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Gyral window mapping of typical cortical folding using MRI

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Abstract

Using the NIH Pediatric MRI Data Repository for normative developmental studies, white matter depth within the gyri of the frontal, temporal, parietal, and occipital lobes, and of the left and right hemisphere was identified for 312 typically developing children and young adults (168 male and 144 female) between 4 and 23 years of age. There was no significant age difference between male and female groups overall ($F_{1,867} = 0.0002$; $p = 0.99$) or per-visit ($F_{2,867} = 2.18$; $p = 0.86$). There was significant dependence of gyral window upon age ($F_{1,6544} = 115$, $p < 0.0001$), lobe ($F_{3,6544} = 229$, $p < 0.0001$), hemisphere ($F_{1,6544} = 5.23$, $p = 0.022$), age*sex ($F_{1,6544} = 13.8$, $p = 0.0002$), age*lobe ($F_{3,6544} = 120$, $p = 0.0001$), and age*hemisphere ($F_{1,6544} = 4.41$, $p = 0.036$). Gyrification increased with age in both males and females in the frontal, temporal and parietal lobes with opposite effects observed in the occipital lobe. Relative gyral depth, as measured in this study, was significantly ($p < 0.0001$) inversely correlated with gyrification index. Previous studies relate gyral window measurements to the differential expression of short and long corticocortical projections. Our results therefore suggest that the pattern of corticocortical connections is malleable during the first two decades of development.

Keywords

cerebral cortex; gyral window; gyrification index; magnetic resonance imaging

Introduction

During childhood and adolescence, the brain undergoes cortical changes in progressive myelination and regressive pruning [1, 2]. As the brain develops, it establishes new cortical folds. A quantitative measure of cortical folding is referred to as the gyrification index (*GI*). *GI* has been described as a measure of the ratio between the total gyral cortical surface over the perimeter of the brain. This metric reflects the amount of cortex entrenched within cortical folds and has been found to vary with age, hemisphere and lobe [3, 4]. Another anthropometric measure of gyrification is the gyral window. The concept of the gyral window (Figure 1) was first posited by Prothero and Sundsten [5] who defined it as, “the hypothetical plane between a gyrus and the underlying white matter through which the afferent and efferent cortical fibers enter and leave the cortex”. However, there were a few disadvantages of Prothero and Sundsten's gyral window design. For one, its straight, close-packed cube model does not adapt well to the curved convolutions of human brains [5]. Secondly, Prothero's gyral window theory was not conceptualized formally and, by our standards, engaged poor intra- and inter-rater reliability. To address these concerns, our

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laboratory implemented an automated, unbiased computer model that randomly generates points onto a section of gyral white matter. Each point then expands into a sphere. The software measures the radius from the center of the sphere to the boundary of the gyral white matter and calculates the mean distance map of all the points generated for the entire section.

Gross anatomical and MRI investigations of typical brain growth in relation to age and gender have revealed that gyrification occurs in a pattern from ventral to dorsal and caudal to rostral structures [6]. According to Giedd et al. [7], the Child Psychiatry Branch cohort reported that by age 6, the total brain is estimated to have achieved 95% of its peak volume, reaching its apex at about age 10.5 in females and age 14.5 in males.

It has been theorized that a reduction in gyral window space limits the amount of white fiber tracts that can enter and leave the individual gyrus, thus favoring short-range connection fibers at the expense of long-range fibers [8]. In addition, an observed relationship between gyral window size and corpus callosum size suggests that a reduced gyral window constrains the total number of long range projections such as commissural fibers. The aforementioned studies suggest that gyral window measurements serve as a proxy index for corticocortical connectivity. In this study, we identified both the gyral index and gyral window depth of 312 typically-developing children and young adults from the NIH Pediatric MRI Data Repository (NIHPD) to investigate changes accrued to age and gender.

Experimental procedures

Data source

Volumetric data and associated metadata were obtained from the NIH Pediatric MRI Data Repository (NIHPD) in accordance with the repository's data usage agreement. NIHPD is a product of the NIH MRI Study of Normal Brain Development, a multi-center, longitudinal study of over one thousand healthy children across the United States [9].

