Heritable changes in regional cortical thickness with age

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Abstract It is now well established that regional indices of brain structure such as cortical thickness, surface area or grey matter volume exhibit spatially variable patterns of heritability. However, a recent study found these patterns to change with age during development, a result supported by gene expression studies. Changes in heritability have not been investigated in adulthood so far and could have important implications in the study of heritability and genetic correlations in the brain as well as in the discovery of specific genes explaining them. Herein, we tested for genotype by age ($G \times A$) interactions, an extension of

genotype by environment interactions, through adulthood and healthy aging in 902 subjects from the Genetics of Brain Structure (GOBS) study. A “jackknife” based method for the analysis of stable cortical thickness clusters (JASC) and scale selection is also introduced. Although additive genetic variance remained constant throughout adulthood, we found evidence for incomplete pleiotropy across age in the cortical thickness of paralimbic and parieto-temporal areas. This suggests that different genetic factors account for cortical thickness heritability at different ages in these regions.

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Introduction

Regional indices of brain structure such as cortical thickness, surface area or grey matter volume exhibit spatially variable patterns of heritability. For instance, the highest estimates of heritability for these measures are commonly found in prefrontal and temporal areas (Hulshoff Pol et al. 2006; Joshi et al. 2011; Kremen et al. 2010; Lenroot et al. 2009; Rimol et al. 2010; Thompson et al. 2001; Wright et al. 2002). Moreover, genetic correlation studies have shown that common genetic factors appear to influence distributed brain regions with mostly bilateral patterns. This organization is explained largely by the similarity of genetic influences in spatially adjacent regions and in homologous regions of the left and right hemispheres (Chen et al. 2012, 2013; Rimol et al. 2010; Schmitt et al. 2010).

Heritability, however, is an estimate that can change with age. In one study of pediatric development, Lenroot et al. found primary sensorimotor areas to exhibit decreasing genetic effect with age. Conversely, genetic variance increased in the dorsal prefrontal cortex and temporal lobes up to 18 years old, where regional patterns of heritability resembled those observed in adults (Lenroot et al. 2009). These results suggest higher initial heritability in regions developing earlier in childhood and increasing genetic effects in late-developing regions associated with higher cognitive functions. Such genotype by age ($G \times A$) interactions have not been investigated in adulthood so far and could have important implications in the study of heritability and genetic correlations in the brain as well as in the discovery of specific genes explaining them. Additionally, global measures of brain structure such as mean cortical thickness, intracranial volume or total gray matter volume are also highly heritable (Panizzon et al. 2009; Pennington et al. 2000; Pfefferbaum et al. 2000). These global effects can mask spatial variation in heritability at the regional level (Schmitt et al. 2010; Yoon et al. 2012), which in turn can mask variation in heritability at the vertex or voxel level (Eyler et al. 2012). Thus, appropriate scale and global covariate selection is very important for the study of genetic effects in the brain.

In this study, we tested for $G \times A$ interactions in regional cortical thickness by estimating age-related changes in additive genetic variance and regional decreases in genetic correlation with increasing age difference (Blangero 1993). To reduce the computational load of these advanced variance component analyses, we used the validated approach of cortical thickness clustering based on correlated variations. In addition to efficient data reduction, this method has

also been shown to exhibit features that have functional significance in healthy and diseased conditions (Bassett et al. 2008; Chen et al. 2008; Kelly et al. 2012). The stability of the clusters was assessed prior to the genetic analyses with a novel “jackknife” method for the analysis of stable cortical thickness clusters (JASC) and a silhouette analysis was also introduced to select the appropriate scale for data reduction.

