

# Changes in Thickness and Surface Area of the Human Cortex and Their Relationship with Intelligence

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**Changes in cortical thickness over time have been related to intelligence, but whether changes in cortical surface area are related to general cognitive functioning is unknown. We therefore examined the relationship between intelligence quotient (IQ) and changes in cortical thickness and surface over time in 504 healthy subjects. At 10 years of age, more intelligent children have a slightly thinner cortex than children with a lower IQ. This relationship becomes more pronounced with increasing age: with higher IQ, a faster thinning of the cortex is found over time. In the more intelligent young adults, this relationship reverses so that by the age of 42 a thicker cortex is associated with higher intelligence. In contrast, cortical surface is larger in more intelligent children at the age of 10. The cortical surface is still expanding, reaching its maximum area during adolescence. With higher IQ, cortical expansion is completed at a younger age; and once completed, surface area decreases at a higher rate. These findings suggest that intelligence may be more related to the magnitude and timing of changes in brain structure during development than to brain structure per se, and that the cortex is never completed but shows continuing intelligence-dependent development.**

**Keywords:** brain development, cortex, intelligence, MRI, plasticity

## Introduction

The size and surface area of the human brain are considered critical determinants of human intellectual ability (Lui et al. 2011; Geschwind and Rakic 2013). Although in comparison with other species humans do not have the largest brain nor the biggest cortex either in absolute or relative terms, owing to the thickness and relatively high cell density in the cortex, man does have the largest number of cortical neurons of all species (Roth and Dicke 2005). Indeed, intelligence has been associated with larger brain volumes in children (Reiss et al. 1996), (pre)adolescents (van Leeuwen et al. 2009), and adults (Haier et al. 2004) as well as with a thicker cortex (Narr et al. 2007; Karama et al. 2011), and this association is partly of genetic origin (Thompson et al. 2001; Posthuma et al. 2002; Deary 2012). For a review of brain imaging (and genetics) studies on intelligence, see Deary et al. 2010.

Although much of the expansion of the human cortex takes place during the prenatal period (Rakic 1988), recent findings suggest that postnatal structural brain development is considerable (Giedd et al. 1999; Brans et al. 2010; Raznahan, Lerch, et al. 2011; Raznahan, Shaw, et al. 2011). Prenatal growth, as measured by birth weight, has been related to cortical maturation into adolescence, and it has also been shown that this

postnatal development of the cortex is related to intelligence (Raznahan et al. 2012) and may be influenced by genetic and epigenetic factors (Petanjek and Kostović 2012). The cortex reaches its peak thickness later in children with a higher intellectual ability than in their peers (Shaw et al. 2006). In (pre) adolescence, associations between cortical thinning and (improved) cognitive abilities have been found (Sowell et al. 2004; Tamnes et al. 2011). In adulthood, higher intellectual ability is associated with more pronounced thickening and postponed thinning of specific areas of the cortex (Brans et al. 2010). Both during childhood and adolescence and also in adulthood, these changes in cortical thickness and intelligence are heritable (Peper et al. 2007; Brans et al. 2010; van Soelen et al. 2012). Thus, individual differences in the developmental brain changes seem to play an important and specific role in human intelligence.

That intellectual functioning is both associated with cortical thinning and cortical thickening is puzzling. In a meta-analysis of longitudinal magnetic resonance imaging (MRI) studies, we recently found that a decline in whole-brain volume in adolescence is followed by a period of stability in young adulthood, before a second period of decline sets in as shown in Hedman et al. (2012). A similar pattern may be followed by the cortex, with periods of thinning followed by stability and (local) thickening.

The contrasting relationships between cortical thickening/thinning and intelligence during brain development are poorly understood. These changes may reflect important transitions from childhood to adulthood. Moreover, change in cortical thickness is only one aspect of cortical development; the surface area of the cortex is also of importance (Raznahan, Shaw, et al. 2011). Interestingly, changes in cortical surface area in relation to intelligence have not been studied in longitudinal designs in man, despite the fact that changes in the surface area may be as relevant to intelligence as those in cortical thickness have proven to be. Therefore, we examined the relationship between intelligence and cortical development, defined as changes in cortical thickness and surface over time in healthy human subjects.

## Materials and Methods

### Subjects

We included 504 healthy individuals who each had 2 MRI scans. Subjects (282 males/222 females) were aged between 9 and 60 years at baseline ( $t_0$ ). At follow-up ( $t_f$ ), the subjects were between 1.75 and 7.60 years older [mean (SD)  $t_f - t_0 = 4.10$  (1.26) years]. The numbers of

individuals per age range were distributed as follows: 114 individuals below the age of 12 at their first measurement, 76 between 12 and 20 years of age, 152 between 20 and 30 years of age; 105 between 30 and 40 years of age and 57 above 40 years of age. The subjects were taken from samples that have been published previously (van Haren et al. 2008; Boos et al. 2012; Brans et al. 2010; van Soelen et al. 2012; Ziermans et al. 2012); 373 (74%) of the subjects had no family relationship; the other subjects were co-twins (108) or siblings (23). Details on the inclusion criteria are provided in the respective studies and also in Supplementary Material.

All participants gave written informed consent to participate in the study. This study was approved by the Medical Ethical Research Committee for human research (METC) from the University Medical Centre Utrecht and was approved by the Central Committee for Research on Human Subjects (CCMO) in The Netherlands (children). The study was carried out under the directives of the Declaration of Helsinki (Amendment South Africa 2000).

