covariate in the SA analyses. As expected, CT clusters showed mainly monotonous negative relationships to age (Figure 2), with steeper reductions in childhood and adolescence, while SA increased in the first part of the age-span (Figure 1), peaking in early teenage years, followed by reductions for the rest of the life-span.

To test whether the clusters showed unique age-trajectories, analyses were repeated with all clusters for each modality (SA, CT) as simultaneous predictors of age. For SA, this yielded highly significant residual age-relationships for all clusters (all p 's $\leq 4.07^{-5}$). The limbic cluster showed residual reductions with higher age throughout the whole age-span, while the anterior cluster showed slight increases and the posterior a U-shaped trajectory (Figure 1, right panel, bottom). The analyses were also re-run without the cluster-forming development sample, and all clusters were still highly significantly related to age when run separately (all p 's $< 2e^{-16}$) and simultaneously ($n = 502, 860$ observations, all p 's $< .05$), both for CT and SA.

Random clusters

To test whether the independent lifespan trajectories of the developmental clusters reflected an inherent feature of any cortical cluster of a given size, we created random clusters of approximately the same size and repeated the GAMMs with all clusters as simultaneous predictors of age (Figure 5). The developmental clusters performed substantially better than the random clusters on all model fit

measures (CT: developmental clusters - random clusters, $\Delta\text{AIC} = -150.75$, $\Delta\text{BIC} = -150.75$, $\text{logLik} = 75.38$ / SA: $\Delta\text{AIC} = -53.57$, $\Delta\text{BIC} = -53.58$, $\text{logLik} = 26.79$).

[Insert Figure 5 about here]

In conclusion, we were able to detect large cortical regions with unique and independent trajectories across the lifespan through data-driven clustering of longitudinal change in children. We proceeded to test whether the clusters were related to cognitive performance.

Cognitive components – relationship to developmental clusters

All cognitive components showed highly significant ($p < 2e^{-16}$) and non-linear ($\text{edf} \geq 4.9$) age-trajectories (Figure 6A, Table 3). Each component was then used as dependent variable in separate GAMMs, with age and each developmental cluster as predictors, intercept as a random effect and subject time point as covariate to control for retest effects. Selected results are presented in Figure 5C and numeric results in Table 4 and 5 (full results in SI). All SA clusters were positively related to GCA ($p < .0002$). The anterior cluster was also related to working memory span ($p = .008$), while the limbic ($p = .03$) and posterior ($p = .018$) did not survive Bonferroni corrections. None were related to memory or executive-speed. In contrast, the CT superior cluster ($p = .005$) was related to memory, while the limbic and inferior (both p 's = $.02$) did not survive corrections. The limbic ($p = .01$) and inferior ($p = .005$) were related to executive-speed (after corrections). The relationships were non-linear, as would be expected based on the monotone negative thickness–age relationships coupled with the typical inverse U-shaped cognition-age relationships. The differential relationships between cognitive function and CT and SA are illustrated in the heat maps in Figure 6B.

[Insert Figure 6, Table 3, Table 4 and Table 5 about here]

Discussion

The present results show that cortical expansion in childhood development follows the major gene expression patterns of factors responsible for shaping the partitioned and specialized human neocortex during prenatal development (Rakic et al. 2009). Through a data-driven parcellation of the cerebral cortex based on longitudinal change in SA in 4-12 year old children, we were able to detect the major anterior-posterior developmental gradient known from embryonic development (Bishop et al. 2000). This demonstrates a continuity in cortical expansion from the earliest stages to the period when regional arealization reaches its peak. While this represents continuity between the

fundamental principles for embryonic brain development (Rakic 1988; Rakic et al. 2009) and later childhood SA maturation, in line with known influences of neonatal characteristics on SA (Walhovd et al. 2012), CT change more strongly followed adult genetic organization principles, as predicted from previous work on genetic cortical patterning (Chen et al. 2013). Importantly, the developmental clusters showed statistically distinguishable trajectories through more than eight decades of life, in accordance with the view that fundamental principles governing brain development in children have lasting impact on the brain. Thus, brain regions that develop together also change together through the rest of life. Finally, since SA is highly determined by prenatal factors, we expected correlations with GCA, which loads highly on the *g*-factor (Deary et al. 2010) and has high between-person lifespan stability (Lyons et al. 2009; Deary et al. 2012). This was confirmed, in contrast to CT, which was more strongly related to cognitive domains with lower loading on the *g*-factor (Deary et al. 2010), such as memory and executive-speed. This suggest that cortical characteristics (arealization and thickness) beyond anatomical boundaries are the more important in defining relationships to cognition.

