

CEREBRAL CORTEX DISEASES & CORTICAL LOCALIZATION

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The cerebral cortex, or outer cell layer of the brain, is divided into a mosaic of discrete areas with different functions: specific regions control vision, sensory and motor function, hearing, and language. We review how the cortex is organized, and describe the major cortical diseases that impact brain function and behavior.

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CEREBRAL CORTEX DISEASES & CORTICAL LOCALIZATION

Paul M. Thompson and Arthur W. Toga

Glossary

Brodmann Areas. A subdivision of the human cerebral cortex into 52 regions with different cellular and functional characteristics, developed by the German anatomist Korbinian Brodmann (1868-1918).

Neurofibrillary Tangles. A pathologic hallmark of Alzheimer's disease, in which filamentous deposits of hyperphosphorylated proteins accumulate within neurons.

Positron Emission Tomography (PET). A brain imaging technique that uses injected radioactive compounds to map patterns of blood flow, glucose, or oxygen utilization in the brain.

Functional Magnetic Resonance Imaging (fMRI). A brain imaging technique, based on the paramagnetic properties of hemoglobin in the blood, which creates maps of brain activation during cognitive tasks such as language comprehension, vision, memory, and emotional processing.

Sensory/Motor homunculus. A representation of the body surface found in part of the human cerebral cortex, showing regions that process sensory or motor information for specific body parts.

Radial Glia. A system of brain cells, created during brain development, which serves as a scaffolding to guide migrating neurons to their destinations in the cortex.

Introduction

Recent advances in neuroscience have revolutionized our knowledge of how the brain is organized. The brain's functional layout can be understood at several levels, from the distributions of gene products, neurotransmitters, and other molecules, to the properties of single cells, and ultimately to the activity of neural networks that underlie brain function and behavior. The cerebral cortex, which is the folded outer layer of the brain, is only 2-4 mm thick, and contains 50-100 billion neurons. It produces our thoughts, perceptions and emotions. Structurally, the cortex is organized into discrete sectors that contain different cell types. These components control distinct functions such as vision, hearing, memory, language, sensation and movement. When the cortex degenerates in Alzheimer's disease and other dementias, cognitive function is profoundly impaired. If abnormalities occur during cortical development, disorders such as mental retardation, epilepsy, and autism often ensue. Even the psychotic symptoms of schizophrenia are accompanied by neurotransmitter imbalances in the cortex, which affect how it processes information. Intriguingly, many brain diseases selectively impact particular cortical regions, leaving others relatively intact. As we begin to understand how the cortex is organized, we are learning how these diseases affect cognitive function and behavior, as well as discovering new therapeutic approaches.

Cortical Structure

The human cerebral cortex is a folded sheet of cells that covers the cerebral hemispheres. It is typically divided into the allocortex (comprising the primary olfactory cortex and hippocampus), and the neocortex, which covers the remaining 90% of the brain surface. The allocortex has 3 layers of neurons, and lies deep in the temporal lobe, where olfactory input reaches the cortex. Strictly speaking, there are also 5 transition zones between the allocortex and neocortex. These include important limbic regions involved in memory and emotion, such as the cingulate, parahippocampal gyrus, orbitofrontal cortex, insula and the temporal pole.

In the nineteenth century, anatomists used histologic stains (e.g., Nissl stains for cell bodies, myelin stains for axons, and the Golgi stain, which labels neurons black; **see Figure 1**) to reveal that the neocortex is divided into 6 layers (I being the outermost). Each layer has particular cell types that predominate. Layers II, III, and V are rich in pyramidal cells (**see Figure 2**). They send vast numbers of output axons down to the basal ganglia, brain stem, and spinal cord. Layer IV is rich in non-pyramidal cells; it primarily receives input from the thalamus and other afferents. Layer I is rich in glial cells and axons that interconnect cortical areas, while layer VI primarily sends axons back down to the thalamus. Visible columns of nerve cells also appear. In these, functional connections run vertically across all 6 layers. Only 0.5-1.0 mm in diameter, over a million of these functional units are found in the human cortex (Hubel and Wiesel, 1962). Single unit recordings from visual cortex have shown that these columns can perform simple information-processing tasks, such as encoding location, orientation, and color for objects in small regions of visual space.

