Hierarchical Genetic Organization of Human Cortical Surface Area

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Hierarchical Genetic Organization of Human Cortical Surface Area

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Surface area of the cerebral cortex is a highly heritable trait, yet little is known about genetic influences on regional cortical differentiation in humans. Using a data-driven, fuzzy clustering technique with magnetic resonance imaging data from 406 twins, we parceled cortical surface area into genetic subdivisions, creating a human brain atlas based solely on genetically informative data. Boundaries of the genetic divisions corresponded largely to meaningful structural and functional regions; however, the divisions represented previously undescribed phenotypes different from conventional (non–genetically based) parcellation systems. The genetic organization of cortical area was hierarchical, modular, and predominantly bilaterally symmetric across hemispheres. We also found that the results were consistent with human-specific regions being subdivisions of previously described, genetically based lobar regionalization patterns.

As early as the 1950s, Bergquist and Kallen postulated that the entire embryonic brain is divisible into an anteroposterior series of segmented neuromeres, each forming a complete ring around the brain's longitudinal axis (*1*). Almost 40 years later, experimental data showed that many gene expression domains respect segment boundaries in the embryonic vertebrate hindbrain, suggesting a role of genetic control in regional differentiation (*2*, *3*). This important finding prompted a search for similar genetic regulatory organization in other regions of the developing vertebrate brain (*4*). In particular, in the past decade the cerebral cortex has received substantial attention. Studies have shown, for example, that several signaling molecules and transcription factors are involved in establishing boundaries between mouse cortical regions (*5*, *6*). Animal data demonstrate that the regional or positional identity of cortical regions is defined by the combinatorial expression pattern of various genes controlling for regional differentiation, each of which is expressed in a graded and restricted pattern with distinct spatiotemporal characteristics (*7*). Little is known, however, about the genetic patterning underlying the human cortex. In our previous work (*8*), we showed that genetic patterning underlying the anteroposterior gradient and four basic cortical divisions of cortical surface area demonstrated in mouse models (*7*) also existed in the human cortex. Furthermore, region-specific cortical areal expansion in humans has been linked to specific genetic polymorphisms (*9*, *10*). We sought to go beyond the fundamental commonalities that humans share with other species and to investigate the genetic patterning specific to the human cortex with its 1000-fold increase in surface area relative to the mouse brain (*11*). In effect, we sought to develop a brain atlas of human cortical surface area that was based entirely on genetic correlations, rather than a priori structural or functional information.

To delineate the genetic patterning of the cortical area, we measured relative surface areal expansion using cortical surface reconstruction and spherical atlas mapping developed by Dale and colleagues (*12*–*14*). We divided the area measured at each location by the total surface area in order to account for global effects. Using the twin design, which compares monozygotic and dizygotic twins, we then estimated genetic correlations between different points on the cortical surface. These genetic correlations represent shared genetic influences on relative areal expansion between cortical regions (*15*). Details of these methods have been previously described (*8*, *16*). After computing pairwise genetic correlations, we used an unsupervised pattern recognition method—fuzzy cluster analysis (*17*)—to demarcate the genetic topography of cortical surface area based on the genetic correlations of relative surface area measures. To determine the appropriate number of clusters, we computed the widely used silhouette coefficient.

On the basis of the peak of the silhouette coefficients (fig. S1), we identified 12 natural clusters. These clusters correspond closely to meaningful structural and functional regions (Fig. 1), even though the registration procedure did not rely on prespecified anatomical landmarks; rather, it makes use of the continuous pattern of surface curvature (*13*). In describing the subdivisions, we use conventional labels, but these only approximate the observed clusters. Subdivisions of the frontal cortex include the motor-premotor, dorsolateral prefrontal cortex extending to the anterior and superior parts, dorsomedial frontal, and orbitofrontal (Fig. 1, clusters 1 to 4). Another cluster is found between the frontal and parietal cortices, extending from pars opercularis to the subcentral region, including the inferior pre- and post-central gyri (Fig. 1, cluster 5). The temporal cortex includes the superior temporal, posterolateral temporal cortex extending to temporal and parietal junction, and anteromedial temporal cortex (Fig. 1, clusters 6 to 8). The parietal