Material and methods

Subjects

The sample included 902 subjects from randomly selected families enrolled in the Genetics of Brain Structure and Function Study (GOBS) before December 31st 2012 (see Table S.1 for a summary of the pedigree structure). The GOBS study is a collaborative effort between Texas Biomedical Research Institute, University of Texas Health Science Center at San Antonio (UTHSCSA), Yale University School of Medicine and McGill University. Subjects were recruited if they were part of a large family of Mexican-American ancestry from the San Antonio, TX, area (see Olvera et al. 2011 for recruitment details). Exclusion criteria were MRI contraindications, history of neurological illness, stroke or other major neurological event. Mean age was 43 ± 15 (mean $\pm$ SD) with a range of 18 to 77 and 546 of the subjects were women. All participants provided written informed consent and the study was approved by the institutional review boards at the UTHSCSA, Texas Biomedical Research Institute, Yale University and McGill University.

Image acquisition and analysis

All MRI images were acquired at the UTHSCSA Research Imaging Center on a Siemens 3T Trio scanner (Siemens, Erlangen, Germany). High-resolution (isotropic 800 μm) 3D Turbo-flash T1-weighted images were acquired with the following parameters: TE/TR/TI = 3.04/2100/785 ms, flip angle = 13° . Seven images were acquired consecutively using this protocol for each subject and the images were then co-registered and averaged to increase signal-to-noise ratio and reduce motion artifacts (Kochunov et al. 2006). Native averaged T1-weighted MRI scans were corrected for non-uniformity artifacts with the N3 algorithm (Sled et al. 1998). The corrected volumes were then masked (Smith 2002) and registered into stereotaxic space (Collins et al. 1994). The registered, corrected images were segmented into gray matter (GM), white matter (WM), cerebrospinal fluid (CSF) and background using an advanced neural net classifier (Tohka et al. 2004). The WM and GM

surfaces were extracted using the Constrained Laplacian-based Automated Segmentation with Proximities algorithm (Kim et al. 2005; MacDonald et al. 2000) and were resampled to a stereotaxic surface template to provide vertex based measures and lobar segmentation (Lyttelton et al. 2007). Cortical thickness was measured in native space using the linked distance between the two surfaces across 81,924 vertices (Im et al. 2008). The processing pipeline was executed on the Canadian Brain Imaging Network (CBRAIN) platform, a network of five imaging centers and eight High Performance Computers for collaborative sharing and distributed processing of large MRI databases (Frisoni et al. 2011).

Cortical surface parcellation and clustering

The automatic anatomical labeling (AAL) atlas was used to parcellate the surface into 78 cortical regions (Tzourio-Mazoyer et al. 2002). Cortical thickness was averaged over all vertices in each region of interest for each subject (He et al. 2007) and the effect of mean cortical thickness was regressed to allow for regional analysis (Eyler et al. 2012). The residuals were clustered using a customized version of the Bootstrap Analysis of Stable Clusters (BASC) pipeline (Bellec et al. 2010). Briefly, a jackknife procedure was used to generate B subsamples where Pearson's correlation coefficients were computed for each possible pair of the 78 regions of interest. This yielded a correlation matrix C_{ij} (where $i, j = 1, 2, \dots, 78$) that was then clustered using a Hierarchical Agglomerative Clustering (HAC) algorithm based on Ward's criterion with K clusters (Batagelj 1988). The resulting B adjacency matrices were averaged to generate a group stability matrix where each cell represented the proportion of time that regions i and j were considered as connected over the subsamples:

$$S_{ij} = Pr \left(\Phi_{ij}(y) = 1 | Y \xrightarrow{f} y \right) \quad (1)$$

This group stability matrix was itself entered into one last consensus HAC to build a final set of K group clusters (Fred and Jain 2005), that captured the most stable associations of the cluster replications over B jackknife subsamples. A modified version of the silhouette criterion was then computed using the consensus clusters and the group stability matrix (Bellec et al. 2010; Rousseeuw 1987). This criterion represents the difference of average within-cluster stability minus the maximal average between-cluster stability. In order to select the first stable scale of regional organization, we selected the lowest scale where an increase in the number of clusters stopped resulting in a substantial increase in the silhouette criterion.