### General Intelligence

An estimate of the intelligence quotient (IQ) was obtained using the full-scale WISC-III (Wechsler Intelligence Scale for Children; Wechsler 1997) in children and adolescents, and the short forms of the WAIS (Wechsler Adult Intelligence Scale; Stinissen et al. 1970), and the WAIS-III-NL (Wechsler 1997) in adults, as has been described before (Brans et al. 2010; van Soelen et al. 2011). The short form of the WAIS (1970) was administered to 269 subjects and consisted of either Comprehension, Vocabulary, Block Design, and Picture Arrangement or Information, Vocabulary, Block Design, and Picture Completion. For 70 subjects, the short version of the WAIS-III-NL (1997) was administered, including Arithmetic, Digit Symbol-coding, Block Design, and Information (Christensen et al. 2007). The procedure to calculate IQ from 4 subtests has been described before (Hijman et al. 2003). We were able to adjust for using norms from 1970 and 1997, because a subgroup of 81 individuals (representative for age and IQ range of the adults in the whole sample) tested with the WAIS (1970) was also tested around the same time with the WAIS-III-NL (1997). We found a difference of 16 IQ points (WAIS 1970: IQ = 117; WAIS-III-NL 1997: IQ = 101). This is higher than the expected Flynn effect of 0.3 IQ points per year (Flynn 2006). We adjusted all WAIS (1970) IQ scores by subtracting 16 points to be able to pool these data with the WAIS-III-NL (1997) IQ scores. To ensure that this adjustment in IQ scores did not influence the analyses, we rerun significant analyses excluding the 70 individuals tested with the WAIS-III-NL (1997). Leaving out these, 70 individuals did not alter the findings. Verbal IQ (VIQ) and performal IQ (PIQ) were calculated by following the same procedure but only including the respective subtests. If IQ was measured at baseline and follow-up, the average of these values was used; otherwise, the one available measure was used in the analyses.

### MRI Acquisition

Participants were scanned twice on a Philips 1.5-T MRI Gyroscan (NT or Achieva) scanner in the University Medical Centre Utrecht (Philips Medical Systems, Best, the Netherlands). A  $T_1$ -weighted (field-of-view = 256 mm, echo time = 4.6 ms, repetition time = 30 ms, flip angle =  $30^\circ$ ) whole-brain image was acquired in all individuals using the same protocol twice. Voxel size differed slightly between individuals varying from  $1 \times 1 \times 1.2 \text{ mm}^3$  (in 479 individuals) to  $1 \times 1 \times 1.5 \text{ mm}^3$  (in 25 individuals).

### Image Processing

Images were processed using our standard processing pipeline, and included automatic transformation into Talairach orientation (no scaling) (Talairach and Tournoux 1988), scanner nonuniformity correction (Sled et al. 1998), and segmentation of gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) using a partial volume method (Brouwer et al. 2010). For cortical measurements, we used a custom implementation of the CLASP algorithm (Kim et al. 2005; Lyttelton et al. 2007; Lerch et al. 2008), which starts from the GM and WM segments created by our own algorithm. A surface consisting of 81 920

polygons and 40 962 vertices was fitted to the WM/GM interface of each subject's left (LH) and right (RH) hemisphere, which was then expanded out to fit the GM/CSF interface, thereby creating the outer cortical surface. A middle cortical surface was created half-way the 2 surfaces. Cortical thickness was estimated vertex-wise by taking the distance between corresponding vertices on the inner and outer surfaces. The surfaces of each subject were nonlinearly registered to an average surface created from 152 subjects (ICBM; Lyttelton et al. 2007), allowing comparison of cortical measures between subjects. The automatic anatomical labeling (AAL; Tzourio-Mazoyer et al. 2002) of this average surface template was applied to assign each vertex of a subject's surface to one of the 78 (39 in each hemisphere) anatomical regions.

### Creation of Relevant Quantities

Total cortical surface area was calculated per hemisphere by summing the areas of all triangles that made up the WM/GM interface. For each of the AAL regions, its area was calculated by summing the areas of triangles that were labeled as part of this region. Mean thickness measures were calculated by averaging vertex-wise thickness over AAL regions and the whole hemispheres. Cortical volume was calculated by summing the local product of thickness and area over all vertices, again for each AAL region and for the whole hemisphere.

For each subject, change or difference values were calculated for all quantities  $Q$  by subtracting the  $t_0$  values from the  $t_f$  values:  $\Delta Q = Q_f - Q_0$ . Change rates were calculated by dividing the differences by the scan interval ( $\Delta t = t_f - t_0$ ), and relative change rates were calculated by dividing the change rates by the mean value of the 2 measurements:  $R_Q = \Delta Q / (\Delta t \times Q_m)$ , where  $Q_m = (Q_0 + Q_f) / 2$ . After multiplication by 100%, these are expressed in %/year.

### Statistical Analysis

To calculate the dependencies of the global change measures ( $R_Q$ ) on the individual's age, a locally weighted running line smoother was applied to the data (Cleveland and Devlin 1988; Hastie and Tibshirani 1990; van Haren et al. 2008). Since initial fits indicated that much larger degrees of freedom were necessary to follow the rapid changes in growth/shrink rates at ages up to about 20 years, when compared with the slow rate variations in adulthood, age was transformed: By taking the cubic root of age, younger ages were stretched when compared with older ages. By comparing fits with different degrees of freedom, the best fit to the data was determined at a significance level of  $\alpha = 0.05$ . A zero-crossing of the fit to  $R_Q$  determines a maximum or minimum of  $Q$  itself. To estimate the (age-dependent) associations with intelligence, the global and regional change rates were linearly regressed on IQ, locally weighted by (cubic root transformed) age (Gaussian kernel size = 0.2). To test the significance of each regression, we randomly permuted the IQs of the individuals and performed the regression again. We repeated this procedure 2000 times to determine a null distribution of regression coefficients  $b$  and to calculate the  $P$ -value. A false discovery rate (FDR) of 0.05 was used to correct for multiple comparisons over the AAL regions, thereby accounting for dependencies between these regions (Li and Ji 2005). To correct for dependency due to family relationship between subjects, we repeated the permutation tests using only unrelated subjects. This is a very conservative correction, since it assumes family members to be identical in brain and IQ measures. To obtain the quantity's mean value as a function of age (and IQ), the fitted change rates were integrated over age, starting from the quantity's mean value at age 10 (calculated from the 149 subjects aged 9–10 at  $t_0$ ).

Since there is evidence for gender differences in the IQ/brain structure relationship (see, e.g., Haier et al. 2005 using voxel-based morphometry, and Schmithorst 2009 using diffusion tensor imaging), we repeated the analyses for females and males separately.