Functional Anatomy. In 1909, the German anatomist Korbinian Brodmann divided the human cortex into 52 cytoarchitectural areas (some being further subdivided). He assigned them numbers that are still used by neuroscientists today (Brodmann, 1909; **see Figure 1**). Within the cortical sheet, Brodmann observed that there were sharp boundaries where marked transitions occur in cell sizes, and the densities of cells and myelinated axons. Brodmann's areas were subsequently found to be functionally different as well, and each has its own characteristic pattern of connections. Primary visual cortex (area 17), for example, receives direct input from the lateral geniculate nucleus; the areas that surround it (18 and 19) are secondary visual areas, and they perform higher-order computations on visual features. The first areas Brodmann studied, areas 1, 2, and 3, include the primary sensory strip in the postcentral gyrus, which process sensations from the body surface. Areas 6 and 8 contain the motor and premotor cortex, which control voluntary movements. Other key areas and their Brodmann designations include: Broca's speech area (44/45), the primary auditory cortices (41, 42; 41 is also known as Heschl's gyrus), the angular gyrus (39), and the frontal eye fields (8), which are involved in visual reflexes.

Laminar Thickness. Motor and sensory cortices also differ in their laminar thickness, consistent with their functional differences. Motor cortex has the thickest pyramidal cell layer of all; essentially an output layer, this contains giant Betz cells whose axons reach motoneurons as far down as the spinal cord. Motor cortices have a virtually non-existent layer IV (the granular layer), while sensory cortices have the thickest (layer IV even splits into three sublayers in primary visual cortex). Association cortices, which combine information from multiple sensory modalities, have a balanced representation of each.

Lesion Studies. The function of individual cortical sectors became clear from studying patients with focal brain damage, whose location could be confirmed at autopsy. Selective damage to the cortex often led to distinct patterns of cognitive or behavioral deficits. The French neurosurgeon Paul Broca noted that damage to the inferior frontal gyrus (now known as Broca's speech area) led to aphasia. This is an inability to produce coherent language in any form, spoken, written or signed. By contrast, patients with damage to Wernicke's area (at the border of the temporal, occipital and parietal lobes) have difficulty understanding language (receptive dysphasia). These patients can still speak language, but form meaningless sentences. In the region of the primary motor cortex that controls the speech generating muscles, lesions result in speech apraxia. Here patients are unable to articulate words, although they can form meaningful sentences in their heads. Lesions in

association cortices lead to selective deficits as well. Parietal association areas integrate auditory, visual and somatosensory information with temporal memory stores. Lesions here can result in agnosias, i.e. the inability to recognize familiar objects, even in the absence of primary motor or sensory deficits. In a similar way, lesions to auditory association areas (in the posterior superior temporal gyrus) can lead to language deficits, if they occur in the dominant hemisphere, or if they occur in the non-dominant hemisphere, the inability to recognize sounds and music.

Electrophysiological Maps. A second revolution in our understanding of cortical function came with the advent of electrical stimulation mapping. Operating on epileptic patients, Wilder Penfield and other neurosurgeons applied electric currents to the brain surface to map the locations of the motor and sensory areas, to avoid harming these regions during surgery. Electrical stimulation of sensory cortices led to paresthesias (numbness or tingling) in distinct parts of the opposite side of the body. Probing of motor areas led to twitching or involuntary movement on the contralateral side. Penfield compiled these studies to construct a sensory map, sometimes called the sensory ‘homunculus’, on the post-central gyrus of the parietal cortex, showing the body regions that map to it. This neural map of the body surface reveals an orderly layout of neurons that innervate different parts of the body. This serial pattern of sensory projections has been invoked to explain some epilepsy symptoms, where numbness can move across the body surface as the seizure propagates across the cortex. An analogous map body map, or ‘homunculus’, exists for the motor cortex. Bizarre distortions are seen in which vastly greater amounts of tissue are devoted to body regions with substantial motor innervation (e.g., the fingers and the mouth). Subsequent microelectrode recordings by Kaas and Merzenich revealed four independent, fairly complete body maps in areas 3a, 3b, 1, and 2 of primary somatosensory cortex (S1; Kaas et al., 1979). Further studies of these regions showed that they are capable of dramatic functional changes even in adulthood. If a body part such as a limb is lost, the cortical areas that previously controlled it can reorganize, after extensive training, and can adapt to represent other bodily regions. This remodeling effect is known as *cortical plasticity*, and is thought to underlie the re-learning of cortical functions after stroke or brain trauma.