Quantitative genetic analyses

Estimation of heritabilities

The additive polygenic variance (σ_a^2) of a normally distributed trait can be estimated from familial data by modelling the covariance of two individuals as a function of kinship. This method assumes that the pedigree is drawn from a non-inbred population in Hardy-Weinberg equilibrium with random mating. The covariance between individuals i and j is expressed as:

$$\Omega_{ij} = 2\Phi_{ij}\sigma_a^2 + \delta_{ij}\sigma_e^2 \quad (2)$$

where Ω_{ij} is the phenotypic covariance of subject i and j , Φ_{ij} is their kinship coefficient and δ_{ij} is an identity matrix. Here σ_e^2 is a residual term containing all effects not accounted for by the additive component. Heritability (h^2) is obtained by expressing σ_a^2 as a proportion of the phenotypic variance (Falconer and Mackay 1996). For all networks we used age, age², sex, the product of age and sex and the product of age² and sex as covariates.

$$h^2 = \frac{\sigma_a^2}{\sigma_p^2} \quad (3)$$

Genotype $\times$ age interaction

Blangero defined genotype by environment interaction as a significant additive component of variance in response to the environment (Blangero 1993; Glahn et al. 2013). This additive genetic variance in response ($\sigma_{G\Delta}^2$) is a function of the additive genetic variance of the trait expressed in the two environments and the additive genetic correlation between the trait's expression in the two environments:

$$\sigma_{G\Delta}^2 = (\sigma_{G1} - \sigma_{G2})^2 + 2\sigma_{G1}\sigma_{G2}(1 - \rho_G) \quad (4)$$

The null hypothesis of no polygenic interaction, $\sigma_{G\Delta}^2 = 0$, requires the additive variances to be equal ($\sigma_{G1}^2 = \sigma_{G2}^2$) and full pleiotropy ($\rho_G = 1$) between the two environments. Pleiotropy generally refers to a given gene influencing two or more traits. In the context of $G \times A$ interactions, the requirement of full pleiotropy means that the same set of genes must account for the observed additive variance of the trait across age. For a continuous environment (z), the first requirement can be tested by modelling the polygenic variance as an exponential function of the environment:

$$\sigma_{Gz} = \exp(\kappa_G + \gamma_G z) \quad (5)$$

where γ_G determines the rate of change in σ_{Gz} . The second requirement can be tested by modelling the genetic correlation as a function of the difference between environmental indices:

$$\rho_G = \exp(-\lambda_G |z_i - z_j|) \quad (6)$$

Fig. 1 Clustering of cortical thickness regions **a** Changes in the silhouette criterion with increasing number of clusters, the vertical dashed line marks the scale shown in panels B, C and D. **b** Group matrix showing the stability of individual correlations between each cortical region over the jackknife subsamples. The matrix was reordered based on the consensus clustering to facilitate comparison with panel C. **c** Consensus clustering of the cortical regions based on the group stability matrix **d** Surface representation of the consensus clusters. Color scales are shared between panels C and D

where λ_G determines the rate of exponential decay in the genetic correlation as environmental difference increases. Using these variance functions, the phenotypic covariance between two non-inbred individuals i and j is given by:

$$\begin{aligned} \Omega_{ij} = & 2\Phi_{ij}\rho_G\sqrt{\exp(\alpha_G + \gamma_G(z_i - \bar{z}))} \\ & \times \sqrt{\exp(\alpha_G + \gamma_G(z_j - \bar{z}))} \\ & + I_{ij}\sqrt{\exp(\alpha_E + \gamma_E(z_i - \bar{z}))} \\ & \times \sqrt{\exp(\alpha_E + \gamma_E(z_j - \bar{z}))} \end{aligned} \quad (7)$$