A number of post hoc analyses were carried out to test the validity of the main age/IQ trajectories: (1) The analyses were repeated including only the adult subjects with a WAIS (1970) IQ score; (2) the analyses were repeated for PIQ and VIQ instead of full-scale IQ; (3) the subjects were split into 3 IQ groups with about equal numbers (IQ < 100;  $100 < \text{IQ} < 113$ ;  $\text{IQ} > 113$ ); for each group, standard linear regressions of cortical thickness and surface area on age were

**Table 1**  
Cortical surface area and thickness changes in the human brain

Structure ( <i>Q</i> )	At <i>Q</i> 's maximum			At <i>R<sub>Q</sub></i> 's minimum			At plateau		
	Age (years)	<i>Q</i>	<i>R<sub>Q</sub></i> (%/year)	Age (years)	<i>Q</i>	<i>R<sub>Q</sub></i> (%/year)	Age (years)	<i>Q</i>	<i>R<sub>Q</sub></i> (%/year)
Surface area (cm <sup>2</sup> )	12.7	1947 <sup>a</sup>	0	18.8	1913	−0.39	40.0	1842	−0.01
Mean thickness (mm)	<10.5	3.37	−0.66	<sup>b</sup>	<sup>b</sup>	<sup>b</sup>	47.5	3.11	−0.07
Cortical volume (mL)	<10.5	621	−0.31	16.0	596	−1.17	47.8	530	−0.05

Note: The first 3 columns give the maximum value of structure *Q*, the age at which it is measured, and the relative annual change rate *R<sub>Q</sub>* at this point.

The second 3 columns give the strongest decline of *Q*, the age at which it is measured, and *Q*'s value at this point.

The third 3 columns give the age at which the decline of *Q* is smallest, the change rate and *Q*'s value at this point.

<sup>a</sup>1935 cm<sup>2</sup> at age 10.5.

<sup>b</sup>Falls at *Q*'s maximum (left column).

calculated; these cross-sectional results were compared with the trajectories from the longitudinal analyses; (4) the individual AAL surface area trajectories were summed per hemisphere and compared with the total area trajectory of that hemisphere; weighted averages of the individual AAL thicknesses were compared with the mean hemispheric thickness trajectories.

## Results

### Cortex: Thickness

Mean cortical thickness decreased rapidly around age 10, and then slowed down until a plateau was reached at about age 30. Between 30 and 60 years, total cortical thinning was marginal (Table 1). Hemispheric differences were found between 10 and 20 years of age with the left hemisphere lagging behind the right by approximately 3 years.

### Cortex: Surface

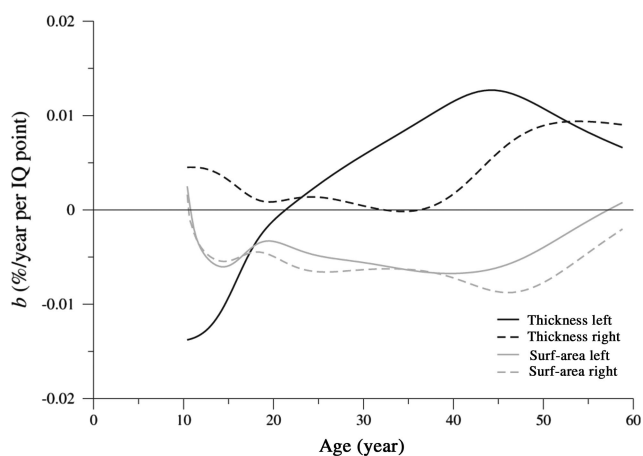
The cortical surface expanded until approximately 12.7 years and then shrank at a relatively modest rate until after the age of 45 surface contraction became more pronounced (Table 1). Hemispheric differences in surface development were found between the ages of 10 and 20 years with the left hemisphere lagging behind the right by approximately 1 year.

### Cortex: Volume

The cortex reached its maximum volume before the age of 10 years, showing the steepest decline in volume at around age 16 after which the decline became less pronounced (Table 1). The decrease in cortical volume found between the ages of 9 and 13 was due only to cortical thinning. After the age of 13 years, surface contraction also contributed to the decrease in volume.

### Cortex and IQ: Thickness

Individual differences in intellectual ability were reflected in different age-dependencies for cortical development throughout life (Figs 1 and 2). Higher IQ was associated with more pronounced cortical thinning in the left hemisphere in childhood. During adolescence, the association between IQ and left hemisphere cortical thinning weakened until in adulthood (from around age 21) higher IQ became associated with more pronounced cortical thickening in the left hemisphere, reaching significance at age 29. This was the most evident in the left superior (medial, orbito-) frontal cortex\*, superior motor area, gyrus rectus\*, Rolandic operculum, Heschl's gyrus, insula\*, and (pre)cuneus ( $P < 0.05$ ; \*significant at FDR = 0.0023; Fig. 3 and see Supplementary Fig. 1). Cortical thickness changes in



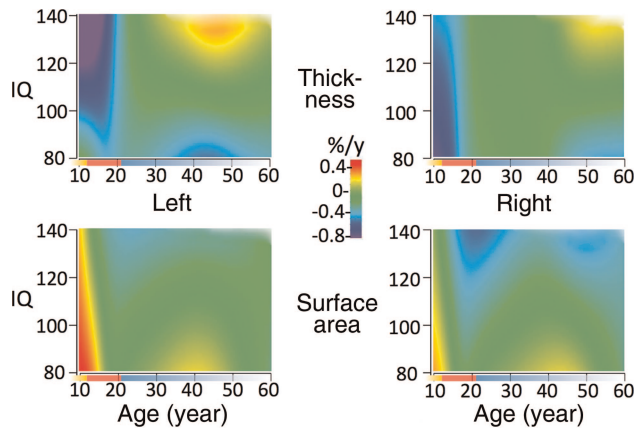
**Figure 1.** Cortical brain plasticity and human intelligence. Regression coefficients *b* from the relationship between quantity *Q*'s relative change rate and IQ:  $R_Q = a + b \times IQ$ , for ages from 10 to 60 years. A *b*-value of 0.01 represents an additive 0.1%/year change in *Q* if one's IQ is 10 points higher. At age 10, LH thickness change (full black line) is negatively associated with IQ ( $P = 0.009$ ), and at age 40 positively ( $P = 0.006$ ). The association crosses zero around the age of 21.5 years. RH thickness change (dashed black line) does not show these effects. Surface area change is negatively associated with IQ at all ages ( $P = 0.02$  [LH, full gray line],  $P = 0.01$  [RH, dashed gray line]).

the right hemisphere showed significant positive associations with IQ only after age 47 (significant in the medial orbitofrontal gyrus at FDR = 0.0074). Higher IQ was associated with an earlier onset of cortical thinning in childhood.

