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High-Expanding Cortical Regions in Human Development and Evolution Are Related to Higher Intellectual Abilities

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Cortical surface area has tremendously expanded during human evolution, and similar patterns of cortical expansion have been observed during childhood development. An intriguing hypothesis is that the high-expanding cortical regions also show the strongest correlations with intellectual function in humans. However, we do not know how the regional distribution of correlations between intellectual function and cortical area maps onto expansion in development and evolution. Here, in a sample of 1048 participants, we show that regions in which cortical area correlates with visuospatial reasoning abilities are generally high expanding in both development and evolution. Several regions in the frontal cortex, especially the anterior cingulate, showed high expansion in both development and evolution. The area of these regions was related to intellectual functions in humans. Low-expanding areas were not related to cognitive scores. These findings suggest that cortical regions involved in higher intellectual functions have expanded the most during development and evolution. The radial unit hypothesis provides a common framework for interpretation of the findings in the context of evolution and prenatal development, while additional cellular mechanisms, such as synaptogenesis, gliogenesis, dendritic arborization, and intracortical myelination, likely impact area expansion in later childhood.

Keywords: cerebral cortex, development, evolution, macaque monkeys, magnetic resonance imaging

Introduction

Human cortical surface area has tremendously expanded during evolution (Kaas 2008), with large scaling effects in some regions and smaller in others (Van Essen and Dierker 2007). Interestingly, Hill et al. (2010) demonstrated similarities between cortical expansion in evolution and development—evolutionary high-expanding cortical areas tended to show high developmental expansion, suggesting that evolutionary factors have shaped ontogenetic cortical development. To a certain extent, cortical regions supporting mental capacities in which humans excel compared with other primates have expanded the most (Haug 1987; Sherwood et al. 2008), and it has been suggested that human-specific cognitive adaptations are correlated with enlargement of the neocortex (Sherwood et al. 2008). This made us speculate whether expansion of specific cortical regions could be a general feature associated with improved intellectual function during both ontogenetic and phylogenetic development. If so, one would expect high-expanding regions also to show the strongest correlations with intellectual function within the human species. As the superior intelligence of humans is likely caused by the combination and improvement of properties found in nonhuman primates rather than from unique features (Roth and Dicke 2005), intelligence may have some of the same neural substrates across primates. A similar principle could also apply to development—areas of greater expansion during ontogeny may be more related to late-maturing intellectual functions than those of lesser expansion. Improved cognitive function related to cortical expansion in evolution and human development would suggest a general condition for the advancement of intellectual functions, although the absolute magnitudes of expansion in evolution and development are very different.

Intellectual function and gross brain volumetric measures appear moderately related in humans (McDaniel 2005; Deary et al. 2010), but the regional pattern of correlations between local cortical arealization and cognitive abilities is not known. Simplified, local cortical arealization is computed as the distance a given point on the brain surface has to move to align with a similar point on a template surface, this yielding a measure of area at every given point (see Materials and Methods for a more accurate description). There are relationships between cortical thickness and general intellectual function in development (Karama et al. 2009; Tamnes et al. 2011b), with different developmental trajectories for children with different ability levels (Shaw et al. 2006). In the present context, area may be a more appropriate measure than thickness; however, as cortical expansion and associated gyrification likely are more important in evolution and development (Rakic 2009; White et al. 2010). Area expansion during evolution, without comparable thickness increases, can be understood within the radial unit hypothesis. Even single gene mutations during evolution could potentially increase the number of proliferative founder cells in the ventricular zone, triggering a cascade of events culminating in an increased number of radial units and consequently, expansion of cortical surface area without a parallel increase in thickness (Rakic 2009). Area expansion will cause the formation of gyri that bring strongly interconnected regions more closely together, leading to spatially compact neural circuitry (Van Essen 1997). Computational modeling has also indicated that increased gyrification and areal expansion are more efficient means to facilitate brain connectivity and functional development than increasing the thickness of the cortex (White et al. 2010).

In this study, we address the hypothesis that cognitive functions where humans excel compared with primates reside in

evolutionary recent regions that also show considerable ontogenetic expansion. Thus, we tested whether the regional distribution of relationships between general intellectual function and local cortical arealization in humans mapped onto areas of high cortical expansion during development and evolution.

Materials and Methods

Sample and Cognitive Testing

Sample descriptive are provided in Table 1. One thousand and forty-eight healthy participants between 8 and 89 years (mean 45.9, SD = 21.6) satisfied all inclusion criteria and underwent testing with matrix reasoning and vocabulary subtests from Wechsler's Abbreviated Scale of Intelligence (WASI; Wechsler 1999). They were drawn from 3 related research projects; neurocognitive development (Tamnes et al. 2011a), cognition and plasticity through the life span (Westlye et al. 2010; Fjell et al. 2011), and the Norwegian Cognitive Neurogenetic project (Espeseth et al. 2008, 2012). Details regarding recruitment and screening can be found in the mentioned references. All projects were approved by the Regional Committee for Medical and Health Research Ethics of Southern and Western Norway, and all participants (or a parent in case of minors) gave informed consent. Briefly, participants were recruited through local schools and workplaces and newspaper ads. All participants were screened by a health interview and underwent a neuropsychological examination. History of self- or parent-reported neurological or psychiatric conditions thought to affect normal cerebral functioning, including clinically significant stroke, serious head injury, untreated hypertension, diabetes, and use of psychoactive drugs within the last 2 years, were exclusion criteria. Further, participants reporting worries concerning their cognitive status, including memory function, were excluded. All included subjects' magnetic resonance' (MR) scans were examined by a specialist in neuroradiology and deemed free of significant anomalies. For 646 of the older adults, Mini-Mental Status Examination (Folstein et al. 1975) was administered, with none scoring <26. No participants scored below the normal Intelligence Quotient (IQ) range (82–148), and the mean was about 1 SD above the expected population mean (115.1, SD = 10.9).