where γ_G and λ_G are the parameters of interest in the polygenic genotype by environment interaction test (Blangero 1993). These parameters are estimated using Maximum Likelihood variance-decomposition methods and significance is tested by comparing the log-likelihood for the two restricted models (with γ_G or λ_G constrained to 0) with the log-likelihood for the model where they were estimated. A significant test for σ_{Gz} or ρ_G after Bonferroni correction for the number of clusters is considered as evidence for a polygenic variance component in response to age. For the current analyses, an inverse normal transformation was

applied to all traits of interest to ensure normality of the data and sex was used as a covariate for the interaction analysis. All quantitative genetic analyses were carried out using the Sequential Oligogenic Linkage Analysis Routines (SOLAR) package (Almasy and Blangero 1998).

Results

Clustering and regional age effects

The Silhouette Criterion peaked early (see Fig. 1a) and scale 9 was chosen as the lowest scale at high stability to parcellate the cortical surface. The stability matrix, consensus clustering and surface representation of the clusters for this scale are shown in Fig. 1b, c and d, respectively. Details on the attribution of each AAL region to each cluster can be found in Table S.2. Of interest for the $G \times A$ results, cluster 2 included the cingulate gyrus, the medial orbital part of the superior frontal gyrus and the insula (all bilaterally). The stability of correlations within this cluster (S_{intra}), based on Eq. 1, was very high with values of 0.99 to 1. Conversely,

Table 1 Cluster level age effects and heritability

Cluster	$p_{value}(Age)$	h^2	SE	$p_{value}(h^2)$
1	0.14	0.55	0.10	9.9×10^{-11}
2	< 0.001	0.52	0.09	3.3×10^{-10}
3	0.14	0.40	0.09	2.0×10^{-7}
4	< 0.001	0.60	0.09	3.1×10^{-14}
5	0.78	0.47	0.08	9.9×10^{-10}
6	0.03	0.36	0.09	3.8×10^{-6}
7	< 0.001	0.57	0.09	1.4×10^{-13}
8	< 0.001	0.46	0.09	3.7×10^{-8}
9	0.74	0.42	0.09	1.0×10^{-7}

the stability of correlations with regions outside this cluster (S_{inter}) was very low, ranging from 0 to 0.003. Cluster 5 included the parahippocampal, fusiform and inferior occipital gyri ($S_{intra} = 0.66$ to 0.91 , $S_{inter} = 0$ to 0.29) and cluster 8 consisted of the superior and inferior parietal gyri, the supramarginal, angular and middle temporal gyri as well as the right superior temporal gyrus ($S_{intra} = 0.47$ to 0.81 , $S_{inter} = 0$ to 0.37). Also of note, language-related areas formed a lateralized cluster (#7) involving the bilateral inferior frontal gyri (opercular and triangular parts), rolandic operculum and Heschl's gyrus, along with the left superior temporal gyrus ($S_{intra} = 0.59$ to 0.80 , $S_{inter} = 0$ to 0.46).

Genetic and age related variance components

Estimates of additive genetic heritability were significant for all clusters after Bonferroni correction ($p < 1 \times 10^{-5}$) and ranged from 0.36 to 0.6. Detailed results can be found in Table 1. The highest values ($h^2 > 0.5$) were found in cluster 4 (inferior temporal gyrus and temporal pole), cluster 7 (language-related areas), cluster 1 (frontal areas) and cluster 2 (cingulate gyrus, insula and medial orbital part of the superior frontal gyrus). Significant age-related variance was found in four of the nine clusters, see Table 1, corresponding to parieto-temporal cortices, primary sensorimotor areas and language areas. The absence of age effects in five clusters is likely due to the removal of mean cortical thickness from the data and the four significant clusters thus represent regional effects of age, beyond those observed in the mean. Although not all regions showed fixed effects of age on phenotypic variance, it remains possible for anticorrelated effects on the additive and environmental variance components to be present. Also, different sets of genetic factors might explain an otherwise stable additive variance component. Hence, all networks were included in the $G \times A$ analysis.