Figure 4 shows the left and right hemisphere mean cortical thickness development with age, for different IQs. At the age of 10, there was a modest effect of IQ on mean thickness, which was comparable between left and right. During adolescence, the decrease in mean thickness was larger in the left than in the right hemisphere, and there was a large effect of IQ on the rate of left cortical thinning: from  $-0.25\%/year$  for  $IQ = 80$  up to  $-1.08\%/year$  for  $IQ = 140$ . In adulthood, left mean thickness continued to decrease for  $IQ < 110$ , but turned into increase for  $IQ > 110$ . A comparable effect was seen in the right hemisphere after age 47.

Correcting for dependency between the subjects did not change the results significantly: The negative and positive associations between changes in left cortical thickness and IQ remained significant (the positive association reaching significance at age 32); the right hemisphere's association reached trend-level significance ( $P < 0.10$ ) at age 51.

Separate analyses for males and females showed that the positive association between IQ and left hemisphere's cortical



**Figure 2.** Cortical thickness and surface area changes depend on age and IQ. Changes (in %/year; center color bar) with age in mean cortical thickness (top panels) and total surface area (bottom panels) in relation to intellectual functioning for the left and right hemispheres, as estimated by locally age-weighted linear regression. Individuals with above average intelligence (i.e., with IQ over 120) show a pronounced cortical thinning in the left hemisphere (in blue/purple) during adolescence, which is followed by a second period of cortical growth (orange) in adulthood starting around age 30. For cortical surface change, the pattern seems reversed with surface expansion completing in early adolescence followed by surface contraction in adulthood. Individuals with below average intelligence (i.e., with IQ below 90) show cortical thinning (in blue) and (more prolonged or delayed period of) surface expansion during adolescence (in red/yellow), and virtually no surface change in adulthood. Color bars along the x-axis mark the 3 periods of development (yellow, red, and blue) mentioned in the Discussion.

thinning in childhood remained significant in males ( $P=0.01$ , until age 14) but not in females. In adulthood, the association between IQ and cortical thickening remained significantly positive in females (ages 26 and up), but could not be shown to be significantly different from zero in males. In the right hemisphere, the association between IQ and cortical thickening, which was found to be positive and significant above 47 years of age, reached trend-level significance in females only (ages 45 and up;  $P=0.06$  at age 50).

### Cortex and IQ: Surface Area

Individuals with higher IQ showed less pronounced (or already completed) surface expansion in both hemispheres in childhood and adolescence and more pronounced surface contraction in adulthood, although the association with IQ reached significance only in adulthood (Figs 1 and 2), particularly for the left and right precentral cortices, the left medial frontal cortex, and the right supramarginal, parietal (superior and inferior) cortices, operculum, and cuneus (all significant at  $P < \text{FDR} = 0.0063$ ; Fig. 3 and see Supplementary Fig. 1). Overall, higher IQ was associated with earlier completion of cortical surface expansion during childhood development. Figure 5 shows left and right hemisphere cortical surface area development with age for different IQs. The surface area was larger in individuals with higher IQ, but the effect decreased with age: from about 3 cm<sup>2</sup> per IQ point at age 10 to about 0.7 cm<sup>2</sup> per IQ point at age 60 (left) or even vanishing (right).

The negative associations between IQ and left and right surface changes remained significant after correcting for dependency between the subjects.

Separate analyses for males and females showed that the negative association between IQ and change in the surface area remained significant in females ( $P < 0.01$  in both

hemispheres for all subjects together), but not in males ( $P=0.5$  and 0.2 for the left and right hemispheres, respectively). The vanishing association in early adolescence appears to be the result of a (small) positive association in males (n.s.), and a negative association in females (significant up to age 13 in both hemispheres; see Supplementary Fig. 2).