Parcellation of the developing human cerebral cortex

The results showed that the cortex can be parcellated in meaningful ways based on developmental change data alone. The anterior-posterior SA axis followed the major gene expression gradient identified in animal studies (Bishop et al. 2000; Rakic et al. 2009). This link was further supported in the present study through the finding of significantly different gene expression in the anterior vs. the posterior cluster for PAX6 and P75, both established anterior gradient factors in embryonic development (Bishop et al. 2000). Such correspondence between childhood SA maturation and cortical ontogenesis is in line with the protomap (Rakic 1988) and radial unit tenets (Rakic et al. 2009). According to these, neural progenitors in the ventricular zone form a mosaic of proliferative units that establish an embryonic cortical map in early development. During migration of neurons into the cortex, their position is then retained by restraints imposed through the radial glial scaffolding. However, it has not been established that these principles laid down in the first stages of CNS development are reflected in cortical maturation in later childhood in humans.

Although there was good overlap between SA and CT for the two-cluster solution, this dropped substantially with higher cluster numbers. CT and SA are shaped by independent genes (Rakic 1988; Panizzon et al. 2009) and different neurobiological mechanisms in early fetal life (Rakic et al. 2009), and they also follow fundamentally different trajectories in development (Raznahan, Shaw, et al. 2011; Amlien et al. 2016; Walhovd et al. In press) and aging (Storsve et al. 2014). As expected, there

was a fundamental difference in the principal axis distinguishing CT and SA even for the two-cluster solution, with the CT clusters adhering to an inferior-superior axis, with the plane of the cluster division tilted 19° for SA. While the anterior-posterior SA division was seen also in a previous developmental study, the inferior–superior CT axis was not (Krongold et al. 2017). This could possibly result from methodological differences, e.g. that the previous study used both combined cross-sectional and longitudinal information. A second longitudinal study with an alternative analysis approach reported indirect evidence for an inferior-superior gradient in CT development (Alexander-Bloch et al. 2013), and it has previously been suggested that such a division could be due to cytoarchitectonic features and connectivity patterns (Chen et al. 2013).

The three- and four cluster solutions revealed additional interesting patterns. Not only local clusters were seen, but also relationships between functionally connected regions crossing lobar boundaries. For instance, lateral prefrontal cortex and the lateral anterior temporal cortex were included in the same SA and CT clusters. This fronto-temporal connection fits earlier observations (Raznahan, Lerch, et al. 2011; Krongold et al. 2017), and would be expected from structural connections represented by the uncinate fasciculus (Schmahmann and Pandya 2006). A limbic cluster encapsulating the medial temporal lobe, the cingulum and insula, and extending backward covering the lingual gyrus, cuneus and occipital cortex, was also seen for both SA and CT. This demonstrates that cortical maturation not necessarily follows lobar boundaries, but rather extends beyond what would be expected from anatomical proximity. Similarly, SA of auditory cortex in the superior temporal lobe clustered together with somatosensory, motor and visual cortices in the two-cluster solution, i.e. mimicking functional clusters. Still, morphological change did not follow functional boundaries in a clear-cut manner, as calcarine sulcus (V1) and ventral visual areas clustered with the inferior/ anterior cortex, not the rest of the visual cortex.

Importantly, the developmentally defined clusters showed statistically distinct lifespan trajectories. Although the general form of the trajectories is well known (Fjell et al. 2015; Walhovd et al. 2016), the analyses revealed residual age-relationships for single clusters independently of other clusters. This finding was in accordance with the hypothesis that variations in cortical development has life-long impacts, and consequently that regions that develop together tend to change together through the rest of life. We have previously shown that correlations between longitudinal changes in CT across predefined smaller ROIs are similar in development and aging (Fjell et al. 2015). Here we show that the trajectories of clusters based solely on coordinated developmental change, with no anatomical restrictions imposed on the clustering, can be delineated in a sample spanning more than

80 years, both for SA and CT. Cluster solutions above four were not stable, which caused the clusters to be anatomically extensive. Consequently, they encompassed sub regions found in previous research to show partly different developmental trajectories (Fjell et al. 2015; Amlien et al. 2016). Importantly, however, the clusters consist of regions of correlated developmental change, not necessarily regions with similar trajectories. These main regions of coordinated change will naturally generalize across sub-regions, but the coordination of change across the sub-regions was not stable enough to allow identification of coordinated change across anatomically more fine-grained regions.