Retinotopic and Tonotopic Maps

At least in primary somatosensory and motor systems, dedicated regions were beginning to be found that performed surprisingly specific functions. These findings ignited the search for additional cortical maps. In primary visual cortex (Brodmann area 17, also known as V1), visual signals from each eye were found to be segregated into functional units, or *ocular dominance columns* (Powell and Mountcastle, 1959; Hubel and Wiesel, 1962). Regions receiving signals from each eye were arranged in a striped, alternating pattern (like a pattern of zebra stripes on the cortex). This feature was first observed by electrophysiological recording from single neurons in monkeys. As the recording electrode was moved tangentially within sensory layer IVc, there was an abrupt shift as to which eye drove the neuron. This alternated every 50 microns or so. A further finding was that neurons in V1 are also laid out retinotopically: they are organized in a spatial order that corresponds to the layout of their receptive fields in visual space (and also reflects the layout of ganglion cells in the retina). The receptive fields of these neurons, mapped with an electrode that moves tangentially through layer IVc, correspond systematically to locations moving from the fovea to the periphery (with jumps at the ocular dominance borders). This finding agreed with observations in patients with focal damage to the primary visual cortex, due to stroke or tumor growth. Such lesions typically lead to a primary sensory deficit (cortical blindness), with loss of a portion of the visual field. The size of lesions also correlates with the amount of the visual field that is lost.

The notion that cortical sensory areas contain topological maps reflecting the layout of corresponding sensory organs greatly empowered the analysis of cortical function. First, the topographic maps began to demonstrate how the cortex is organized in a modular way. Similar ‘tonotopic’ maps were found in auditory cortex, in which neurons are tuned to sounds with a specific range of frequencies. Here, the maps reflect the layout of a sheet of receptors in the cochlea, which respond to different frequencies of sound. A further advantage of finding cortical maps was that they made it easier to study the effects of varying the characteristics of sensory stimuli, revealing how cortical cells actually process information. Vertically integrated columns of cells (ocular dominance columns) were identified in visual cortex. These sets of cells can process the orientation, and

color, of features at a specific location in the visual field. Within each ocular dominance column, neurons with different orientation tunings can be found, which respond maximally to patterns of bars oriented at a particular angle. Optical imaging of the cortex can even identify this orientation response *in vivo*.

Functional Brain Imaging. Since the 1980s, it has also been possible to image cortical blood flow and metabolism in living humans. These techniques were first used to localize vision-related activity in the brain, building on prior physiological findings. The major functional brain imaging techniques are particular positron emission tomography (PET) and functional magnetic resonance imaging (fMRI). PET scans map brain function using positron-emitting radioisotopes. These are injected into the blood stream, and their 3D distribution in the brain is computed using a radiation counter in the scanner, and a mathematical back-projection technique. With different tracer compounds, PET scans can map rates of regional blood flow, as well as oxygen and glucose utilisation. Activity patterns can then be mapped that correlate to the activity of large neuronal populations in the cortex.

A further advance occurred with the development of functional MRI. This is a variation of normal MRI scanning. It maps blood flow based on the paramagnetic effect of deoxygenated hemoglobin. Unlike the radioisotope techniques, fMRI requires no injected contrast or tracer and does not appear to have any risks with repeat exposure. MRI scanners equipped with rapid acquisition echo-planar imaging hardware now acquire whole-brain 3D images in under 2 seconds, with 2 mm resolution or better. This makes it possible to map patterns of cortical activation, during cognitive tasks, in real-time.