Genetic interaction with age

Complete results for the $G \times A$ interaction test are shown in Table 2. For the test of additive genetic variance in response to age (σ_{Gz}), we found marginal significance in cluster 3 (sensorimotor cortices), but this did not survive correction for multiple comparisons. Estimates of γ_G over all brain regions were thus not statistically different from 0 and we consider additive genetic variance to be stable over our age range. For the test of incomplete pleiotropy across age (ρ_G) significant effects were found in cluster 2 (cingulate gyrus, insula and medial orbital part of the superior frontal gyrus), cluster 5 (fusiform, parahippocampal and inferior occipital gyri) and cluster 8 (parieto-temporal areas). These effects survived the Bonferroni corrected threshold (0.006) for nine tests at $\alpha = 0.05$ and are shown in Fig. 2.

Discussion

Here we report the first evidence for incomplete pleiotropy across age in regional cortical thickness, showing that different sets of genetic factors contribute to heritability over healthy aging. The strongest effects were observed in a network of paralimbic regions including the cingulate gyrus, the medial orbital part of the superior frontal gyrus and the insula (cluster 2). Significant effects were also found in a cluster of temporal paralimbic cortices (cluster 5) and in parieto-temporal areas (cluster 8). Human gene expression studies have shown that healthy aging is accompanied by a reduction of gene expression levels and a diversification in gene expression patterns throughout the brain, a finding consistent with the notion of incomplete pleiotropy (Somel et al. 2006; Lu et al. 2004). The heterogeneity of the set of expressed genes peaks around the ages of 40 to 70 years old, also consistent with the later end of our age range (Lu et al. 2004). This finding has important implications for the genetic analysis of cortical thickness, especially regarding methods based on pleiotropy such as genetic correlations.

We also found estimates of additive genetic variance for regional cortical thickness to be constant over our age range. Such age-related changes have previously been investigated in a developmental study by Lenroot et al. (2009). Although changes were found during childhood, they reported that by the age of 18 years old heritability patterns were similar to those reported in adults. Together with our results, this suggests that heritability reaches steadier values during early adulthood. This is also supported by gene-expression studies showing more variance in expression levels before the age of 15 (Stern et al. 2012) while the set of expressed genes and expression levels then seems to remain homo-

Table 2 Results for the test of $G \times A$ interaction

Cluster	Test for σ_{Gz}			Test for ρ_G		
	γ_G	χ^2	p_{value}	λ_g	χ^2	p_{value}
1	−0.007	0.04	0.83	0.006	0.28	0.30
2	0.007	0.74	0.39	0.057	16.31	2.7×10^{-5}
3	0.042	3.88	0.05	0.010	0.74	0.20
4	−0.001	0.00	0.95	0.019	4.34	0.02
5	−0.003	0.09	0.77	0.050	8.74	0.002
6	0.023	2.16	0.14	0.020	1.28	0.13
7	0.014	2.28	0.13	0.010	2.96	0.43
8	−0.008	0.48	0.49	0.039	8.30	0.002
9	−0.006	0.25	0.62	0.000	0.00	0.50

geneous until the age of 40 (Lu et al. 2004). Although heritability cannot be directly equated to the number of genes expressed and their expression levels, our findings agree in that they reach a steady state during adulthood. Similarly, the decline in expression levels from the ages of 40 to 70 might be offset by the diversification of expressed

genes, yielding a similar total amount of genetic contributions. It is also interesting to note that expression patterns become more homogeneous again at ages above 70, where they correlate negatively with those observed during development (Somel et al. 2010; Lu et al. 2004). Therefore, heritability estimates might change again past this point.