### Cortex and IQ: Thickness and Surface Area

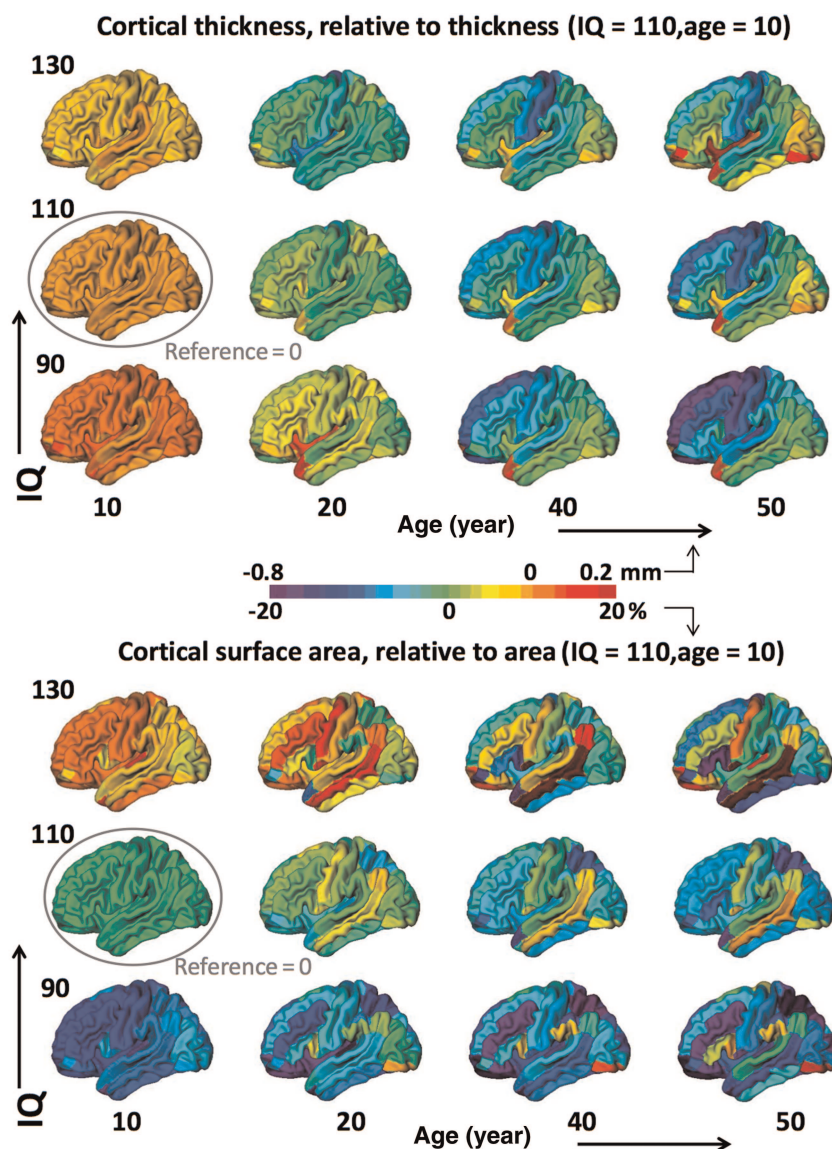
The relationship between the rates of change of cortical thickness and surface area altered with age (Fig. 6). While in general the most rapid changes in the left cortex were found in younger subjects, individuals with the highest intelligence appeared to have the most extreme course in phase-space ( $\Delta\text{th}/\Delta t$ ,  $\Delta\text{area}/\Delta t$ ): They showed the most pronounced thinning in adolescence, the largest surface contraction in (young) adulthood, followed by attenuated thinning (and even some thickening) of the cortex at age 30 and above.

### Post hoc Analyses

- (1) Age trajectories using only data from adult subjects with a WAIS (1970) IQ resembled the all-data trajectories qualitatively.
- (2) The reversing full-IQ/thickness change relationship found in the left hemisphere is also found for PIQ (significant for age <14 years and 21 years < age < 41 years) and VIQ (significant for age <15 years and 25 years < age < 38 years). In the right hemisphere, the association between change in thickness and PIQ or VIQ no longer reached significance after age 47. The full age range's association between change in the surface was significantly negative with PIQ but not with VIQ, although the latter reached significance between 30 and 40 years of age.
- (3) Linear regressions of the cross-sectional thickness and area data (not their changes) on age for the 3 IQ groups replicated the following main findings: (1) The initial rather large surface area surplus in the higher IQ groups decreases with age and (2) for ages 35 and up, thickening of the left cortex is seen in the highest IQ group but not in the 2 other IQ groups. The stronger thinning of the left hemisphere's cortex during adolescence could not be found for the higher IQ groups in this cross-sectional analysis.
- (4) (i) Adding all AAL surface area trajectories yielded hemispheric surface area trajectories that resembled the directly calculated trajectories, showing all main features, including the diminishing IQ effect on area with age and the left hemisphere's lagging behind the right hemisphere. (ii) Hemispheric mean thickness as a weighted average of all AAL regional thicknesses: The trajectories' main features were found again, including the crossings around age 40, the sharper decrease for higher IQs in the left hemisphere during adolescence, and the almost nonexistent IQ effect in the right hemisphere (until age 40).

### Discussion

In a large longitudinal sample of over 1000 magnetic resonance scans from healthy subjects aged 9–60 years, we analyzed the development of cortical thickness and surface area in relation to intelligence.



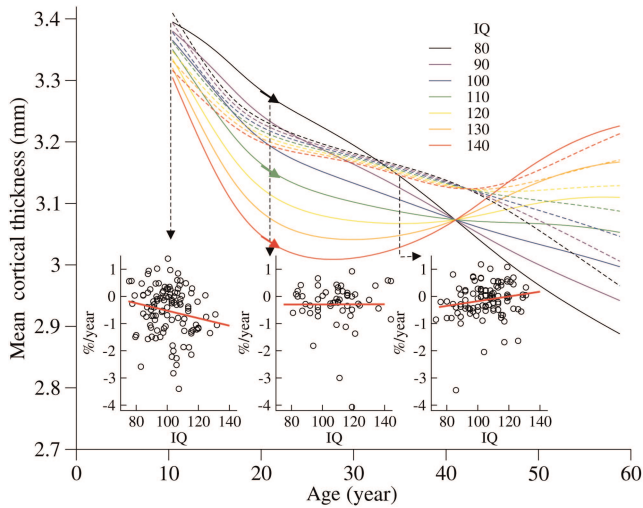
**Figure 3.** Development of left cortical thickness (top) and surface area (bottom) with age (from left to right: 10, 20, 40, and 50 years) for 3 selected IQ values (rows: 130, 110, and 90). All thickness values (in mm) are relative to those for IQ = 110 at age 10 ("Reference = 0"), which consequently has value zero everywhere on the cortex. All surface area values indicate the relative difference (in %) in area with respect to the area values for IQ = 110 at age 10 ("Reference = 0"). The 4 ages mark the following stages: age 10: modest global thickness differences between IQs, sizeable (global) area differences; age 20: maximum thickness differences between IQs; age 40: local but no net differences in thickness between IQs; age 50: higher IQs have a thicker cortex, mainly due to thicker frontal and occipital cortices. During the latter 3 stages, surface area decreases most for the highest IQ, especially in the frontal lobe, while parts of the parietal and temporal lobe remain relatively large.