Adherence to genetic patterning

The clusters were tested against genetic cortical patterning results (Chen et al. 2013). For CT, we found overlap between developmental and genetic patterns. This fits with our previous finding that regional differences in cortical thinning adhered to genetic organizational principles (Fjell et al. 2015). In the present study, we defined clusters based on developmental change, independently of the genetic patterning. Although the genetic overlap was lower with a higher number of clusters, certain similarities between developmental and genetic organization patterns remained, for instance the prefrontal-temporal relationship (Chen et al. 2013). Thus, partly the same genes seem to govern absolute frontal and temporal CT. A genetic fronto-temporal relationship was also seen in a developmental twin sample for CT and SA (Schmitt et al. 2017).

In contrast, there was limited overlap between the developmental SA clusters and the genetic clusters, revealing interesting differences. Genetic SA relationships seem local or lobar, lacking strong long-distance or cross-region correlation patterns, with generally lower – and more age-invariant - correlations across the cortex (Chen et al. 2011; Schmitt et al. 2017; Strike et al. 2018). The developmental organizational patterns crossed anatomical boundaries, such as the fronto-temporal and the limbic clusters. Another difference was that premotor and postcentral/ somatosensory regions clustered together in development, as seen in previous fetal work (Johnson et al. 2009), but have distinct adult genetic patterns (Chen et al. 2013). Notably, the genetic-developmental similarity for CT is in line with the prediction from the original genetic patterning paper that CT clusters would show genetic relatedness with clusters of similar maturational timing (Chen et al. 2013).

The difference in genetic overlap for CT and SA further illuminates the developmental origins hypothesis. We expected SA change to adhere to major gradients from embryonic development, and CT change to overlap with genes responsible for CT at a later point in life. SA reaches its maximum expansion in early adolescence (Amlien et al. 2016), with the major determinant likely being the

number of cell division cycles of the neural stem cell pool at the premitotic stage of neural development (Rakic 2009). The width of the cortical mini-column at birth is around one-third of its adult size (Buxhoeveden and Casanova 2002), and expansion of cortical SA in childhood can likely be explained by growth of these (Lyll et al. 2015). The developmental SA clusters likely reflect the last part of an expansion that can be traced back to embryonic stage, as also evidenced by the demonstrated adherence to the anterior-posterior gradient of gene expression patterns. In contrast, CT ceases to increase early after birth and reaches 97% of adult values in two years (Lyll et al. 2015). Early CT is affected by asymmetric cell division cycles of the cortical founder pool, determining the number of cells within each column (Rakic 2009). However, the number of neurons in each column is hardly a determinant of cortical changes after the initial CT increase, which rather can be attributed to dendritic branching, synaptogenesis and gliogenesis (Huttenlocher and Dabholkar 1997). Thus, CT change from 4 to 12 years likely reflects either different processes or differences in the relative contributions of the same processes compared to CT change in very early development. Studies show that the genetic contribution to CT but not SA changes during development (Schmitt et al. 2017; Teeuw et al. 2018), and CT shows steeper slopes during adolescent development (Amlien et al. 2016) and later aging (Storsve et al. 2014) than SA. We argue that CT to a greater extent than SA reflects accumulated life-long genetic and environmental impact. Thus, SA is usually more strongly related to early life factors and CT relatively more also to later life factors. Empirical support comes from studies showing larger effects of birth weight and other obstetric factors on SA than CT (Martinussen et al. 2005; Raznahan et al. 2012; Walhovd et al. 2012; Jha et al. 2018), and environmental interventions affecting CT (Engvig et al. 2010; Wenger et al. 2012).

Cognitive correlates of developmental clusters

SA and CT were expected to correlate with different cognitive domains. We hypothesized that SA would be related to GCA, which shows high between-person stability across life (Lyons et al. 2009; Deary et al. 2012), likely due to the impact from early life-factors. Accordingly, we found highly significant lifespan relationships between GCA and the SA clusters, but not CT clusters, in line with previous observations (Vuoksima et al. 2015; Walhovd et al. 2016). In contrast, we speculated that since CT is more strongly related to age and sensitive to environmental influences, it would be related to more specific cognitive functions with lower loadings on the *g*-factor and less established lifelong between-person stability. Episodic memory and executive-speed have lower *g*-loadings than GCA (Deary et al. 2010) and declines steeply with age (Salthouse 2004). We found relationships between these components and all CT clusters. No significant relationships were seen between executive-speed and SA, while the relationships between SA and memory were just significant (limbic