Magnetic Resonance Imaging and Analysis

Participants were scanned on 4 different 1.5-T magnets (Siemens Symphony, $N = 74$; Sonata, $N = 214$; Avanto, $N = 660$; and General Electrics Signa Echospeed, $N = 100$)—detailed scanning protocols are given in Table 2. All scans were preprocessed in the Neuroimaging Analysis Laboratory at the Department of Psychology, University of Oslo, by the use of FreeSurfer version 5.0 (http://surfer.nmr.mgh.harvard.edu). The basic methods are described in depth elsewhere (Dale et al. 1999; Fischl, Serena, Dale 1999, Fischl, Serena, Tootell, et al. 1999). Briefly, processing steps include motion correction, removal of nonbrain tissue, automated Talairach transformation, and intensity correction. Intensity and continuity information from the 3-dimensional (3D) volume are used in segmentation and deformation procedures to reconstruct a gray/white matter boundary throughout the brain (Dale et al. 1999). Cortical surfaces then undergo inflation, registration to a spherical atlas, and identification of gyral and sulcal regions (Desikan et al. 2006). Individual surfaces were inspected for accuracy, and manually corrected if judged inaccurate. All segmentations were manually inspected for accuracy by an experienced operator, and corrected in case of errors. Minor manual edits were performed on most participants (>80%), usually restricted to the removal of nonbrain tissue, typically dura/vessels adjacent to the cortex. Additionally, the presence of local artifacts sometimes caused small parts of the white matter (WM) to be segmented as gray matter (GM). Such errors were routinely corrected. Surface area maps of the GM–WM boundary were then computed for each subject by calculating the area of every triangle in the cortical surface tessellation. The triangular area at each point in native space was compared with the area of the analogous point in registered space to give an estimate of surface area expansion or contraction continuously along the cortical surface ("local arealization") (Fischl, Serena, Dale 1999; Hogstrom et al. 2012). Before statistical analyses, maps were smoothed with a Gaussian kernel of full-width at half-maximum of 20 mm. A large smoothing kernel was chosen since we did not expect small and spatially highly restricted relationships across evolution and development.

A previously generated map of evolutionary cortical expansion between the macaque monkey and 12 young adult humans (Van Essen and Dierker 2007; Hill et al. 2010), computed based on a combination of functional and structural homologies (Orban et al. 2004), were registered to the same template brain that was used for visualization of the human arealization results. Profound differences between the macaque brain and the human brain render shape features generally not optimal as the only constraint on registration—landmarks based on known or suspected homologies may increase the accuracy of the registration and hence the calculation of regional arealization (Van Essen and Dierker 2007). In contrast, much smaller differences in overall shape features between 4-year-old child brains and young adult brains exist, making a spherical registration based on these feasible. Thus, the method used for generation of the evolutionary expansion map and the developmental expansion map was not identical, but the resulting maps of cortical arealization are comparable.

Evolutionary expansion maps were available for the right hemisphere only. The right hemisphere evolution map was registered to the left hemisphere template surface by a FreeSurfer tool designed for interhemispheric overlay registrations. We believe that this interhemispheric registration procedure represents a valid approach for the following reasons: (1) Evolutionary expansion from macaque to humans is very large, with a cortical area being 15–30 times larger in humans across almost the entire surface (Van Essen and Dierker 2007). To the extent that asymmetric cortical expansion is seen across evolution, these variations would be minute and hardly visible compared with the very large overall expansion. (2) Studies identifying evolutionary asymmetries have mainly focused on temporal and frontal language-related regions, where larger left-than-right expansion has been demonstrated (e.g. Schenker et al. 2010; Lyn et al. 2011). These regions are classified as high expanding in the present data, and additional expansion in the opposite hemisphere would thus not affect the results. It can also be added that the general pattern of surface asymmetry in fossil species of Homo was not found to be different from anatomically modern Homo sapiens (Balzeau et al. 2012), and that, for instance, the evolutionary development that gave rise to planum temporale asymmetry occurred before our split with the chimpanzees (Lyn et al. 2011).

Expansion maps for human development were computed based on a sample of 331 healthy children from 4 to 20 years, including the 204 participants under 20 years described in Table 2. We used a smoothing spline approach (Fjell et al. 2010), modified to surface-based arealization analyses (Fjell, Westlye, et al. 2012), to estimate the mean annualized rate of change for each surface vertex across the age range. Compared with the evolutionary expansion, the cortical expansion from 4 years in humans is very small, which can possibly allow for hemispheric differences to become evident on top of the overall developmental expansion. Thus, hemispheric expansion maps are created per hemisphere for development.