### Thickness and IQ

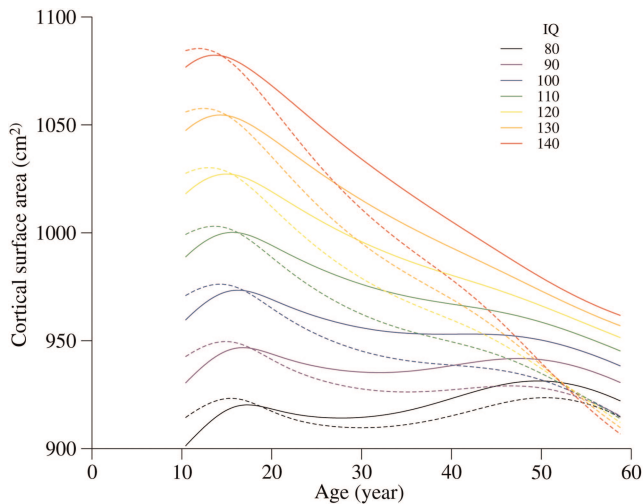
At 10 years of age, more intelligent children have a slightly thinner cortex than children with a lower IQ. The relationship between thinner left cortex and higher intelligence becomes more pronounced with increasing age: The higher the IQ, the faster the thinning of the left cortex over time. In more intelligent young adults, this relationship reverses: while in individuals with an IQ of <110 thinning of the left cortex continues after the age of 21, in subjects with an IQ of >110 thickening of the left cortex is related to higher IQ so that by the age of 42 a thicker cortex is associated with higher intelligence. The net effect is that the large "changes" in cortical thickness over time are associated with high IQ, while cortical thickness changes least in those individuals with the lowest IQ. Strikingly, the association between intelligence and cortical thickness is

particularly prominent in the left inferior frontal gyrus and left planum temporale, also known as Broca's area and Heschl's gyrus, both involved in language processing. The association between cortical thinning and IQ in (pre)adolescence was earlier found cross-sectionally (Tamnes et al. 2011) and in a longitudinal study (Sowell et al. 2004). The latter study found a negative association between changes in cortical thickness and changing (vocabulary) cognitive abilities in the left, but not in the right, hemisphere. Although our sample did not permit analysis of change in IQ, this finding corresponds to the results of our study (Fig. 4: thinning with age, thinner for higher IQ). We add the finding of accelerated thinning for higher IQ (diverging lines in Fig. 4).

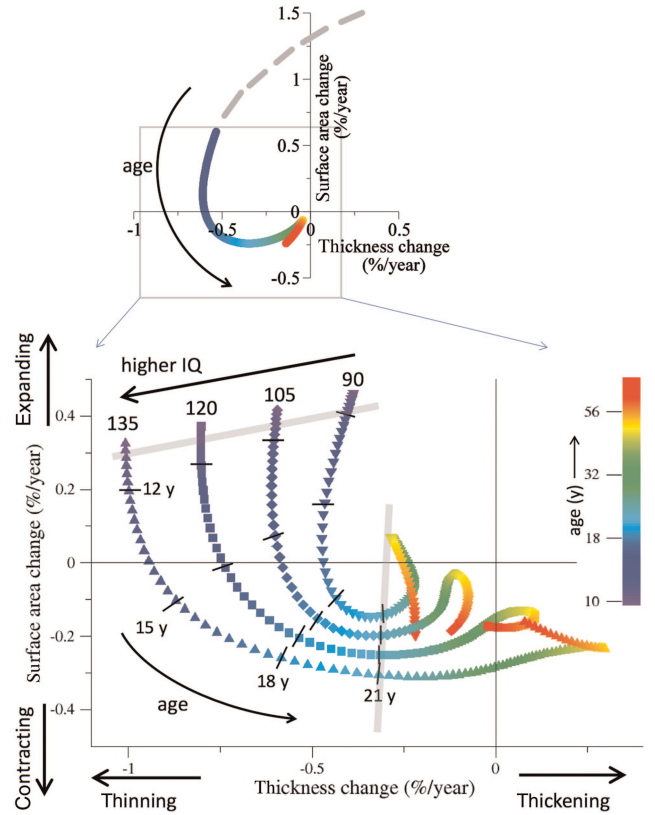
The more dynamic thickness changes for increasing IQ, reflected by a thinner cortex at age 10 and an accelerated



**Figure 4.** Cortical thickness development and its relationship with intelligence. Development of left (LH, full lines) and right (RH, dashed lines) hemisphere's mean cortical thickness with age for different IQs. Annual change rates as function of age and IQ (as shown in Fig. 2) were integrated to obtain thickness as function of age, for a number of IQ values (colored lines). At age 10, LH and RH's mean thicknesses are comparable (3.3–3.4 mm) with a similar modest negative IQ effect. During adolescence, thickness decreases rapidly, showing an increasing spread with IQ for LH. The effect of IQ on LH's change rate, however, decreases, leading to a vanishing association at age 21 (visible as parallel lines; arrows; see also Fig. 1). After this age of maximal spread with IQ (0.2 mm difference between IQs 80 and 130), the IQ effect is reversed: lower IQs show an (unchanged) decrease with age, whereas higher IQs stabilize or even start to thicken (e.g., IQ 140 from age 28 on), ultimately leading to a thicker LH cortex for higher IQs from age 42 on. The RH shows a slower thinning and hardly any IQ effect until age 42. The insets show the varying association between the IQ and LH change rate in youth (negative, at age = 10 years, left), around the turning point (zero, at age = 21.5 years, middle), and adulthood (positive, at age = 35 years, right).



**Figure 5.** Cortical surface area development and its relationship with intelligence. Development of left (LH, full lines) and right (RH, dashed lines) hemisphere's cortical surface area with age for different IQs. Annual change rates as function of age and IQ (as shown in Fig. 2) were integrated to obtain the surface area as function of age, for a number of IQ values (colored lines). At age 10, spread in area due to IQ is largest, and comparable between LH and RH. After reaching maximum area in adolescence, the surface starts to contract at a rate that is higher for higher IQs, thus gradually decreasing the positive effect of IQ on cortex area.