and posterior clusters) or showed a trend ($p = .06$, anterior cluster). Working memory span, which was relatively invariant during adult life, showed comparable relationships with CT and SA. Importantly, however, greater age effects do not equal less between-person stability, and it is as of yet not clear whether memory and executive-speed show less between-person stability over the life-course than GCA. People differ in the amount of change in memory and speeded tasks over time (Salthouse 2016), and change in GCA is more strongly related to “global cognitive” change than changes in episodic memory and speed are (Tucker-Drob 2011). Still, correlations of change within and across cognitive domains tend to increase with age (Tucker-Drob et al. 2014), and a recent meta-analysis showed that 59% of the variance in change is shared across abilities (Tucker-Drob et al. 2018). In any case, a conclusion from the present results is that relationships between cognitive function and cortical morphometry adhere more strongly to modality than anatomical region. Vertex-wise analyses across the cortex could potentially detect more anatomically specific relationships with cognition, but at the levels of major clusters, measurement type seems more important than anatomical location.

Conclusion

In conclusion, cortical SA expansion during childhood was organized according to an AP gradient, seen also during early embryonic development, and related to gene expression and genetic patterning. Clusters of cortical development showed statistically distinct trajectories through 8 decades of life, and correlated with cognitive function in predictable ways, demonstrating continuity of human cortical development from early to late stages of life.

Funding

This work was supported by the Department of Psychology, University of Oslo (to K.B.W., A.M.F.), the Norwegian Research Council (to K.B.W., A.M.F.) and the project has received funding from the European Research Council’s Starting Grant scheme under grant agreements 283634, 725025 (to A.M.F.) and 313440 (to K.B.W.).

Acknowledgement

We thank Jon Skranes for organizing the NTNU part of MoBa.

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Figure legends

Figure 1 Surface area

Left panel: Clusters of coordinated surface area in development, two- (top), three- (middle), and four- (bottom) cluster solutions. Right panel: The lifespan trajectories of each cluster from the three-cluster solution. Top: Trajectories residualized on age (x-axis). Bottom: The residual age-relationship (y-axis) for each cluster accounting for the other two clusters. These curves show the relationship between each cluster and age, if the common variance shared with the other clusters are accounted for. *Relative to the other clusters*, the anterior cluster shows a slight increase with age (larger cluster area goes with older age), while the limbic cluster shows a linear decline (larger cluster area goes with younger age). The colors of the curves correspond to the cluster color in the left figure. The shaded area denotes ± 2 standard errors of the mean.

Figure 2 Cortical thickness

Left panel: Clusters of coordinated cortical thickness in development, two- (top), three- (middle), and four- (bottom) cluster solutions. Right panel: The lifespan trajectories of each cluster from the three-cluster solution. Top: Trajectories residualized on age (x-axis). Bottom: The residual age-relationship (y-axis) for each cluster accounting for the other two clusters (see Figure 1 legend for explanation). The colors of the curves correspond to the cluster color in the left figure. The shaded area denotes ± 2 standard errors of the mean.

Figure 3 Genetic patterns

A: Surface area (SA) developmental clusters, top view. B: Anterior-posterior gradient of PAX6 (left) and P75 (right) from (Rakic et al. 2009). The error bar plot (bottom) shows higher expression of Pax6 in the anterior cluster and higher expression of P75 in the posterior cluster in the BrainSpan database.

Figure 4 Comparison of developmental and genetic clusters

Thickness clusters in the left panel, area clusters in the right panel. 1st column is the development clusters (left hemisphere only shown), middle column is the genetic clusters from (Chen et al. 2013), right column is a conjunction map of the concordance/ discrepancy of development vs. genetics. Vertices belonging to the same cluster across the developmental and the genetic clusters are shown in blue/ red/ yellow. Vertices that are discordant between the developmental and the genetic clusters are shown in green. Thus, the size of the green area represents amount of discrepancy

between the developmental and the genetic cluster solutions. As can be seen, the overlap is better for the two- compared to the three-cluster solutions, and better for thickness than area.

Figure 5 Random clusters

The random clusters generated using the k-means algorithm.