NIHPD release 4.0 (June 26, 2010) contains data from 431 individuals collected for “Objective 1”, i.e. aged 4.5 years or older at the beginning of the study. For each participant, data was collected at three time points approximately two years apart. Some data were excluded by the NIHPD's internal quality control criteria; available data for a given participant may include all three time points or only one or two of them. These data include but are not limited to: T1 weighted, T2 weighted, and proton density weighted MRI; affine transformations (4×4 matrices) relating patient-based (MRI scanner) space to stereotaxic space; label arrays assigning an anatomical region (e.g. parietal white matter, left hemisphere) to each MRI voxel containing brain tissue; and triangular meshes approximating the outer and inner surfaces of the cerebral cortex.

Sample size

For purposes of this study, certain scans and derived data were unsuitable, (e.g. motion artifact) to compute gyral depth as explained below. Constructing accurate white/gray matter surfaces was problematic for the same reason. For purposes of this study, we did not measure gyral depth for those individuals/time points that had a labeled volume but did not have surface meshes in the NIHPD. Excluding those cases, the sample of useful data comprised 312 individuals. Of these, 82 (51 male and 31 female) provided MRI data at three visits; 119 (64 male and 55 female) provided MRI data at two visits; and 111 (53 male and 58 female) provided data at only a single time point.

Image processing

Gyral depth—Measurement of gyral depth used the labeled volume data. Labeled volumes L were transformed into native anatomical space at $(0.5 \text{ mm})^3$ voxel size using the NIHPD-provided affine transformations along with nearest-neighbor interpolation. Now let C denote the set of voxels labeled as cerebrum; let G comprise voxels labeled as cerebral cortex; let $I = C - G$; and let W comprise voxels labeled as subcortical (i.e. lobar) white matter. The Euclidean distance map $D(\mathbf{x})$ was computed, yielding the distance from the center of each voxel $\mathbf{x}$ to the nearest voxel in G . A threshold depth θ was computed by modeling the histogram of $D(W)$, i.e. D over the domain of lobar white matter, as a mixture of two Gaussian distributions [10]. Then I was eroded to depth θ and the result dilated to the point where it made contact with G . Denote by I' be the result of those operations; then $Y = W - I'$ is the *gyral white matter* (Figure 2). Mean gyral depth d is the mean value of $D(Y)$, the restricted distance distribution inside the gyral white matter. In order to be independent of brain volume, analysis was done on the *relative* mean gyral depth, defined as

$$\tilde{d} = \frac{d}{\frac{1}{12} \left(\frac{3}{2\pi} V \right)^{1/3}}. \quad (\text{Eq. 1})$$

The normalization factor in the above equation is the theoretical d for a hemispherical “gyrus” with volume V equal to the volume of gyral white matter. For each MRI, we calculated eight values for $\tilde{d}$, one per lobe in each hemisphere, using (Eq. 1) with d and V computed from the appropriate subsets of Y .

Gyrification index—The gyrification index (GI) of a closed surface is its area divided by the surface area of its convex hull [4]. It provides for a scale-independent measure of non-convexity. The NIHPD includes several measurements of GI for each cerebral hemisphere, computed using the gray matter surface, the white matter surface, and the medial surface equidistant between the other two. We considered only GI of the white matter surfaces as most relevant for comparison with $\tilde{d}$.

Statistical analysis

Let $\tilde{d}_{ijkm}$ be the observed relative gyral depth for participant i at visit j in lobe k of cerebral hemisphere m . Denote the participant's age at time of scan, in years, by A_{ij} . Dummy variables $\mathbf{L}_k$, H_m , and S_i encode lobe, hemisphere, and the sex of the participant, respectively. Then the mixed-effects model used for $\tilde{d}_{ijkm}$ was

$$\begin{aligned} \log \tilde{d}_{ijkm} &= \beta_0 \\ &+ \beta_1 S_i + (\beta_2 + \beta_3 S_i) \log(A_{ij}) \\ &+ \beta_4^T \mathbf{L}_k \\ &+ \beta_5 H_m + \beta_6^T \mathbf{L}_k H_m \\ &+ (\beta_7^T \mathbf{L}_k + \beta_8 H_m + \beta_9^T \mathbf{L}_k H_m) \log(A_{ij}) \\ &+ (\beta_{10}^T \mathbf{L}_k + \beta_{11} H_m + \beta_{12}^T \mathbf{L}_k H_m) S_i \\ &+ (\beta_{13}^T \mathbf{L}_k + \beta_{14} H_m + \beta_{15}^T \mathbf{L}_k H_m) S_i \log(A_{ij}) \\ &+ \mu_i + \varepsilon_{ijkm}, \end{aligned}$$