Table 1
Sample characteristics

	Full sample mean (SD)	8–20 years mean (SD)	20–40 years mean (SD)	40–60 years mean (SD)	60–89 years mean (SD)
N	1048	204	210	273	361
Age	45.9 (21.6)	14.8 (3.6)	28.6 (5.5)	51.8 (5.3)	68.9 (5.7)
Sex	622 f/426 m	106 f/98 m	127 f/83 m	171 f/102 m	218 f/143 m
Education	14.8 (2.8)	NaN	15.3 (2.1)	15.1 (2.3)	14.4 (3.3)
Vocabulary	61.3 (10.7)	48.2 (11.4)	62.9 (7.5)	65.1 (7.0)	64.8 (8.3)
Matrix reasoning	27.0 (5.0)	27.8 (4.3)	30.1 (2.8)	28.0 (3.3)	23.9 (5.8)
IQ	115.1 (10.9)	109.0 (10.7)	116.6 (9.1)	115.9 (9.0)	117.2 (12.1)
MMSE	29.0 (0.9)	NaN	29.2 (0.8)	29.2 (0.8)	28.9 (1.0)

Note: Information about education was available for 856 and MMS for 646.
F, female; M, male; IQ, Intelligence Quotient (age-adjusted), vocabulary and matrix reasoning are subtests from the Wechslers Abbreviated Scale of Intelligence (raw scores, not age-adjusted); MMSE, Mini-Mental Status Examination; NaN, not a number (information was not obtained).

Table 2

Participants were scanned on 4 different 1.5 magnets, with T_1-weighted scans with the parameters given in the table

	Siemens Sonata ($N = 214$)	Siemens Avanto ($N = 660$)	Siemens Symphony ($N = 74$)	GE Sigma Echospeed ($N = 100$)
Sequence	3D MPRAGE	3D MPRAGE	3D MPRAGE	3D FSPGR IR
TR (s)	2.730	2.400	2.730	9.5 ms
TE (ms)	3.43	3.61	4.0	2.2
TI (ms)	1000	1000	1000	450
FA	7°	8°	7°	7°
Voxel size (mm)	1.0 × 1.0 × 1.3	1.25 × 1.25 × 1.20	1.0 × 1.0 × 1.3	0.94 × 0.94 × 1.4
Matrix	256 × 256	192 × 192	256 × 192	256 × 256
Number of acquisitions	2	2	2	2
Acquisition plane	Sagittal	Sagittal	Sagittal	Sagittal

MPRAGE, magnetization-prepared rapid gradient echo (Siemens); FSPGR, fast spoiled gradient-echo inversion recovery (General Electrics); TR, repetition time; TE, echo time; TI, inversion time; FA, flip angle.

For all magnets were 2 identical sequenced ran to allow averaging during postprocessing to increase the contrast-to-noise ratio.

Both the evolution and developmental expansion maps were z-transformed, yielding a mean of zero and a standard deviation of one for each map, to remove scaling differences between evolutionary and developmental expansion and to make the maps directly comparable.

Statistics

Relationships between raw scores on the matrix reasoning and vocabulary subtests and local arealization were tested by separate general linear models (GLMs). Separate models were fitted for each vertex across the brain surface, with area as a dependent variable, and test score as independent, with age, square of age, sex, scanner model, and the interaction between sex and scanner model as covariates of no interest. The statistical results were thresholded corresponding to a false discovery rate (FDR) of <0.05 to correct for multiple comparisons across space. For the significant vertexes, Pearson's correlations coefficients (r) were calculated, and projected onto a template brain as color-coded surface maps. The expansion maps for evolution and childhood development were z-transformed as described above, and displayed on the same template brain as the correlations. For each vertex, the z-transformed expansion values were extracted from the development and the evolution maps separately. Expansion values for the evolution and development were then correlated (Pearson's r) across the brain surface, yielding a global estimate of degree of anatomical coherence between development and evolution. High-expansion values across the same vertices in development and evolution would contribute to a high correlation, as would low expansion values. High values in evolution and low values in development, or vice versa, would contribute to a lower correlation coefficient.

Next, the development and evolution expansion maps were thresholded at ±0.5 SD to yield high- ($z > 0.5$ SD) versus medium- ($-0.5 \leq z \leq 0.5$) versus low- ($z > 0.5$) expanding areas. A conjunction map was created, where vertices of high expansion during both development and evolution, and that of low expansion during both development and evolution, were identified. Within the high- and low-expanding areas, the number of vertices showing a significant relationship between cognitive scores and local arealization was counted. T-tests were used to compare the number of vertices with significant area correlations across high- and low-expanding regions. Finally, conjunction maps were created, showing regions where area–cognition correlations overlapped with regions of high versus low expansion across both development and evolution.

