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Mapping genetic influences on cortical regionalization

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Abstract

In this issue of *Neuron*, Chen and colleagues combine structural MRI and a twin-study design to investigate the influence of genetics on human cortical regionalization. Their results resonate with findings from animal studies and certain human syndromes of developmental cortical malformation.

Keywords

MRI; twins; cerebral cortex

Over the past several decades, there has been considerable interest and debate among developmental neurobiologists regarding the factors that drive the development and differentiation of the areas that comprise the neocortex. These neocortical areas are, classically, considered unique and distinguishable on the basis of architecture (cyto, chemo, myelo-), afferents, efferents, and, of course, function (O'Leary et al., 1994). More recently, differential gene expression has been added to the list of potentially distinguishing features. This array of features allows one to delineate clearly, for example, primary motor cortex from primary visual cortex.

Why has this topic garnered so much interest? At least 3 compelling reasons come to mind. First, from a strictly developmental neurobiology perspective, how functional specializations in the brain come to exist is of fundamental interest. Second, understanding how intrinsic and extrinsic mechanisms drive differentiation of neocortical areas can inform our understanding of developmental plasticity phenomena such as critical and sensitive periods. Third, delineating the origins of so-called higher cortical functions that likely arose from neocortical expansion, including those seemingly unique to humans such as language, is of fundamental significance to understanding the evolution of human behavior.

Historically, there has been considerable debate regarding mechanisms for areal differentiation. Specifically, does the ventricular neuroepithelium that gives rise to the neurons destined to make up the primary visual cortex possess the information necessary to produce areas devoted to visual processing (i.e. intrinsic determinism)? Or does information carried by afferents to those neurons instruct them about their ultimate function (i.e. extrinsic determinism)? In the late 1980's, these questions were formalized into Rakic's protomap model (Rakic, 1988) and O'Leary's protocortex model (O'Leary, 1989). Both models recognized roles for genetic and epigenetic mechanisms, including important

interactions with thalamocortical afferents. They differed substantially, though, in scope and emphasis with the former arguing for primacy of intrinsic information and the latter emphasizing extrinsic information in the ultimate determination of areal fate (O'Leary et al., 1994).

With the identification in the 1990s of transcription factors involved in telencephalic development, such as Emx2 and Pax6 (e.g. (Bishop et al., 2000)), these hypotheses could be tested with state of the art molecular approaches and genetic manipulations. As a consequence, over the past 20 years, considerable progress has been made in understanding the mechanisms that lead to the patterning of the neocortex though the story is far from complete. Little debate remains at present regarding whether or not intrinsic and extrinsic mechanisms interact so that functional specialization and areal differentiation can occur. The nascent neocortex has been demonstrated to possess robust intrinsic information for regionalization; normal appearing molecular patterning is evident even in mice genetically altered to lack thalamocortical afferents (Myashita-Lin et al., 1999), for example. Several groups of investigators using animal models have worked to delineate the basic mechanisms underlying this early regionalization of the nascent neocortex (e.g. O'Leary et al., 2007). Based on these studies, a complex hierarchy of transcription factor expression that controls cortical patterning has been described. Patterning centers along the anterior and posterior midline, such as the anterior neural ridge (which becomes the commissural plate) and the cortical hem (located posteriorly) set up gradients of transcription factor expression important for the establishment of patterning. Gradients of transcription factor expression are also established in the neuroepithelium along anterior-posterior and medio-lateral axes. Thus, these genetically determined factors comprise the molecular framework for an early and coarse regionalization. Such intrinsic mechanisms provide the template for the establishment of appropriate thalamocortical and other afferent inputs, as well as other aspects of architectural and connectional features. These features are influenced by the afferents themselves or by information regarding the status of the periphery carried by those afferents (*e.g.*, (O'Leary et al., 1994; Sur and Rubenstein, 2005). From an initial regionalization comes sharpening of boundaries and the emergence of identifiable areal boundaries, mostly, it turns out, along the anterior-posterior axis.

Whether or not similar mechanisms control cortical regionalization in humans has been difficult to establish, since manipulating transcription factor expression in highly controlled genetic backgrounds is not feasible. In this issue, Chen and colleagues (Chen et al., 2011) take on this challenge by using a potent combination of analytical strategies, a twin-study design and structural MRI, to address whether latent genetic factors contribute to regionalization of the cerebral cortex in humans. Specifically, by obtaining and analyzing MRI data from over 200 monozygotic and dizygotic twin pairs (from the Vietnam Era Twin Study of Aging), the authors derived cortical surface reconstructions using a spherical atlas mapping procedure to measure the relative contributions of genetic and environmental influences on the regional expansion of cortical surface area. In this way, they could generate a map that reveals a regional pattern of shared genetic influence on cortical surface area.