Brain Mapping. Statistical mapping techniques (Friston et al., 1995) were subsequently developed to process these functional images and map task-related fluctuations (in both PET and fMRI). Color-coded maps can be created showing cortical regions that are activated while subjects carry out specific mental tasks, such as willed movements, reading, hearing, or speaking. The worldwide expansion of brain mapping efforts (Toga and Mazziotta, 2000) has produced large databases of maps of cortical function and structure. These provide new insights into how the cortex is organized, and describe anatomical and functional variations due to age, gender, disease, and even genetic factors (Thompson et al., 2001). The success of brain mapping has been promoted by the international adoption of a coordinate-based 3D reference system for brain data. This helps in pooling brain data from multiple studies. Based on the Talairach stereotaxic atlas (Talairach and Tournoux, 1988), images and maps are aligned with a standard brain template. Cortical maps and locations can then be referenced in standard 3D coordinates; mathematical techniques are then applied to detect disease-specific patterns, hemispheric asymmetries, and subtle group differences in cortical function, in whole populations (see **Figure 2**).

Now that we have reviewed how the cortex is organized, structurally and functionally, in the next few sections we review numerous diseases that affect the cortex and severely impair cortical function.

Cortical Degeneration. Cortical diseases fall into two major categories, degenerative and developmental. In degenerative conditions such as Alzheimer's disease, progressive cell loss leads to functional deficits and cognitive decline. In developmental disorders however, failures in cellular migration, cortical maturation or synaptic pruning, can lead to dysplasias or learning disorders. Not all of these disorders affect the cortex in a uniform way. Some affect specific cortical systems, leaving others relatively intact.

Alzheimer's Disease. About 5 percent to 8 percent of all people over the age of 65 have some form of dementia, and this percentage doubles with each five years of age after 65. In Alzheimer's disease (AD), intraneuronal filamentous deposits, or neurofibrillary tangles (NFTs), accumulate within neurons. This cellular pathology disrupts axonal transport and induces widespread metabolic decline. Amyloid protein deposits also build up, throughout the cortex. Abnormally swollen cellular processes surround these amyloid cores, forming neuritic (or 'senile') plaques. Amyloid ('starch-like') plaques are so-called because they are visualized at autopsy with histologic dyes that stain starch-like compounds. They are however made up of protein, which builds up outside cells and in blood vessels. This protein accumulation in the cortex is typical of many degenerative diseases (although the proteins differ in Parkinson's disease, Creutzfeldt-Jakob disease, and the polyglutamine

disorders such as Huntington's disease). In Alzheimer's disease, amyloid plaques result from abnormal cleavage of amyloid precursor protein (APP), producing the insoluble beta-amyloid. The enzymes that regulate these changes have become a key target for new Alzheimer's drugs.

Eventually the abnormal cells and their processes disappear. The resulting neuronal loss is observable as gross atrophy on MRI scans. Mirroring the sequence of neurofibrillary tangle accumulation, a dynamically spreading wave of gray matter loss can be observed, if repeated MRI scans of a patient are compared over time. This tissue loss spreads, as the disease progresses, from temporal and limbic cortices to invade frontal and occipital brain regions (see **Figure 2**; Thompson et al., 2002). Sensorimotor cortices are comparatively spared until late in the disease.

Spreading Pathology. In early stages of AD, cortical cell loss is most pronounced in the cholinergic systems of the basal forebrain. Cholinergic drugs are effective, at least initially, in bolstering cognitive function in patients. NFT accumulation spreads from the limbic cortex (layers II/IV), and the hippocampus/amygdala into temporo-parietal and frontal association cortices (layers III/V). Memory and executive function sharply decline. Neuropathologic studies also reveal that cortical layers III and V selectively lose large pyramidal neurons in association areas, with an 11%-50% synaptic loss in superior temporal and inferior parietal cortices in AD. Metabolic scans in AD, acquired with [¹⁸F]-fluorodeoxyglucose positron emission tomography (FDG-PET), show a similar shifting deficit pattern. Decreased metabolic activity shifts from temporo-parietal cortices into the frontal lobes, over several years. These decreases predict the rate of cognitive decline (usually measured by the Mini-Mental State Exam) and also survival. Cognitive deficits (aphasia, visuospatial disturbances) soon combine with memory loss to produce extensive social and behavioral impairment.