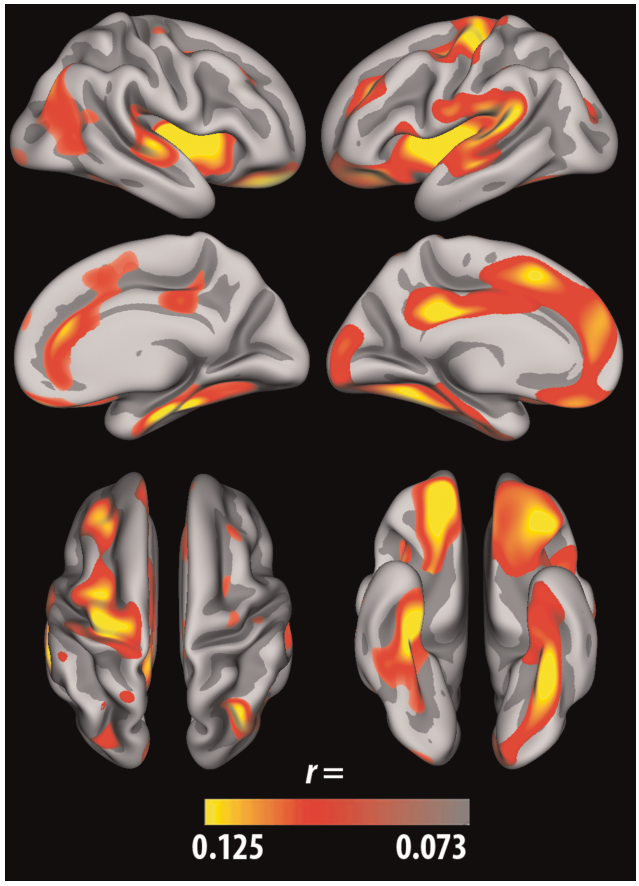

Figure 1. Performance ability–area correlations in humans. The maps show regions where high scores on the matrix reasoning test were correlated with cortical area. All relationships were positive. The results are corrected for multiple comparisons using a FDR threshold of <0.05. Age, sex, and scanner were used as covariates. The brain was semi-inflated to allow visualization of effects within sulci. No negative correlations were observed.

Results

The relationship between local cortical arealization and cognitive function was tested by repeated GLMs with the area at each point of the brain surface as a dependent variable, 2 subtests from WASI (matrix reasoning and vocabulary) in turn as predictors, with scanner, age and sex, as well as the interaction between them, included as covariates of no interest. The correlations between local cortical arealization and matrix reasoning (performance abilities), corrected for multiple comparisons by an FDR of <0.05, are shown in Figure 1. Widespread positive relationships were found in all lobes, covering 20.9% of the right and 36.0% of the left hemisphere surface. Effects were seen across hemispheres in anterior and posterior parts of the cingulate cortex, superior temporal gyrus, medial temporal lobe (parahippocampal and entorhinal cortices),

fusiform gyrus, insula, and lateral and medial orbitofrontal cortices. Additional relationships were seen around left central sulcus and cuneus/posterior lingual gyrus. The strength of the correlations were modest, and the relationships exceeding $r = 0.125$ for few vertices only. No negative relationships were observed, meaning that higher cognitive scores were associated with a larger cortical surface area. For vocabulary (verbal abilities), only in one region (entorhinal cortex in the right hemisphere) did the relationship survive correction for multiple comparisons (Fig. 2). Further analyses for vocabulary were thus not performed.

The evolutionary cortical expansion map was registered to the same template brain used in the cognitive analyses. The maps were z-transformed to remove scaling differences between evolution and development. The resulting maps show vertices with higher ($z \geq 0$) versus lower ($z < 0$) cortical expansion (Fig. 3). Likewise, developmental expansion maps were computed based on z-transformation of estimated percentage area change, averaged across from 4 to 20 years ($N = 331$, see Materials and Methods; see Supplementary Figure 1 for left hemisphere developmental expansion maps). Similarities were seen between the evolution and development maps. Across the surface, expansion values correlated 0.22 (left hemisphere) and 0.15 (right) (both $P' < 0.05$, corrected) between development and evolution. Regions of higher than mean expansion in both development and evolution included the lateral temporal cortex, superior frontal gyrus, insula, inferior parietal/supramarginal gyrus, inferior frontal gyrus, lateral orbitofrontal cortex, and the anterior cingulate. However, there were also regions of high expansion in development and low expansion in evolution, or vice versa. For instance, inferior and posterior cortical areas, including the lateral occipital cortex, cuneus, lingual gyrus, fusiform gyrus, and the medial temporal cortex, were low expanding in evolution but not in development, while parts of the cuneus, lingual gyrus, posterior cingulate/retrosplenial cortex, and medial temporal cortex were high expanding in development but not in evolution.

The evolution and development maps from Figure 3 were thresholded to show high- versus low-expanding cortical regions common for development and evolution, that is, regions exceeding ±0.5 SD relative to the rest of the cortex in both development and evolution (Fig. 4). We tested whether the number of vertices showing a significant relationship with matrix reasoning differed between high- and low-expanding areas. For both the right (t [df = 36 466] = 56.4, $P < 10^{-6}$) and left (t [df = 36 548] = 106.8, $P < 10^{-6}$) hemispheres, significantly more vertices were related to cognition in both the high- versus low-expanding areas, and also in the high- versus medium- ($-0.5 \leq z \leq 0.5$) expanding areas (right: t [df = 32 586] = 4.8, $P < 10^{-5}$; left: t [df = 33 178] = 25.5, $P < 10^{-5}$).

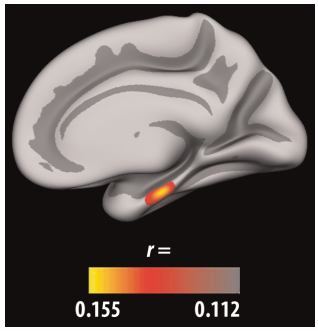

Figure 2. Verbal ability–area correlations in humans. The maps show positive correlations between high scores on the vocabulary test and cortical area. The results are corrected for multiple comparisons using a FDR threshold of <0.05. Age, sex, and scanner were used as covariates of no interest. The brain was semi-inflated to allow visualization of effects within sulci. No negative correlations were observed.