**Figure 6.** Phase plot showing the relationship between thickness and area changes in the left hemisphere. Top panel: Age trajectory of “the average subject” in phase-space ( $\Delta\text{th}/\Delta t$ ,  $\Delta\text{area}/\Delta t$ ). Age is shown in color according to the bar: purple, 10 years; green, 30 years, orange, 50 years; the dashed gray line roughly indicates the trajectory for age < 10 years. The line indicates the evolution of LH thickness change (x-axis) and surface area change (y-axis) in aging subjects. During late childhood/young adolescence, the curve runs through the upper left quadrant: the cortex is thinning but its area is still increasing; in late adolescence, both the thickness and the area are decreasing (lower left quadrant); from age 21, both rates are diminishing (curve heading for the origin), reaching the “point” of smallest cortical changes at age 48, after which thinning and contraction speed up again. Bottom panel: The age trajectory split for selected IQ values (triangle down, IQ = 90; diamond, 105; square, 120; triangle up, 135). For example, an “average” subject with IQ = 120 has, at age 10, a thickness change rate of  $-0.80\%/year$  and a surface area change rate of  $0.37\%/year$  (top purple square). When the subject's age increases, the change rates evolve according to the position on the curve: the area change rate starts to decrease while the thickness change rate stays constant for the next few years. Comparisons between different IQs can be made by comparing points on the curves with the same color (same age). The group of most intelligent individuals appears to take the “outside bend.”

thinning in (late) adolescence, were earlier found by Shaw et al. (2006), although their finding that individuals with superior intelligence reached a thicker cortex in adolescence could not be replicated. The comparison between the 2 studies is hindered by many methodological differences. Shaw et al.'s most prominent cluster displaying the shift in age at maximum thickness with increasing IQ largely coincides with the right superior medial frontal region. We found a negative association between IQ and thickness at the age of 10 in this region, after which subjects with lower IQ displayed a thinning cortex, whereas the cortex of subjects with superior IQ (>130) is still thickening, reaching its maximum at age 14, after which an accelerating thinning sets in as shown in Supplementary Figure 1.

### **Thickness Versus Surface Area**

In contrast to cortical thickness, cortical surface area is larger in more intelligent children at the age of 10. At this age, the cortical surface is still expanding; it reaches its maximum area during adolescence. We found that the cortical expansion is completed at a younger age in more intelligent individuals (age 13 for IQ = 140) than in less intelligent individuals (age 16.5 for IQ = 80). Once the surface expansion is complete, surface area begins to decrease, but at a higher rate in more intelligent individuals. Thus, similar to the relationship between intelligence and cortical thickness, it is a greater change in cortical surface over time that is related to higher IQ rather than the absolute surface area: It is the individuals with highest IQ who showed the largest changes in the surface area during development.

Contraction of the cortical surface was more prominent in more intelligent adults in the left and right precentral cortices, the left medial frontal cortex, and the right supramarginal, parietal (superior and inferior) cortices, and cuneus. Frontal and parietal brain structures have been associated with intelligence before (Haier et al. 2004; Gläscher et al. 2010; Barbey et al. 2012), especially in the framework of a parieto-frontal integration theory (P-FIT) of intelligence (Jung and Haier 2007; Langeslag et al. 2013). Interestingly, in adulthood, the cortical change/IQ relationship appears to separate the P-FIT regions: while higher IQ is mainly associated with a thicker (pre) frontal and medial occipital cortex, it is associated with a larger parietal and middle temporal surface.

Furthermore, higher intelligence has often been associated with larger brain volumes (Thompson et al. 2001; Haier et al. 2004; Deary 2012), where approximately 6% of the variation in IQ can be explained by GM or WM volume (Posthuma et al. 2002). Based on the current findings, we submit that this association may be attributable to the positive association between surface area and IQ. In addition, we found that IQ is related to changes in surface area and thickness over time. Depending on age, variation in IQ may be better explained by the rate of change in brain structures rather than by volume per se. For example, at age 40, 8.2% of the variation in IQ was explained by change in cortical thickness compared with 2.6% by thickness itself. These findings emphasize that plasticity of the brain may be as important to intelligence as brain structure itself. This study extends the conclusion by Shaw et al. (2006) that, until age 20, the trajectory of change in thickness is more closely related to intelligence than thickness itself.

### **Periods of Cortical Development**

A closer inspection of the relationships between IQ and (changes in) cortical measures suggests that there are (at least) 3 distinct periods of cortical development. The first period (the largest part of which is before our first measurements) runs until ages 10–12 and is marked by expansion of the cortical surface. In this period, cortical surface expansion is larger in those individuals with higher intelligence. In the second period, which lasts until approximately age 21, the relationship between IQ and surface expansion is reversed: Full cortical expansion is reached at an earlier age in more intelligent individuals, and followed by accelerated contraction. Simultaneously, the cortex is thinning, a process that is exaggerated in the left hemisphere of more intelligent subjects. In the third period, surface contraction continues and while its relationship with

IQ remains unaltered, the association between IQ and cortical thickness change reverses: Thinning of the left cortex continues in individuals with an IQ of <110, but it thickens in individuals with an IQ of >110, eventually leading to a positive association between thickness and IQ in more intelligent individuals from age 42. The 3 periods and the (smooth) transitions between them are illustrated in the phase plot of the changes in thickness and area (Fig. 6); individuals with the highest IQ have the most extreme course, with the greatest magnitude of change.

Based on the global development of cortical thickness, the transition between periods 2 and 3 around age 21 could define the finishing of cortical maturation and thus as a mark of an “adult brain stage.” However, the local increases and decreases of both thickness and surface area of the cortex found after this age could be interpreted as continuing regional development. From this point of view, cortical adulthood does not exist in the form of a matured cortex, but may at best be defined as a stage in which the relationship between cortical changes and IQ differs from that at younger ages. Speculatively, one might say that individuals with a higher intelligence may keep their brains developing, probably due to continued education and training (Draganski et al. 2004).