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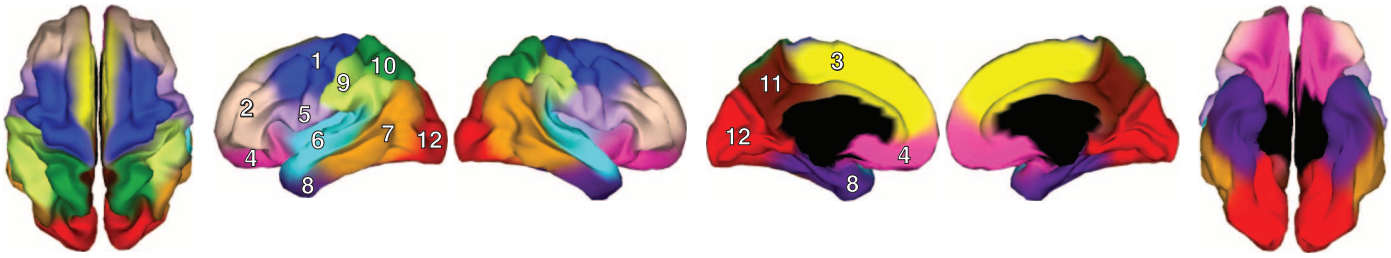

Fig. 1. Genetic clustering map for 12-cluster solution. 1, motor-premotor cortex; 2, dorsolateral prefrontal cortex; 3, dorsomedial frontal cortex; 4, orbitofrontal cortex; 5, pars opercularis and subcentral region; 6, superior temporal cortex; 7, posterolateral temporal cortex; 8, anteromedial temporal cortex; 9, inferior parietal cortex; 10, superior parietal cortex; 11, precuneus; and 12, occipital cortex. Views shown from left to right are, respectively, superior, left hemisphere lateral, right hemisphere lateral, left hemisphere medial, right hemisphere medial, and inferior.

cortex includes the inferior parietal cortex, superior parietal cortex, and precuneus (Fig. 1, clusters 9 to 11). The occipital cortex constitutes a single cluster (Fig. 1, cluster 12). Some anatomical boundaries of these clusters map onto traditionally parcellated regions, such as cytoarchitectural areas or gyrus patterns; however, others do not follow classically defined boundaries (such as Brodmann areas). For example, there is no natural sulcal-gyral boundary between our dorsomedial and orbitofrontal clusters, but they still correspond reasonably well to the division between Brodmann areas 10 and 11. Conversely, the well-defined cytoarchitectural differentiation between Brodmann areas 17 and 18 is not manifest as separate genetically based clusters in our analyses.

The genetically based clusters presented a spatially contiguous pattern within hemispheres. However, the cluster algorithm placed no constraint against noncontiguous clusters. Indeed, all 12 clusters were noncontiguous clusters bilaterally located in the homologous regions between hemispheres. There were some indications of surface-area asymmetry around perisylvian regions (8), but the patterns of the left and right hemispheres were almost mirror images of one another. Because the clustering was conducted on both hemispheres simultaneously with no constraint for hemispheric symmetry, the results clearly indicate a predominantly bilateral symmetric and within-hemisphere modular pattern.

In order to obtain reliable estimates of the genetic correlations, we applied spatial smoothing, which limited our ability to address the fine spatial structure of the genetic patterning (*16*). We focused on the large-scale, primary structure of genetic patterning. Other techniques, such as gene expression analysis of brain tissue, could reveal finer-scale genetic patterning that may show more asymmetrical features or more subdivisions (*18*, *19*) than can our magnetic resonance imaging (MRI)–based approach.