We then computed conjunction maps from the high- and low-expanding areas from Figure 4, and the vertices showing significant area–cognition correlations in Figure 1 (Fig. 5). High-expansion regions across development and evolution generally mapped well onto cognition–arealization relationships. This was especially true for a large bilateral cluster covering a major part of the anterior cingulate, extending into the medial superior frontal gyrus. A large cluster was also seen in the left middle frontal gyrus, with 2 smaller but overlapping effects in the right hemisphere. In addition to these major effects, smaller and more scattered effects were seen in frontal and lateral temporal areas. A small cluster of opposite effects (low-expanding areas across development and evolution in areas correlating with cognition) were seen in the right lateral occipital cortex.

Validation Analyses

Scanner/sequence was entered as a covariate in the GLM analyses. Still, to ensure that no residual effects of scanner or sequence affected the cognition–area relationship, we performed a validation analysis on the 660 participants scanned on the Avanato scanner with the same sequence (mean age = 41.2, range 8.2–85.4 years, 364/296 females/males). Mean local arealization across all vertices in the left hemisphere showing a significant relationship with the matrix score was calculated and was correlated with the matrix score, with age, square of age, and sex entered as covariates. For the full sample, the area–matrix correlation was 0.17 ($P < 10^{-6}$). When restricting the analysis to the Avanto participants, the coefficient did not change substantially and was still highly significant ($r = 0.18$, $P < 3 \times 10^{-5}$). To ensure that no residual effects of sex did affect the results, further analyses were run for females and males separately in the full sample. The coefficients were highly similar (females, $r = 0.19$ and males, $r = 0.20$; both $P' < 3 \times 10^{-4}$). To ensure that the elderly participants did not affect the results beyond what was controlled for by the inclusion of age and square of age as covariates, the analysis was repeated excluding all participants above 60 years ($N = 673$, mean age 33.8, range 8.2–60 years). The coefficient increased slightly ($r = 0.24$, $P < 10^{-6}$), but was not significantly higher than the full-sample correlation ($z = 1.41$, $P = 0.16$).

Discussion

The main finding was that the area of high-expanding cortical regions during both development and evolution is more related to individual differences in cognitive performance in humans than that of low-expanding regions. High-expanding regions correlating with cognitive function included especially the anterior cingulate and parts of the frontal cortex. These findings suggest that one common macrostructural factor in improvement of cognitive function during development and evolution is regional increases in the cortical surface area.

General cognitive abilities in humans are moderately related to gross structural brain characteristics (McDaniel 2005; Deary et al. 2010). The regional distribution of correlations between

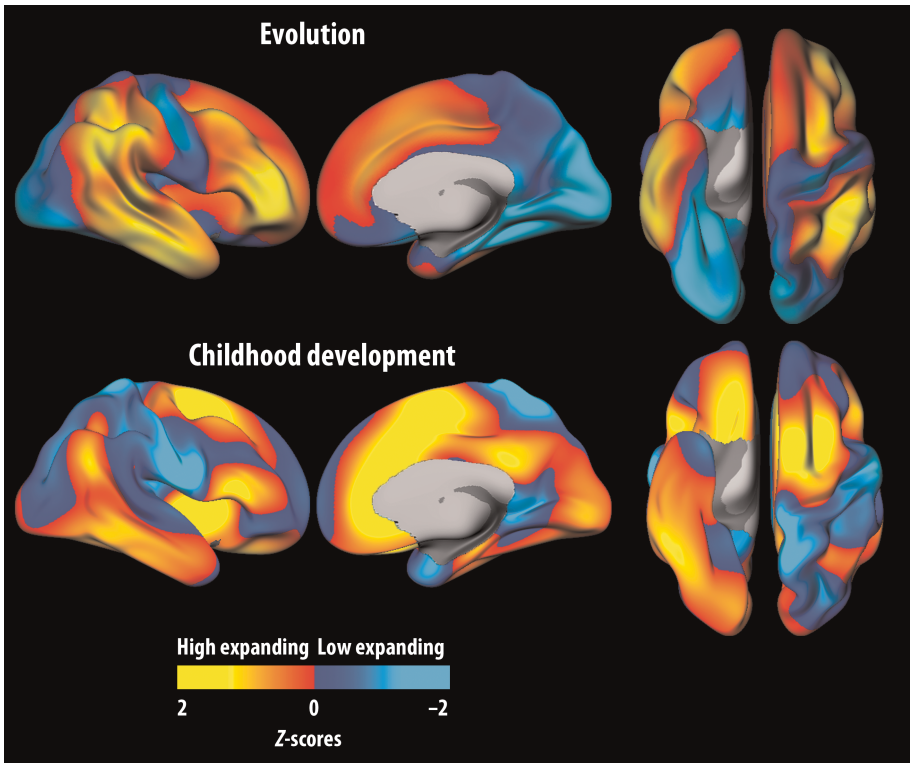

Figure 3. Cortical expansion across evolution and development. The maps show areas with more (red-yellow) versus less (blue-cyan) than average cortical expansion from macaque to adult humans (top row) and from 4- to 20-year-old humans (bottom row). To remove scaling differences, the maps are *z*-transformed, yielding a mean of 0 and a standard deviation of 1, allowing a direct comparison of expansion patterns between evolution and human development.