where the μ_i are independent identically distributed random intercepts drawn from a normal distribution with zero mean, and the errors ε_{ijkm} are likewise independent, identically

distributed normal deviates. The parameter vector β was fit by maximum likelihood estimation, and statistical significance of the effects was ascertained by F -tests. Separate models were used for each of the eight lobe/hemisphere combinations:

$$\log \tilde{d}_{ijkm} = \beta_{0,km} + \beta_{1,km} S_i + (\beta_{2,km} + \beta_{3,km} S_i) \log(A_{ij}) + \mu_{ikm} + \varepsilon_{ijkm} \quad (\text{Eq. 2})$$

with the effects of lobe and hemisphere folded into the random intercept and the coefficients of the fixed effects. These models were fit to the data using *restricted* maximum likelihood (REML) in order to obtain unbiased estimates of the standard errors of the parameters [11].

Gyrification index had been computed per hemisphere, so for comparison the mean gyral depths were aggregated over lobe (q.v. Eq. 1):

$$\begin{aligned} d_{ijm} &= \sum_k V_{ijkm} d_{ijkm} / \sum_k V_{ijkm} \\ \tilde{d}_{ijm} &= \frac{d_{ijm}}{\frac{1}{12} \left(\frac{3}{2\pi} \sum_k V_{ijkm} \right)^{1/3}}. \end{aligned}$$

Then suitably transformed values of GI_{ijm} and $\tilde{d}_{ijm}$ were considered as being drawn from a bivariate normal distribution:

$$\left(\log(GI_{ijm} - 1), \log(1 - \tilde{d}_{ijm}) \right) \sim N(\mu, \Sigma). \quad (\text{Eq. 3})$$

The association of GI with $\tilde{d}$ was tested using the likelihood ratio of the MLE of μ of Σ with the MLE of a nested model where the covariance matrix Σ was restricted to being diagonal.

Statistical calculations were performed using R packages nlme [12] and mclust [13, 14].

Results

Participant age at the time of MRI acquisition ranged from 4.8 y to 18.3 y (mean 11.5 y) at visit 1, from 6.4 y to 20.2 y (mean 12.7 y) at visit 2, and from 8.4 y to 22.3 y (mean 14.1 y) at visit 3. The male and female subgroups did not differ significantly in mean age, either overall ($F_{1,310} = 0.104$, $p = 0.747$) or on a per-visit basis ($F_{2,279} = 0.361$, $p = 0.698$). Fixed effects with statistically significant impact on $\tilde{d}$ included sex (β_1 : $F_{1,310} = 103.6$, $p < 0.0001$); lobe (β_4 : $F_{3,4418} = 29245$, $p < 0.0001$); the interaction of age with sex (β_3 : $F_{1,4418} = 38.14$, $p < 0.0001$) and with lobe (β_7 : $F_{3,4418} = 57.96$, $p < 0.0001$); the interaction of lobe with hemisphere (β_6 : $F_{3,4418} = 28.91$, $p < 0.0001$); and the three-way interaction of age, sex, and lobe (β_{13} : $F_{3,4418} = 2.97$, $p = 0.0308$). The other effects were statistically insignificant ($p > 0.05$). Parameter estimates (Eq. 2) are shown in Table 1, and predicted $\tilde{d}$ as a function of age and 95% pointwise confidence intervals based on these parameters are illustrated (Figure 3).

Relative gyral window depth of the NIHPD series indicates an inverse relationship to gyrification index, in which as gyrification increases, gyral window size decreases. The correlation coefficient of $\log(GI - 1)$ with $\log(1 - \tilde{d})$ assuming a bivariate normal distribution (Eq. 3) was $\rho = 0.331$ in the left hemisphere ($\chi^2 = 917.8$, $p < 0.0001$) and $\rho = 0.421$ in the right hemisphere ($\chi^2 = 957.7$, $p < 0.0001$). Tolerance regions estimated from the fitted distributions are shown (Figure 4).