Fig. 2 Test of incomplete pleiotropy over age **a** Surface representation of clusters 2, 5 and 8 where significant estimates of λ_G were found. The gray area of the color scale marks the Bonferroni corrected threshold for significance ($p = 0.006$). **b** Genetic correlation decay functions for all clusters based on Eq. 6 and estimates of λ_G . The asterisk is set above the three functions where the effects were significant. The color coding of networks in 2B corresponds to the one used in Fig. 1d

In agreement with previous studies, cortical thickness was significantly heritable in all clusters. The highest values were observed in temporal cortices (cluster 4), language areas (cluster 7) and prefrontal areas (cluster 3). This pattern is consistent with previous studies of brain structure where high heritability estimates were commonly found in prefrontal areas (Joshi et al. 2011; Kremen et al. 2010) as well as the anterior, superior and inferior temporal cortices (Hulshoff Pol et al. 2006; Lenroot et al. 2009; Thompson et al. 2001; Wright et al. 2002). Our finding of high heritability in a lateralized language-related cluster is also in agreement with Thompson et al. (2001) who observed high heritability in language areas with significant lateralization in Wernicke's area. High heritability estimates have also been reported for the posterior cingulate gyrus and insula (Hulshoff Pol et al. 2006; Joshi et al. 2011; Wright et al. 2002). Other regions have shown more variable estimates, notably in parietal cortices, visual areas and the pre-post central gyri (Hulshoff Pol et al. 2006; Joshi et al. 2011; Kremen et al. 2010). These discrepancies could be due to differences in the structural traits used, such as gray matter density, cortical thickness or surface area, since they are known to be affected by different sets of genes (Winkler et al. 2010). The most replicable findings of high heritability in prefrontal, temporal and language-related cortices could be attributed to the role of these regions in higher cognitive functions and their recent evolution in humans (Carroll 2003; Fisher and Marcus 2006).

Finally, we report that regional cortical thickness based on an anatomical atlas can be clustered into highly stable networks. The high levels of stability observed for many clusters in the presents study are likely attributable to the large sample size and quality of the anatomical images. The clusters we identified were mostly bilateral, reflecting strong homotopic correlations, with the exception of the language network (#7), which was lateralized to include the left superior temporal gyrus (Fig. 1). The presence of a distinct language module in human cortical thickness data was previously reported by Chen et al. (2008). Although their network was not lateralized for the same regions we found, this discrepancy may be due to the optimization of network modularity rather than correlation stability as the criterion for network definition and to the use of different scales. Our finding is also in agreement with functional data showing left lateralization in language areas, notably in the superior and middle temporal gyri (Parker et al. 2005) and studies of left-right asymmetry showing higher heritability in language areas of the left hemisphere (Yoon et al. 2010). It is interesting to note that our coarse parcellation of the cortical surface yielded patterns of heritability similar to previous studies at the voxel-level (Hulshoff Pol et al. 2006; Lenroot et al. 2009; Thompson et al. 2001; Wright et al. 2002), suggesting that clustering and silhouette analysis are

an effective way to minimize redundant tests while retaining meaningful regional organization. Finally, it is important to note that our analysis was restricted to cortical thickness and that results might differ for other indices of brain structure or function. Future work should extend these analyses to other traits such as surface area and resting-state connectivity. The inclusion of measured genotypes for linkage analysis would also be of interest to uncover specific genetic loci interacting with age in the human brain.

Conflict of interest Francois Chouinard-Decorte, D. Reese McKay, Andrew Reid, Budhachandra Khundrakpam, Lu Zhao, Sherif Karama, Pierre Rioux, Emma Sprooten, Emma Knowles, Jack W. Kent, Jr., Joanne E. Curran, Harald H. H. Göring, Thomas D. Dyer, Rene L. Olvera, Peter Kochunov, Ravi Duggirala, Peter T. Fox, Laura Almasy, John Blangero, Pierre Bellec, Alan C. Evans, and David C. Glahn declare that they have no conflicts of interest.

Informed consent All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, and the applicable revisions at the time of the investigation. Informed consent was obtained from all patients for being included in the study.

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