Figure 6 Cognitive relationships

A: Each cognitive domain plotted against age, residualized on time point to remove retest effects. For trajectories of the tests loading highly on GCA (matrix reasoning, vocabulary) see SI. B: Heat maps of F-values illustrating the relationship between each cluster and each cognitive function, regressed on age and sex (SA). C: Examples of brain cognition-relationships for the limbic cluster for thickness (two plots to the left) and area (two plots to the right). Plots for all variables are presented in SI. The shaded area denotes ± 2 standard errors of the mean.

	Obs	n	Age ¹	Follow-up interval
< 20 years	1021	644	9.2 (4.1-19.7)	1.7 (1.0-3.2)
20-50 years	234	136	35.2 (20-50)	3.2 (0.2-6.3)
> 50 years	378	194	64.8 (50.5-85.3)	1.6 (0.2-6.6)

¹ Age at baseline

Obs: Number of observations

n: Number of participants

Table 1 Number of observations

	Memory	Excecutive -speed	Working memory	GCA
Recall 30min	.86			
Learning	.82			
Recognition	.81			
Stroop words		.92		
Stroop colors		.85		
Stroop colors/ words		.83		
Digit span forward			.87	
Digit span backward			.78	
Vocabulary				.82
Matrix reasoning	.47			.69

Table 2 Rotated component matrix

Values below .40 are suppressed. Rotation Method: Varimax with Kaiser Normalization. Rotation converged in 5 iterations. GCA: General Cognitive Ability. Recall, learning and recognition from CVLT, Vocabulary and Matrix from WASI.

	edf	F	p	R ² (adj)
		s(Age)	s(Age)	model
Memory	7.36	89.5	<2e ⁻¹⁶	.62
Executive-speed	8.25	44.9	<2e ⁻¹⁶	.77
Working memory	4.90	38.8	<2e ⁻¹⁶	.36
GCA	7.01	405.5	< 2e ⁻¹⁶	.78

Table 3 Effects of age on the cognitive components

Generalized additive mixed effects models (GAMM) were run with age as a smooth term, subject timepoint as a linear covariate and subject as random effect. Adjusted R² refers to the full model including covariates. GCA: General Cognitive Ability. Edf: effective degrees of freedom for the smooth term.

	edf	F	p
<i>Memory</i>			
Limbic	1.00	3.4	0.07
Posterior	1.00	2.8	0.09
Anterior	1.00	2.5	0.12
<i>Executive-speed</i>			
Limbic	1.04	0.0	0.88
Posterior	1.00	0.0	0.84
Anterior	1.00	0.1	0.80
<i>Working memory</i>			
Limbic	1.00	4.3	0.03
Posterior	1.00	5.6	0.018
Anterior	1.00	7.1	0.008
<i>GCA</i>			
Limbic	1.00	15.0	0.0001
Posterior	1.00	14.3	0.0002
Anterior	1.00	14.5	0.0001

Table 4 Effects of cluster surface area on the cognitive factors in the full sample

Generalized additive mixed effects models (GAMM) were run with age as a smooth term and cluster as a linear predictor. Subject time point was included as a linear covariate and subject as a random effect variable.

p < .05 corrected (adjusted Bonferroni correction for four cognitive factors and 3 clusters taking between-cluster correlations into account) ***p*** < .05 uncorrected.

GCA: General Cognitive Ability

edf: effective degrees of freedom for the smooth term (a measure of deviation from linearity)

	edf	F	p
<i>Memory</i>			
s(Limbic)	2.16	3.8	0.02
s(Superior)	2.70	6.7	0.005
s(Inferior)	2.70	4.4	0.02
<i>Executive-speed</i>			
s(Limbic)	3.39	8.3	0.01
s(Superior)	2.04	3.4	0.10
s(Inferior)	2.93	9.9	0.005
<i>Working memory</i>			
s(Limbic)	1.00	2.3	0.13
s(Superior)	1.00	4.7	0.03
s(Inferior)	1.00	2.2	0.14
<i>GCA</i>			
s(Limbic)	2.16	2.9	0.06
s(Superior)	1.00	0.0	0.98
s(Inferior)	1.00	0.0	0.90

Table 5 Effects of cortical thickness on the cognitive factors in the full sample

Generalized additive mixed effects models (GAMM) were run with age and each cluster as smooth terms. Subject time point was included as a linear covariate and subject intercept as a random effect variable.

p < .05 corrected (adjusted Bonferroni correction for four cognitive factors and 3 clusters taking between-cluster correlations into account) ***p*** < .05 uncorrected.

GCA: General Cognitive Ability

edf: effective degrees of freedom for the smooth term