Discussion

We investigated the dependence of gyral window size upon age, individual lobe (frontal, parietal, temporal, occipital), and left or right hemisphere for typical developing male and female subjects in this study. We further investigated gyral window size dependence upon interaction of age with sex, age with each lobe, and age with each hemisphere. As expected, significant dependence of gyral window size was found with age and individual lobe. Relative gyral window depth indicated an inverse relationship to gyrification index, such that as gyrification increases with age, gyral window decreases in the frontal, temporal and parietal lobe with reverse effects in the occipital lobe. In keeping with our findings, Sowell et al. [6] reported dramatic cortical changes occurring in the frontal and parietal regions between the ages of 7 and 16 with highly significant reductions in gray matter and concomitant increases in white matter. Significant dependence of gyral window size with left and right hemisphere may be a new finding. Additional results were consistent with our expectations of there being a significant dependence of age-related changes in gyral window on sex, lobe, and hemisphere. The study of De Bellis et al. [1] showed, that if anything, there was a significant age-related decrease in gray matter volume with a concomitant increase in white matter volume and corpus callosal area. Sex differences were found in both cerebral gray matter and white matter maturation from childhood through adolescence in which boys showed a significantly greater loss of gray matter volume and an increase in both white matter and corpus callosum compared with girls of similar age [1]. De Bellis et al. [1] posited that the gray matter decreases were likely a reflection of dendritic pruning and that white matter increases were likely due to either myelination, glial proliferation or both. Significant sex differences may be explained by hormonal influences during brain development [1]. Throughout typical development, gyrification increases with age in both males and females in a pattern from ventral to dorsal and caudal to rostral in the frontal, temporal, parietal and occipital lobes then decreases with age in the occipital lobe [6]. Our findings match those found in previous literature. Gyrification changes with respect to age across the cortex appears to correlate with research indicating that a greater number of fiber connections exist within the frontal, temporal and parietal lobes for the purpose of executing tasks involved in higher cognitive function [15, 16].

Several developmental imaging studies confirm one of the earliest findings that larger brain sizes in males becomes evident during the first four to five years of life [17-19]. Some studies also indicate an increase in cortical gray matter volume to occur earlier in boys than in girls [7, 17, 19] whereas other studies state no significant differences in cortical volume growth in either gender [1, 20]. Our findings are consistent with those of Sowell et al. [20] whose statistical maps showed significant interaction of sex with age in regions of the bilateral dorsal frontal lobe and right inferior temporal lobe. Studies on the cognitive differences of men and women have shown that men perform better than women on mathematical reasoning, mental rotation, perception of vertical and horizontal, and accuracy in hitting a target [21, 22]. Women perform better than men in verbal memory, range of vocabulary and finger dexterity [21]. Research conducted on spatial orientation showed that men are significantly better at mentally rotating an object in space than women [22] and it has been suggested that this is because men use systematic rules to approach spatial tasks [23]. Baron-Cohen [23] provided the example that as early as age 2, males are superior to females in their ability to accurately throw a ball suggesting that there is “an evolved, biologically based sex difference between males and females.” The female cortex is thicker than the male cortex in areas of the right temporal and parietal lobes [20]. Cortical regions in which women had significantly thicker cortices than men might be the result of women having greater amounts of neuronal axons, dendrites, synapses, glia cells or other microunits within those regions [20, 24]. Our findings of there being a significant dependence of gyral window size with interaction between age and sex, age and lobe, and age and hemisphere

support previous observations of gender differences in cortical thickness. We can conclude from these findings that relative gyral window depth is an accurate and viable measure of brain malleability and cortical remodeling with age.

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This manuscript reflects the views of the authors and may not reflect the opinions or views of the Brain Development Cooperative Group Investigators or the NIH.