After identifying the boundaries of the genetically based parcellation, we next sought to examine the genetic relations between the 12 clusters; in particular, we searched for underlying organizational principles among these genetic subdivisions. We calculated the genetic similarity matrix to determine the genetic relatedness between clusters (Fig. 2). We found that genetic correlations are higher between clusters within the same lobe than between clusters in different lobes. Also included in Fig. 2 is a dendrogram derived from hierarchical clustering that summarizes the genetic relations between clusters. The dendrogram depicts a hierarchical structure of genetic patterning. The most distinct genetic partitions located at the highest level of the hierarchy correspond to the basic anteroposterior division between motor and sensory cortices; below that are the functionally specialized subdivisions generally nested within lobes. Similarly, a clear basic frontal/nonfrontal division and lobar-like clusters have been revealed by hierarchical clustering derived from transcriptome analyses of the fetal human brain (*20*, *21*). One exception to these general patterns is that clusters belonging to the perisylvian region have relatively high correlations with one another, even though they are in different lobes. Cross-lobe clustering in these regions is consistent with a human-specific subdivision specialized for language.

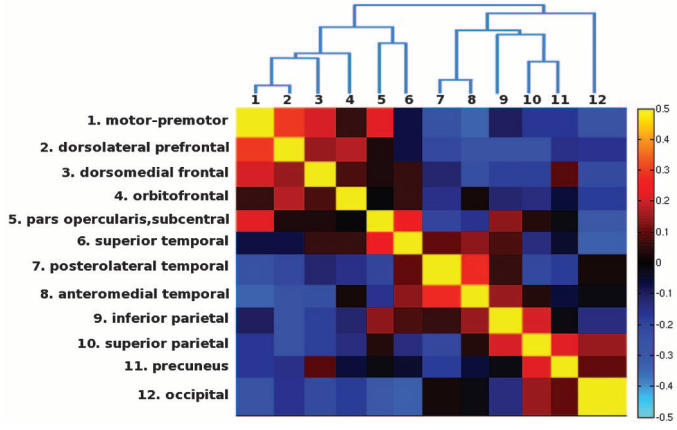

Fig. 2. Genetic similarity matrix and dendrogram. The color scale represents the weighted mean genetic correlations within and between clusters. Negative genetic correlations indicate that the genes that cause areal expansion in anterior regions also cause relative areal contraction in posterior regions and vice versa (*8*).

We also examined the progression of cluster solutions, from 2 to 12 clusters, using fuzzy clustering (fig. S2). If the structure of the data are hierarchical, then successive clusters will tend to be subdivisions of previous clusters (*22*). In contrast to hierarchical clustering, our approach imposed no constraint for hierarchical organization; each level of the fuzzy clustering analysis was performed independently. Yet, the sequentially unfolding pattern revealed that the emerging clusters tended to respect the boundaries of preceding clusters and appeared to be nested subdivisions. The convergence of results of this analysis and the dendogram method thus provide further evidence for a hierarchical structure of genetic patterning that is intrinsic to the data.

The organization of genetic patterning is consistent with a ubiquitous pattern in the development of biological forms—increasing differentiation along with what appeared to be increasing hierarchical integration, as reflected by functionally specialized subdivisions (*23*). We previously showed that the four-cluster solution revealed fundamental genetic divisions comprising primary functional regions largely corresponding to the lobar divisions in all mammalian species (*8*). Our current results demonstrate further differentiation of each of the lobes into several nested subdivisions that correspond specifically to human functional specialization, such as the lateral or granular prefrontal cortex, and regions around Broca's area and the subcentral region associated with vocalization essential for human language (*24*). Our results suggest that human specialization regions are not genetically more distinct than primary functional lobar regions. However, small genetic differences resulting in functional importance have become increasingly recognized (*11*, *25*). These findings support the notion that the human cortex is built on the foundation of the primary functional divisions, which are shared among mammals (*7*). Without any incorporation of prior anatomical knowledge, this statistically constructed

hierarchy demonstrated a biologically sensible organizational structure of the human brain.