cognitive abilities and cortical area has not been known; however, as previous studies have mainly measured volume (Andreasen et al. 1993; Flashman et al. 1997; Haier et al. 2004; Walhovd et al. 2005; Witelson et al. 2006) or thickness (Fjell et al. 2006; Shaw et al. 2006; Narr et al. 2007; Karama et al. 2009; Tamnes et al. 2011a; Karama et al. 2013). The present results show that a regional pattern of area–cognition correlations is present in all lobes. The matrix reasoning task requires relational integration across different stimulus dimensions. This type of test loads highly on the higher-order *g* factor (Deary et al. 2010), and performance on such general tasks are supported by distributed brain networks (Glascher et al. 2009, 2010). Jung and Haier (2007) reviewed a large number of neuroimaging studies and suggested that structural properties of a network of brain regions, including dorsolateral prefrontal, parietal, anterior cingulate, and specific regions in the temporal and occipital cortex, were related to individual differences in intelligence. The present effects overlap with the findings of Jung and Haier, for example, the broad effects in the anterior cingulate, lateral temporal and occipital cortex, temporo-parietal junction, and prefrontal areas. According to a recent review, the left hemisphere seems to be most important to cognitive performance (Deary et al. 2010). The presently observed brain–cognition relationships were rather symmetrically distributed across hemispheres, but the effects were clearly more spatially extended in the left hemisphere, including major language areas. However, more research is needed before a clear picture of systematic hemispheric differences in the brain structural correlates of cognitive tests with high *g*-loadings emerges.

Overlap with the present findings, especially in the occipital and temporal lobe, was also found in the major voxel-based lesion mapping studies by Glascher et al. (2009, 2010). Recently, it was proposed that intelligence is an emergent property of anatomically distinct cognitive systems, and that corecruitment of multiple such networks support the *g*-factor (Hampshire et al. 2012). The widespread correlations seen in the present study are thus not surprising. Additionally, a meta-analysis of functional imaging studies found convergent evidence for medial frontal cortical involvement across tasks with different cognitive tasks ("multiple demand") and task related to fluid intelligence (Duncan 2010), for example, matrix reasoning, overlapping well with the major expansion–matrix reasoning effect in the present study. Extended relationships for matrix reasoning compared with vocabulary have previously been shown for cortical thickness (Karama et al. 2011). Matrix reasoning may have a stronger basis in gross measures of brain structures than the more culturally amendable vocabulary test, which may explain the lack of relationship between vocabulary and cortical area.

Of most interest, cortical regions where area was related to higher cognitive functions generally mapped onto regions showing high expansion during development and evolution. Overlap between cognition–area correlations and expansion was almost exclusively found in the consistently high-expanding areas. Since the most prominent feature of the evolution of the human cerebral cortex is expansion of the surface area, without a similar increase in thickness (Rakic 2009), this is an intriguing finding. Expansion of the human brain seems largely to be due to increased neuronal number rather than increase in neuronal size (Kaas 2008), although there are also substantial differences in cellular structure among primates (Elston et al. 2006). Neuronal number is likely more relevant for intelligence across

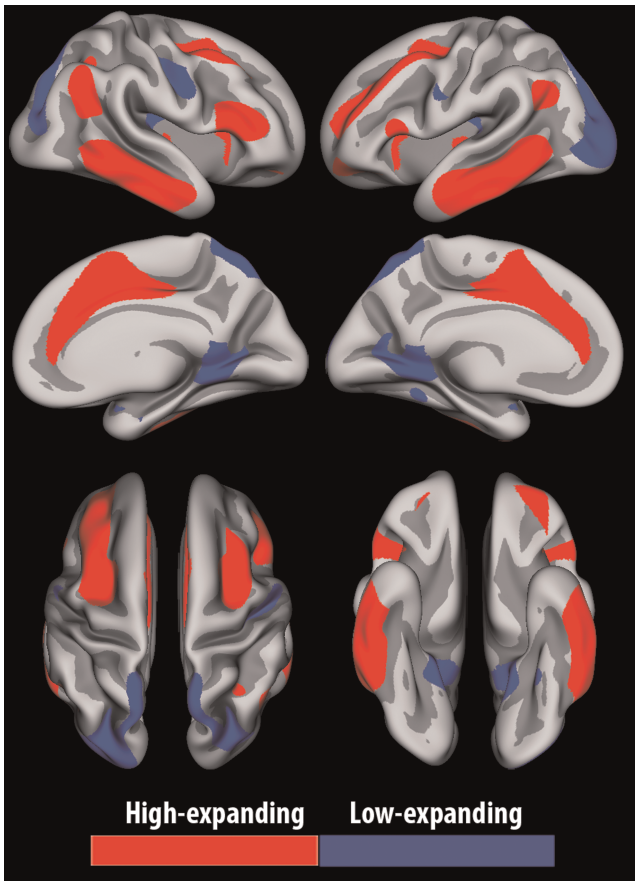

Figure 4. High- and low-cortical expansion consistent during evolution and development. The *z*-transformed maps of evolutionary and developmental expansion from Figure 3 were thresholded at $0.5 < z < -0.5$ standard deviations and combined, yielding maps of high (red) versus low (blue) expansion during both evolution and development.

