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The Architecture of Cortex—in Illness and in Health

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View of the Cortex

In the same way that much can be gleaned by simply listening to a patient, much can be gleaned by simply looking at the brain. The most striking feature of the human brain is the cerebral cortex. The cortex is a 1- to 4.5-mm-thick sheet of cells (totaling 19–22 billion neurons) that delicately wraps the two hemispheres of the brain. Much like foil covering a piece of candy, the cortex drapes and folds over the subcortical structures and coalescing white matter (myelinated axons traversing between brain structures). Unlike a simple covering, however, the cortex is intricately folded into gyri that markedly increase its surface area. When unwrapped and flattened, the human cortex measures around 2500 cm² and constitutes about 77% of the total volume of the brain (by comparison, the cortex in the rat represents only 31% of its brain volume). The expanded cortex in humans enables a range of higher order cognitive functions and, in many ways, can be seen as the defining attribute of what makes us human.

At the cellular level, one of the first aspects of the cortex noted by early neuroscientists was its laminated (or layered) appearance, which varies widely across the brain. Most of the cortex can be classified as “neocortex” (also called “isocortex”): this phylogenetically newer cortex contains six layers and is found only in mammals (Figure 1). In humans, the neocortex comprises visual, somatosensory, auditory, and multimodal sensory regions as well as parts of the prefrontal cortex (PFC). In contrast, simpler and phylogenetically older cortex, called “allocortex,” has only three or four layers and can be found in the medial temporal lobes and posterior orbital cortices—areas that are important for emotion processing. Cortex that is more layered and well defined than allocortex but not as well defined as neocortex is conceptualized as transitional cortex.

Variations in cytoarchitecture (cellular structure and composition) have been used as an organizing principle for defining different anatomic regions in the brain. One of the earliest such attempts was that of the neuroanatomist Korbinian Brodmann, whose regional definitions (referred to as Brodmann areas) are still used today. As an example, the boundary between the frontal eye fields and the dorsal (upper region) premotor cortex can be drawn

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where layer IV of the frontal eye fields disappears (thus, dorsal premotor cortex is defined in part by its lack of layer IV) (Figure 1) (1). Newer maps continue to define cortical regions by changes in layering and associated histochemical properties, while other maps demarcating live human brains have leveraged high-resolution imaging and computational techniques. It is important to note, however, that modern maps continue to be strongly influenced by Brodmann's original cytoarchitectural definitions.

Timing Matters: Cortical Development

The cortex “grows up” under the influence of a multitude of factors, and from a psychiatric perspective, two conceptual themes are worth highlighting: developmental windows and the process of differential development. The formation of cortical neurons and layers is ripe with time-specific developmental windows—i.e., discrete times during which the cortex undergoes specific changes. If development fails to occur during these windows, the opportunity to regain these or subsequent developmental sequences may be lost forever. A prime example of this is the way in which cortical neurons derive in utero from neural progenitor cells. These progenitor cells live below the future cortex, and daughter neurons migrate upward to form cortical layers in an inside-out manner—the deep layers first and superficial layers later (2). Cells in earlier phases of development (forming deep layers) can be coaxed toward later phases of development (forming superficial layers); however, the reverse is not true (i.e., fast-forwarding in time is possible, whereas going backward is not) (3). This specific timing is also stamped within the cortical layers where cells located horizontally have been formed at the same time, and cells located vertically come from the same lineage (2). When cortical neurogenesis is complete (mostly by midgestation), the progenitor cells are thought to undergo apoptosis, and the opportunity for future cortical neurons to be formed in this manner is over.

The second key theme is that of differential development—just as the different regions of the brain have varying cytoarchitecture, they also follow distinct developmental trajectories. For example, whereas all regions undergo myelination and “pruning”—synaptic overproliferation followed by a deliberate trimming—this occurs at strikingly different times. Visual cortex undergoes both early: myelination begins in utero, and synaptic elimination finishes around age 3 years (4). In contrast, PFC mostly myelinates postnatally, and the PFC undergoes protracted synaptic pruning through late adolescence (4). This later cortical shaping in the PFC likely parallels ongoing improvements in cognition and impulse control in adolescents. Neuroimaging work using in vivo longitudinal, whole-brain analyses has demonstrated that cytoarchitecturally distinct regions have discrete trajectories. In particular, measures of cortical thickness suggest that neocortical areas undergo a more complicated cubic trajectory, with a peak and a nadir, whereas allocortical areas have a linear trajectory, with ongoing decline starting earlier in development (5). Throughout development, such differentiation likely allows for improved specialization and functional integration among cortical regions.