Abbreviations

GI	gyrification index
NIHPD	NIH Pediatric MRI Data Repository

References

1. De Bellis MD, Keshavan MS, Beers SR, Hall J, Frustaci K, Masalehdan A, et al. Sex differences in brain maturation during childhood and adolescence. *Cereb. Cortex.* 2001; 11:552–557. [PubMed: 11375916]
2. Sowell ER, Thompson PM, Tessner KD, Toga AW. Mapping continued brain growth and gray matter density reduction in dorsal frontal cortex: inverse relationships during postadolescent brain maturation. *J. Neurosci.* 2001; 21:8819–8829. [PubMed: 11698594]
3. Zilles K, Armstrong E, Schleicher A, Kretschmann H-J. The human pattern of gyrification in the cerebral cortex. *Anat. Embryol. (Berl).* 1988; 179:173–179. [PubMed: 3232854]
4. Moorhead TWJ, Harris JM, Stanfield AC, Job DE, Best JJK, Johnstone EC, et al. Automated computation of the Gyrification Index in prefrontal lobes: Methods and comparison with manual implementation. *Neuroimage.* 2006; 31:1560–1566. [PubMed: 16600639]
5. Prothero JW, Sundsten JW. Folding of the cerebral cortex in mammals: a scaling model. *Brain. Behav. Evol.* 1984; 24:152–167. [PubMed: 6466964]
6. Sowell ER, Thompson PM, Holmes CJ, Batth R, Jernigan TL, Toga AW. Localizing age-related changes in brain structure between childhood and adolescence using statistical parametric mapping. *Neuroimage.* 1999; 9:587–597. [PubMed: 10334902]
7. Giedd JN, Blumenthal J, Jeffries NO, Rajapakse JC, Vaituzis AC, Liu H, et al. Development of the human corpus callosum during childhood and adolescence: a longitudinal MRI study. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 1999; 23:571–588. [PubMed: 10390717]
8. Casanova MF, El-Baz A, Mott M, Glenn M, Hassan H, Fahmi R, et al. Reduced gyral window and corpus callosum size in autism: possible macroscopic correlates of a minicolumnopathy. *J. Autism Dev. Disord.* 2009; 39:751–764. [PubMed: 19148739]
9. Brain Development Cooperative Group. Evans AC. The NIH MRI study of normal brain development. *Neuroimage.* 2006; 30:184–202. [PubMed: 16376577]
10. El-Baz, A.; Farag, A.; Ali, A.; Gimel'farb, G.; Casanova, MF. A framework for unsupervised segmentation of multi-modal medical images. In: Beichel, RR.; Sonka, M., editors. *Computer vision approaches to medical image analysis*. Springer; New York: 2006. p. 120-131.
11. Patterson HD, Thompson R. Recovery of inter-block information when block sizes are unequal. *Biometrika.* 1971; 58:545–554.

12. Pinheiro, J.; Bates, D.; DebRoy, S.; Sarkar, D.; R Development Core Team. nlme: Linear and nonlinear mixed effects models. 2010.
13. Fraley C, Raftery AE. Model-based clustering, discriminant analysis, and density estimation. *J. Am. Stat. Soc.* 2002; 97:611–631.
14. Fraley, C.; Raftery, AE. MCLUST version 3 for R: normal mixture modeling and model-based clustering. University of Washington; Seattle: 2006.
15. Goldman-Rakic PS, Cools AR, Srivastava K. The prefrontal landscape: implications of functional architecture for understanding human mentation and the central executive. *Philos. Trans. R. Soc. Lond. B. Biol. Sci.* 1996; 351:1445–1453. [PubMed: 8941956]
16. Grieve SM, Williams LM, Paul RH, Clark CR, Gordon E. Cognitive aging, executive function, and fractional anisotropy: a diffusion tensor MR imaging study. *AJNR. Am. J. Neuroradiol.* 2007; 28:226–235. [PubMed: 17296985]
17. Caviness VS Jr. Kennedy DN, Richelme C, Rademacher J, Filipek PA. The human brain age 7–11 years: a volumetric analysis based on magnetic resonance images. *Cereb. Cortex.* 1996; 6:726–736. [PubMed: 8921207]
18. Giedd JN, Castellanos FX, Rajapakse JC, Vaituzis AC, Rapoport JL. Sexual dimorphism of the developing human brain. *Prog. Neuropsychopharmacol. Biol. Psychiatry.* 1997; 21:1185–1201. [PubMed: 9460086]
19. Courchesne E, Chisum HJ, Townsend J, Cowles A, Covington J, Egaas B, et al. Normal brain development and aging: quantitative analysis at in vivo MR imaging in healthy volunteers. *Radiology.* 2000; 216:672–682. [PubMed: 10966694]
20. Sowell ER, Peterson BS, Kan E, Woods RP, Yoshii J, Bansal R, et al. Sex differences in cortical thickness mapped in 176 healthy individuals between 7 and 87 years of age. *Cereb. Cortex.* 2007; 17:1550–1560. [PubMed: 16945978]
21. Kimura D. Sex, sexual orientation and sex hormones influence human cognitive function. *Curr. Opin. Neurobiol.* 1996; 6:259–263. [PubMed: 8725969]
22. Roberts JE, Bell MA. Sex differences on a mental rotation task: variations in electroencephalogram hemispheric activation between children and college students. *Dev. Neuropsychol.* 2000; 17:199–223. [PubMed: 10955203]
23. Baron-Cohen, S. The essential difference: the truth about the male and female brain. Basic Books; New York: 2003.
24. Luders E, Gaser C, Narr KL, Toga AW. Why sex matters: brain size independent differences in gray matter distributions between men and women. *J. Neurosci.* 2009; 29:14265–14270. [PubMed: 19906974]