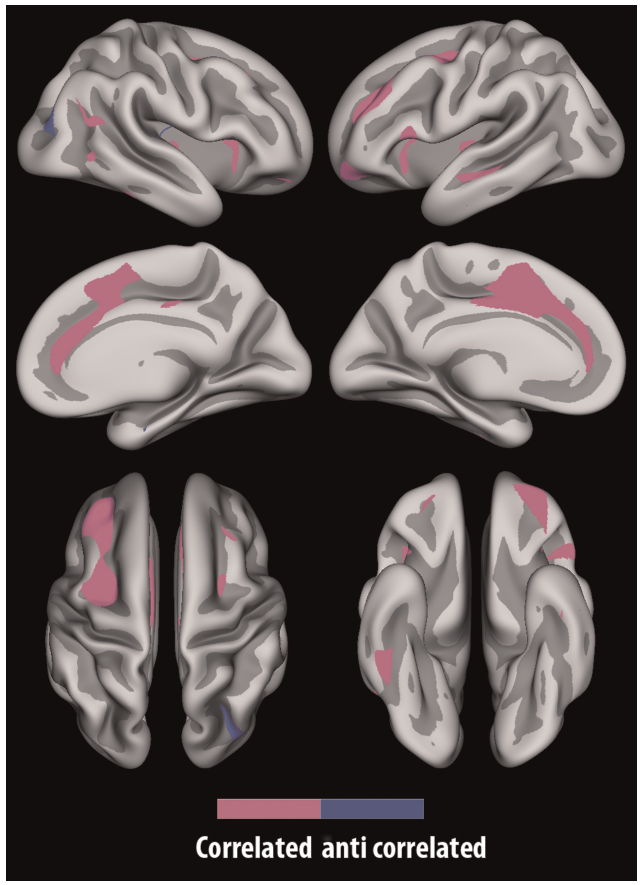

Figure 5. Relationship between cortical expansion and cognition across evolution and development. The maps show cortical regions that are both high-expanding during evolution and childhood development and related to individual differences in cognitive scores among humans (correlated; pink), and common low-expanding cortical regions related to cognitive scores ("anticorrelated"; dark blue). Correlations between cognitive scores and evolutionary and developmental expansion are seen in large regions, while the opposite pattern is hardly evident. The maps were generated by combining results from Figures 1 and 4. Please note that as the entire cortex expands during evolution and development, "anticorrelations" are used to denote correlations between area and IQ in areas expanding <0.5 SD below the mean of the cortex.

species than brain size per se (Roth and Dicke 2005). However, since bigger brains generally have more neurons (Pakkenberg and Gundersen 1997), and overall brain size is a good predictor of cognitive ability across nonhuman primates (Deaner et al. 2007), brain size is a reasonable proxy for the neuronal number. The human brain is a linearly scaled-up primate brain with regard to the relationship between size and neuronal number (Azevedo et al. 2009), and also in humans is a relationship between brain size and neuronal number demonstrated (Pakkenberg and Gundersen 1997). Thus, it is possible that the general mechanisms driving the structural brain changes during evolution also contribute to explain the relationship between cognitive performance and cortical area in humans observed in the present study. Our results suggest that cortical expansion is a common correlate of improvement of higher cognitive functions during ontogenetic as well as phylogenetic development, and that the regional heterogeneity of cortical expansion is at least partly shaped by the benefits of improved intellectual function during development and evolution. However, as discussed in the following, there are almost certainly also fundamental differences in the cellular mechanisms responsible for the area increases.

There is a growing interest in using various neuroimaging techniques to map human cognitive functions to brain evolution. For instance, Mueller et al. (2013) demonstrated correlations between interindividual variability in functional connectivity and evolutionary cortical expansion. High-expanding areas were characterized by more variability between participants in functional couplings. This fits with the present findings that variability in the cortical area in the same high-expanding regions are related to scores on cognitive tests. In another recent study, functional networks were directly compared between humans and monkeys, and both interspecies corresponding and human-specific networks were identified (Mantini et al. 2013). Interestingly, the expansion–IQ correlation regions in the present study (Fig. 4) overlap both a medial prefrontal cluster common to monkeys and humans and a human-specific cingulo-insular cluster. It is possible to speculate that the superior human performance on cognitive tests of the type used in the present study are caused partly by evolutionary novel networks supporting human-specific skills, as well as redeployed networks that are structurally similar across species but serving partially different functions. This is also consistent with the cortical expansion theory, according to which novel human abilities emerged as a result of expansion of specific frontal and parietal regions (Sherwood et al. 2008).

The cellular mechanisms responsible for the enormous area expansion during evolution, without comparable thickness increases, can be understood within the radial unit hypothesis. According to this model, an increase in the number of neural stem cells by symmetrical division before neurogenesis will yield an exponential increase in the founder cells that give rise to the radial cortical columns (Rakic 2009), which again results in the expansion of cortical area. In contrast, asymmetric cell division during neurogenesis determines cortical thickness (Rakic et al. 2009). This hypothesis is powerful as an explanation of cross-species differences in cortical area, area expansion prenatally and for individual differences between humans: As more columns imply more neurons, this theory yields a framework for understanding the parallel increase in cortical area and cognitive abilities in evolution, and the correlations between surface area and cognitive test scores in humans. Individual differences in the cortical area in newborns are affected by a number of genetic and intrauterine environmental factors, possibly having permanent effects on the cerebral cortex (Walhovd et al. 2012). The fetus responds to environmental conditions by long-lasting regulatory change, in part via alterations in gene expression (Blusztajn and Mellott 2012), coined fetal programming or developmental plasticity (Barker 2004). For instance, birth weight was in 2 recent studies shown to have lasting effects on cortical area, but not on thickness (Raznahan et al. 2012; Walhovd et al. 2012). This could possibly be related to differences in progenitor cell division within the subventricular zone, selectively affecting the cortical area but not thickness.