Cortical Changes in Psychiatric Illness

Given the intricacy of the cortical system—a highly complex architecture assembling and unfurling across time—it is not surprising that the cerebral cortex is a site of vulnerability in psychiatric illness. The dynamic development and subregional differentiation mean that the time and space in which cortical insults occur are highly significant. Specifying when in development and where in the cortex are crucial questions for differentiating psychiatric pathophysiology.

Though in relative infancy, psychiatric neuroscience has begun to offer clues about how this process may play out in different disease states. For instance, in adults with schizophrenia, the following has been found: decreased gray matter volumes (neuronal, dendritic, and glial tissue distinct from white matter, as measured by magnetic resonance imaging) in auditory cortex and PFC and smaller neurons and fewer dendritic spines in layer III of dorsolateral PFC (microscopically examined by postmortem studies) (6). Interestingly, prefrontal and temporal cortical changes are also seen in magnetic resonance imaging scans of first-degree relatives of patients with schizophrenia; these may reflect baseline changes that, when combined with additional insults, create disease phenotype (7). In contrast, different regions appear affected in individuals at risk for social anxiety (as characterized by a behaviorally inhibited temperament at 4 months old). At 18 years old, individuals displayed thicker ventromedial PFC and thinner orbitofrontal cortex on magnetic resonance imaging (8). Taken together, it is clear that both disease and risk for disease accrue regionally specific cortical changes—occurrence of these changes at critical time points can shatter the developmental timeline with diverse and long-lasting consequences.

In autism spectrum disorder (ASD), a pioneering study has implicated the prenatal period as a vulnerable window. To arrive at this conclusion, Willsey *et al.* (9) first identified several genes mutated in patients with ASD; they then looked for when and where these genes were expressed in normal postmortem brains across development. The latter experiment allowed them to identify time points and brain regions that could be vulnerable in ASD. They found the genes to be highly expressed during the midgestational development of layer V/VI prefrontal and primary motor/somatosensory cortical neurons. This finding suggests that aberrant development of regionally specific deep layer cortical neurons may contribute to ASD pathophysiology. This study represents the (currently) rare experiment that sheds light on where, when, and how illness may occur in the human cortex, raising excitement for future studies of other illnesses.

In this issue of *Biological Psychiatry*, Maier *et al.* (10) have also highlighted developmental windows. In the largest study to date of adults with attention-deficit/hyperactivity disorder examined using magnetic resonance imaging, limited differences in gray matter volumes were found compared with control subjects. This is in contrast to previous studies that did show differences in gray matter volumes in various cortical regions. The authors posit that their results may reflect a difference in subject population: whereas previous studies focused on adults who had developed attention-deficit/hyperactivity disorder in childhood, their own study examined individuals who developed attention-deficit/hyperactivity disorder in adulthood. This raises the provocative question of whether the onset of symptoms in

childhood versus adulthood may reflect discrete illnesses, further underscoring the importance of developmental specificity.

Future Directions and Therapeutic Implications

Ultimately, a major goal of this research is the translation into new interventions for psychiatric illness. An obvious desire would be therapeutics that can precisely target specific cortical regions and their associated networks. Such interventions would require ongoing microscopic and macroscopic characterization of cortical subregions and an ability to harness differential features. Even more tantalizing would be interventions that could change cortical cytoarchitecture and wiring at critical periods, giving another chance for normal development and forcing downstream developmental windows open again. A prerequisite to any such interventions is an accurate understanding of the cortical subregions and developmental windows involved in different psychiatric illnesses. Characterizing these differential aspects across space and time—along with eventual links to function, behavior, and symptoms—remains an exciting and important area of work.

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Brodmann Areas (BA)

Figure 1.

Brodmann areas (BAs) and differential layers in frontal eye fields and dorsal premotor cortex. Brodmann initially defined 43 cytoarchitecturally distinct regions of the human cortex. Additional areas have been identified in nonhuman species. An example of cytoarchitectural distinction can be seen at the juncture of BA 8 (frontal eye fields) and dorsal BA 6 (premotor cortex). BA 8 has a six-layered structure, whereas the dorsal region of BA 6, missing layer IV, has five layers (1).