Interestingly, they demonstrate that along the anterior-posterior axis, there is evidence for both positive and negative genetic correlation effects on surface area. When related to a seed region in the frontal pole, positive correlations are seen to be strongest nearest the seed and then to taper off posteriorly to the central sulcus where there is an abrupt transition to negative correlations more posterior still. The “push-me/pull-you” nature of these relationships is highly reminiscent of the antagonistic relationship seen along the cortical anterior-posterior axis between transcription factors PAX6 and EMX2 in mouse studies (O'Leary et al., 2007).

The authors also nicely demonstrate that the locations of transitions in shared genetic influence were comparable when derived via a seed-based approach or via a data-driven approach. These findings convincingly illustrate a pattern of genetic correlation for cortical surface area that reflects the aggregate effect of myriad genetic/intrinsic mechanisms. However, these results should not be construed as a cytoarchitectonic map of neocortical arealization or a map that reveals the expression pattern of putative human homologs of the transcription factors described in the mouse literature. Firstly, the granularity of the regionalization is at a scale larger than one would consider to be associated with neocortical areas. Rather, the regionalization appears to be of a lobar (such as frontal or parietal) or sub-lobar, not areal scale. For example, the data reveal no evidence of a delineation between V1 (primary visual cortex) and V2 on the medial surface. Thus, although the authors juxtapose and analogize genetic division of the human occipital lobe with murine V1 arealization, for example, it is important to recognize that the influence of genetic factors in humans converges with murine data only at the level of coarse regionalization attributed to gradients of transcription factor expression and not with the formation of specific cortical areas. Secondly, identifying a genetic pattern in this way is not equivalent to identifying the effects of particular genes or gene products. As the authors point out, the twin design affords the ability to quantify, based on a standard and vetted model, “genetic influences on complex traits that likely involve large numbers of genes and their interactions.” Nonetheless, there is ample evidence to support their claim that an aggregate genetic effect influences cortical regionalization in humans, which is highly consistent with findings from animal studies wherein transcription factor expression was experimentally manipulated.

The clear demonstration of genetic influences on human cortical regionalization has straightforward implications for evolutionary mechanisms of the expansion and functional apportionment of the cortex. The comparisons between prior findings in mice and the current findings on regionalization in humans described by Chen et al (2011), underscore the notion that selective pressure can influence, via an aggregation of genetic influences, the evolution of cortical development such that a “visual” species, like humans (and other primates), have a relatively greater amount of cortical resources for visual processing, whereas a “somatosensory” species, such as the rodent, have a relatively greater amount of cortical resources for somatosensory processing. Chen et al (2011) note similar expansions in the genetic divisions of human frontal and temporal cortex relative to rodents, which they speculate may be linked to the evolution of language and other “higher order” cognitive processes.

Several findings from the study are congruent with observations in human pathologies of cortical development. The anterior-posterior orientation of the genetic effects are consistent with observations from human genetic lissencephalies (“smooth brain” syndromes), now well known to have severity increases or decreases along the anterior-posterior axis depending upon which gene is involved; DCX has greater pathology anteriorly and LIS1 has greater pathology posteriorly (e.g., (Pilz et al., 1998)). The observation that genetic patterning is mostly symmetric between hemispheres is consistent with the phenomenon of certain polymicrogyria syndromes which have a strong propensity to be bilaterally symmetric and regional (Barkovich et al., 1999; Leventer et al., 2010). The lack of genetic effects mapping onto a specific area, such as V1, is also consistent with the observation that cortical migration defects have not been demonstrated to affect a single neocortical area to the exclusion of others. These observations are also congruent with the idea that no one gene affords a neocortical area with its areal identity (O'Leary et al., 2007).

Recent brain imaging studies investigating connectivity often use correlation as the metric of functional, structural, or effective connectivity (e.g. (Rubinov and Sporns, 2010)). However, Chen and colleagues stress that the genetic correlations in cortical surface-area patterning

cannot be used to draw conclusions regarding underlying structural or functional neural connectivity. That said, it is interesting to note that regions whose functional relationships are strongly linked in brain systems such as the default mode network or the dorsal attention system (Zhang and Raichle, 2010), to name a couple, do not appear to have shared genetic correlations. Thus, while genetic factors are likely to have robust influence in the establishment of regionalization, functional areas or systems of functional areas do not appear to be influenced by these same genetic factors.

The study by Chen and colleagues exemplifies the strength of using a twin-study design in the context of brain imaging analyses to decipher the genetic and environmental influences on brain organization. In an effort to promote such studies in the future, the NIH Human Connectome Project (HCP; http://humanconnectome.org/) promises to provide a full complement of behavioral and structural/functional imaging datasets obtained from a genetically informative sample of 1200 subjects composed of kindred sets of twins (monozygotic and dizygotic) and their non-twin siblings. Data from the HCP, freely available to the public, will allow investigators to relate genetic factors not only to cortical surface regionalization, but to brain structure, connectivity, function, and behavior. The potential utility of these datasets, together with the findings from Chen et al (2011), marks an exciting new chapter for the study of human brain development.

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