An interesting line of research has demonstrated how distinct regions of the cortex can be selectively expanded independently of other regions by the expression of specific transcription factors at early developmental stages (Cholfin and Rubenstein 2007). For instance, neonatal frontal cortex subdivision can be regulated through regional transcription factors within specific parts of the initial clustering of embryonic cells of the frontal cortex (Cholfin and Rubenstein 2008). Such findings provide experimental evidence on how cortical regions develop in individuals, and on how they may have emerged during evolution, by integration of radial unit and protomap (Rakic 1988) hypotheses. Global transcriptome analysis of the mid-fetal human brain has yielded additional evidence for genetic differences between functionally distinct regions of the developing prefrontal cortex (Johnson et al. 2009). Interestingly, more than 200 of the genes with possible expression differences within the frontal lobe appear to be absent from or uniformly expressed in the mouse cortex, in line with observed differences in functional specialization in the prefrontal cortex across species.

After completion of the first phase of cell proliferation when neural stem cells are generated, before the onset of neurogenesis (Rakic et al. 2009), additional cellular mechanisms are needed to explain area expansion during childhood development. Regional differences in surface area expansion in later childhood development are likely affected by events such as synaptogenesis, gliogenesis, dendritic arborization, and intracortical myelination (Hill et al. 2010). All these factors have the potential to positively impact cognitive function and contribute to the observed correlations between local arealization and test scores, and we have previously found correlations between cognitive functions and regional cortical area in development (Fjell, Walhovd, et al. 2012). Thus, although cortical area expansion may be a common factor in improved cognitive function in development and evolution, it is likely that the underlying cellular mechanisms are at least partly different in later childhood development when the cortex still expands substantially. Hill et al. (2010) summarize the literature and argue that high-expanding cortical regions are less mature at birth both functionally and structurally, with lower synaptic density and glucose metabolism, that they have greater cellular complexity in adults, for example, larger dendritic fields, arbor complexity, and spine number, and that they tend to mature more slowly. The authors suggested that the regions associated with high expansion in human postnatal development and evolution are implicated in higher cognitive functions that distinguish humans from other primates. The present results extend this idea by showing that high-expanding areas are more strongly related to individual differences in cognitive function in humans.

Limitations

We studied cortical area, which is a gross measure of brain structure. There are a range of different neurobiological adaptations that could contribute to explain the improved cognitive functions in humans besides areal expansion, number of neurons, and cortical columns. Subtle modifications in neural microstructure and gene expression can have a significant impact on behavior, even in the absence of large-scale changes in brain size (Sherwood et al. 2008). Glasser et al. (2013) demonstrated similarities in regional distribution of cortical myelin content between macaques, chimpanzees, and humans, and showed that lightly myelinated regions generally expanded more during evolution than heavily myelinated regions. Recent studies have also compared resting-state functional networks between humans and macaques (Hutchison and Everling 2012). Task-related functional magnetic resonance imaging studies have identified evolution-driven functional changes in the primate brain, showing that functional processes can be executed by neural networks in different species that are functionally but not necessarily anatomically correspondent (Mantini et al. 2012), but also instances of correspondence between specific functional networks in macaques and humans (Miyamoto et al. 2013). Another important line of research regards interspecies structural connectivity comparisons (Markov et al. 2012, 2013; Jbabdi et al. 2013), and in some studies have structural and functional connectivity been compared across humans and macaques (Mars et al. 2011). Still, cortical expansion is the most prominent event in human brain evolution, which makes it a potent measure to study across species. Further, the evolution expansion maps were obtained from comparisons of the macaque brain to human brains and are thus dependent on the species chosen for comparison. Adding to this, all living species are the product of their own evolution, and the comparative approach is thus only an indirect route to study evolutionary adaptation (Sherwood et al. 2008). To this problem, however, no better alternatives exist, and comparative studies have yielded a vast amount of information about human brain evolution. Finally, the cognitive tests used (Walhovd et al. 2005; Tamnes et al. 2010), as well as cortical arealization (Hogstrom et al. 2012), are all related to age. The common variance due to age may influence the relationships to different degree. By including age and square of age as covariates in the analyses, as well as by running validation analyses for the sample below 60 years, we believe that we have accounted for

the possibly confounding effects of age on the brain–cognition relationships.

Conclusion

Improved intellectual function and cortical areal expansion seem closely related in development and evolution, and it has been suggested that regions associated with high expansion in human childhood development and evolution are implicated in higher cognitive functions. In this study, we show that high-expanding regions are more strongly related to cognitive function in humans than low-expanding regions. This suggests that areal expansion is one of the common factor in improved intellectual function during ontogenetic and phylogenetic development.

Supplementary Material

Supplementary material can be found at: http://www.cercor.oxfordjournals.org/.

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Notes

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