Figure 1.

Gyral window. A cutaway view of a simplified gyrus is shown, comprising cerebral white matter (cw) and cortex (Cx) covering the gyral crest and the walls of the surrounding sulci. Cortical afferent and efferent fibers pass through the white matter surface cw. Long-range (commissural, thalamo-cortical, cortico-spinal, etc.) fibers must further pass through the interior white matter surface of the gyrus. This gyral window (*Gwin*) is a bottleneck imposing a physical constraint on the rate of information flow into and out of neurons in the gyrus.

Figure 2.

Segmentation of gyral white matter. (A) The frontal poles and the superior parts of the frontal and temporal lobes have been cut away from this example white matter surface. Inside the cutaway sections, distance from the white matter surface is shown in grayscale, with deeper locations appearing darker. (B) Eroding the volume in (A) to a threshold distance, calculated from the histogram of distance measurements inside the original volume, produces the new volume shown here. (C) The volume (B) is expanded until it intersects the white matter surface. The region interior to (A) but exterior to (C) is the gyral white matter. (D) In this axial section, gyral white matter is that lying outside the dashed lines. Depth is again shown in grayscale.

Figure 3. Relative gyral depth over the course of development. The predicted value of $\tilde{d}$ in each lobe/ hemisphere as a function of age is shown for male (dashed lines) and female (solid lines) individuals. Dotted lines bound the pointwise 95 % confidence limits on mean $\tilde{d}$.

Figure 4.

Relationship between gyrification index and relative gyral depth. Observed values of $(GI, \tilde{d})$ are plotted for all MRI for which both measurements were available, along with tolerance regions at the 50 %, 95 %, and 99 % level, assuming that $\log(GI - 1), \log(1 - \tilde{d})$ follows a bivariate normal distribution.

Coefficients of the fitted model

Table 1

Within each cerebral hemisphere and lobe, relative gyral depth was modeled as a power law, where both the scale and exponent could differ between male and female (q.v. Eq. 2): $\log \tilde{d} = \beta_0 \pm \frac{1}{2}\beta_1 + (\beta_2 \pm \frac{1}{2}\beta_3) \log \left(\frac{\text{age}}{15} \right)$ where the sign before β_1 and β_3 terms is + for female and – for male.

Lobe	Hem.	β_0		β_1		β_2		β_3	
		est.	s.e.	est.	s.e.	est.	s.e.	est.	s.e.
FL	L	-0.912	0.011	0.043	0.022	-0.021	0.004	-0.032	0.009
	R	-0.914	0.011	0.037	0.022	-0.023	0.004	-0.030	0.009
TL	L	-0.823	0.012	0.014	0.024	-0.012	0.005	-0.021	0.010
	R	-0.837	0.012	0.030	0.024	-0.008	0.005	-0.027	0.010
PL	L	-0.816	0.011	0.029	0.022	-0.002	0.004	-0.025	0.009
	R	-0.816	0.011	0.015	0.022	-0.002	0.004	-0.020	0.009
OL	L	-0.749	0.014	0.029	0.029	0.019	0.006	-0.028	0.011
	R	-0.760	0.015	0.027	0.030	0.027	0.006	-0.026	0.012