### **Efficiency**

How can these (shifting) relationships between intelligence and cortical thinning/thickening and expansion/contraction be explained? The initial larger cortical expansion in more intelligent individuals seems logical in view of “more is better.” However, a substantial literature exists on the reversed relationship between IQ and brain activation when performing tasks: There is evidence that more intelligent individuals use their brains more efficiently (Haier et al. 1988; Neubauer and Fink 2009). One explanation may be increasing efficiency of structural brain networks over development (Bullmore and Sporns 2010). Intelligence was recently associated with neural network efficiency, where more efficient network function was associated with higher IQ in young adults (Van den Heuvel et al. 2009). Furthermore, the integrity of WM tracts has also been associated with intelligence, suggesting a similar relationship for structural measures of brain networks (Chiang et al. 2011). One speculative interpretation of the changes observed during (late) childhood and adolescence could be that individuals with higher intelligence have faster cortical surface expansion, thus achieving not only a greater surface area, but also at a younger age. This larger cortex could be more optimally reduced to form the most efficient network, whereas the younger age at which this process can start provides extra time for optimization. Once in adulthood, from about age 30, most long range connections would be expected to have reached their optimal efficiency; and individuals with higher intelligence may further optimize network efficiency by strengthening local connections in specific brain areas, reflected in cortical thickening.

### **In Relation to Postmortem Studies**

We can only speculate about the physiological mechanisms underlying the cortical changes during development. Relating imaging measures to underlying cellular and molecular events is challenging, and changes in cortical thickness and surface area likely reflect many processes, including myelination,

synaptogenesis, neurogenesis, gliogenesis, altering dendritic structure and vasculature, and an interplay between these factors (Zatorre et al. 2012). Cellular mechanisms can be studied in more detail from postmortem material. Using these methods, the maturation of the human cortex through cortical thinning has been associated with a 2- to 3-fold reduction in synapses during adolescence and young adulthood, possibly reflecting dynamic reorganization of the synaptic circuitry during development (Huttenlocher and Dabholkar 1997; Petanjek et al. 2011). The decreases in both thickness and area of the cortex in adulthood may be related to decreases in (dendritic) neuropil (Jacobs and Scheibel 1993). Age-related changes have been found to be region specific (Uylings and de Brabander 2002) and cortical layer specific (de Brabander et al. 1998; Petanjek et al. 2011—with increased interindividual differences at old age). The latter finding illustrates the need of (high field) high-resolution MRI acquisition methods that can image the cortex with contrast between the different layers (Dunin et al. 2007). In the left prefrontal and secondary occipital cortices, dendritic neuropil has been found to be relatively stable after 40 years of age, which, according to the authors (Jacobs et al. 1997) “underscores the importance of life-long commitment to a cognitively invigorating environment.” Speculatively, this could be translated in the stable left cortical thickness and its positive association with IQ, we found for age 40 and higher. In Wernicke’s area, these age-related reductions of the dendritic length have been ascribed to decreases in total dendritic length (Jacobs and Scheibel 1993), which was found to vary considerably between individuals. Education had a consistent and substantial effect on the length of the (distal branches of the) dendrites, suggesting that part of this interindividual variation may be explained by education level, or intelligence (Jacobs et al. 1993). Although the dendritic system is only a part of the neuropil, which in turn forms about 60% of the cortical GM (Chklovskii et al. 2002), the side effect (L > R), aging effect, and the size and direction of education/IQ seem to be reflected more closely by our surface area than by the thickness findings. However, non-neuronal factors, such as dynamic changes in vasculature and glial cells, may contribute to changes in cortical thickness.

### Conclusions and Limitations

This study has several limitations that should be considered. First, the changes do not span effects between 9 and 60 years of age within single individuals, although we report changes within many individual brains all obtained from longitudinal magnetic resonance brain-imaging measurements with 3- to 5-year interval. Secondly, we measured changes in the cortex, and not in the subcortical areas, which also may display developmental plastic changes that relate to intelligence. Thirdly, the sample size did not permit mapping of the dynamic relationships between cortical changes, age, and IQ for females and males separately. The different associations between IQ and change in the cortex area found in early adolescence may reflect developmental differences between males and females. Fourthly, findings near the ends of the IQ distribution should be interpreted with some caution given the relatively low density of subjects in these parts of the distribution, especially for very high IQ (>140). Fifthly, the associations between IQ and brain structure may have been confounded by factors such as socioeconomic status and diet. Sixthly, in the

current study, we could measure overall IQ only. Future study may reveal that specific components of intelligence may be associated with changes in particular brain regions. Finally, we did not assess changes in intelligence. Although intelligence is generally found to be fairly stable throughout life, some dynamic aspects in intelligence have recently been suggested in relation to brain structure and brain function during adolescence (Ramsden et al. 2011).

In conclusion, we found dynamic changes in cortical thickness and surface area in the age range of 9–60 years that varied by IQ. Although the relationships between intelligence and these 2 measures of the cortex were different, they were linked by a common phenomenon: The greater the developmental change, the higher the intelligence. These findings suggest that intelligence is more related to the magnitude and timing of brain changes during development than to brain structure per se. The presence of cortical changes at all ages covered by this study also suggests that the development of the cortex is never completed, but rather continues to change depending on someone’s intelligence.

### Supplementary Material

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

### Funding

A part of this work was supported by the Netherlands Organization for Health Research and Development ZonMw (grants 917.46.370 and 908-02-123 to H.E.H.P.), the Netherlands Organization for Scientific research (NWO 51.02.060 to H.E.H.P., R.S.K., D.I.B., and 480-04-004 to D.I.B.), Utrecht University (high potential grant to H.E.H.P.), and the European Research Council (ERC-230374 to D.I.B.).

### Notes

We thank Jiska Peper, Inge van Soelen, Marieke van Leeuwen, Tim Ziermans, Wiepke Cahn, Rachel Brans, and Gaolang Gong for assisting with data acquisition and processing. *Conflict of Interest:* None declared.

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