We described a previously unidentified parcellation system for the human cortex that reflects shared genetic influences on cortical areal expansion. This system constitutes the first human brain atlas based solely on genetically informative data, which may provide presently undescribed phenotypes that will have greater statistical power for genome-wide genetic association studies in comparison with traditional cortical parcellations. We found evidence for a hierarchical, modular, and bilaterally symmetric genetic architecture. Genetically based lobar regions have been demonstrated across mammalian species (*7*, *8*), and our results are consistent with genetically based regions of human specialization being increasingly differentiated subdivisions of these lobar regions. Our findings may thus be useful for translating results from model organisms into functional and clinical insights about human specializations, so as to understand both order and disorder in the human brain.

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Ecological Context Influences Epidemic Size and Parasite-Driven Evolution

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The occurrence and magnitude of disease outbreaks can strongly influence host evolution. In particular, when hosts face a resistance-fecundity trade-off, they might evolve increased resistance to infection during larger epidemics but increased susceptibility during smaller ones. We tested this theoretical prediction by using a zooplankton-yeast host-parasite system in which ecological factors determine epidemic size. Lakes with high productivity and low predation pressure had large yeast epidemics; during these outbreaks, hosts became more resistant to infection. However, with low productivity and high predation, epidemics remained small and hosts evolved increased susceptibility. Thus, by modulating disease outbreaks, ecological context (productivity and predation) shaped host evolution during epidemics. Consequently, anthropogenic alteration of productivity and predation might strongly influence both ecological and evolutionary outcomes of disease.

Parasites can impose strong evolutionary pressure on their hosts during epidemics (*1*, *2*). Parasites often virulently depress survival and/or birth rate of their hosts. As a result, if epidemics become large enough, host populations might evolve resistance to infection because of parasite-mediated directional selection (*1*). Alternatively, if the susceptibility of a host genotype depends on the parasite genotype to which it is exposed, negative frequency-dependent selection can drive cycling of host genotypes through time [that is, "Red Queen dynamics" (*3*, *4*)]. These two ideas about host (co-)evolution during epidemics, evolution of increased resistance and the Red Queen hypothesis, dominate research on evolutionary epidemiology (*1*). However, theory reveals other possibilities, including the evolution of higher susceptibility to infection (*1*, *5*–*8*). Why would hosts evolve greater susceptibility to their virulent parasites during epidemics? When would host populations evolve this way in nature?

The answers to these questions involve trade-offs and ecologically driven variation in disease prevalence. Resistance to virulent parasites can trade off with reproduction; some genotypes have higher fecundity but lower disease resistance, whereas others are less fecund but more resistant. The fittest strategy, then, depends on the net balance between resisting infection and enhancing fecundity. That balance, in turn, depends on ecologically determined disease prevalence. Environments with high resources for hosts (higher productivity) and lower mortality (lower predation) on hosts should fuel large epidemics (*9*–*12*). In these systems, theory predicts that hosts should evolve increased resistance to disease, even though resistant genotypes have lower fecundity. However, when low productivity and/or higher predation constrain epidemic size, populations should become more susceptible because more susceptible genotypes are more fecund.

We test these predictions in a host-parasite system that exhibits the requisite trade-offs and ecologically driven variation in epidemics. Clonal genotypes of the zooplankton grazer *Daphnia dentifera* face a trade-off between fecundity and resistance to infection by a virulent yeast parasite [*Metschnikowia bicuspidata* (*13*)]. Mechanistically, the resistance-fecundity trade-off is driven by variation in feeding rate: Slow feeders consume fewer free-living propagules (spores) of the yeast (conferring higher resistance) but assimilate energy less quickly (yielding fewer offspring). Neither host-parasite genotype specificity nor Red Queen dynamics appear in this system; host resistance does not depend on the parasite genotype to which it is exposed (*14*). This parasite reduces fecundity and survival (*15*). Epidemics erupt commonly in *Daphnia* populations, with maximal infection prevalence sometimes exceeding 60% (*16*, *17*).

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