The resilience of some cortical systems (e.g. primary sensory regions) in AD have led some to suggest a mechanism for the spread of the disease. Abnormal hyperphosphorylation of tau-proteins (which leads to NFTs) may originate in limbic regions due to their high levels of baseline plasticity. Vulnerability of neocortical association areas may relate to their degree of functional connectivity with limbic structures, where pathology begins.

Other Dementias. Different patterns of cortical atrophy occur in frontotemporal, semantic, and Lewy body dementias. The frontal cortices, in particular, have an organizational role in behavior: they guide the planning and execution of new actions. Patients with frontotemporal dementia (sometimes known as Pick's disease) often fail to consider the consequences of their actions, and have difficulty making plans for the future or appropriate decisions. By contrast with Alzheimer's patients, their cortical atrophy is typically most severe in frontal and anterior temporal cortices, with sparing of the posterior two-thirds of the superior temporal gyrus. Significant neuronal loss occurs in the first three cortical layers.

Primary cortical degeneration (i.e. cell loss that begins in the cortex) is not the only cause of dementia. While Alzheimer's disease is recognized as the most common cause of dementia in the elderly, for many patients, the cause of dementia is vascular, resulting from multiple small strokes in the brain (multi-infarct or vascular dementia). In other rarer diseases, such as HIV/dementia complex and Creutzfeldt-Jakob disease (CJD), diffuse neuronal loss can also lead to deficits characteristic of dementia. CJD is a human prion disease (i.e., the infectious agent is a protein), associated with extremely rapidly progression dementia, muscle twitching (myoclonus), and a median survival of 4 months. It induces spongiform change, neuronal loss, astrocytosis, amyloid plaque formation, and a fine vacuole-like appearance in the cortical layers, distorting the cortical cytoarchitecture.

In summary, the main causes of dementia include primary cortical degeneration (AD, Pick's disease, and Lewy body dementia), cerebrovascular disease (multi-infarct dementia), and sub-cortical degeneration (e.g., Huntington's disease), although cortical deficit can also result from infections (AIDS), prion diseases, tumors, and brain injury.

Cortical Development. Many severe brain disorders result from failures of cortical development. Early in development, the cortex is no more than an undifferentiated sheet of neural tissue. Complex interactions among signaling

molecules, extracellular matrix proteins, and chemical messengers are required to guide migrating cells to their destinations in the cortex. Any failure in these developmental stages can lead to cortical malformations. These malformations are often associated with neurological disturbances: epilepsy, mental retardation, language and behavioral problems, as well as motor dysfunction.

One remarkable feature of brain development is the temporary construction of a radial scaffolding, made up of glial cells, in the embryonic brain. This scaffolding guides neuronal precursor cells to their destinations in the cortex. In primates, these radial glia are extremely elongated: electron-micrographs show waves of migrating neurons in contact with these glial shafts. Once at the cortex, neurons come into contact with a protein known as *reelin*, which signals to them to detach and extend their axons and dendrites, which begin to make synaptic connections. Migrating growth cones are directed to their synaptic targets by adhesion molecules in the extracellular matrix. They are also guided by glycoproteins on the surfaces of neighboring cells, and by chemotropic factors such as neurotrophins.

Synaptic Elimination. Many cortical neurons initially project axons and dendrites to a much wider set of targets than are eventually found in the adult brain. Shortly after birth, a massive attrition of axons and synapses occurs. The number of synapses peaks around 1 year of age in humans. Activation of neural systems appears to be crucial in determining which connections are retained and which are lost. Synaptic elimination occurs first in primary sensory cortices, but in frontal and parietal regions it persists into the teenage years and beyond. Recent MRI studies have revealed a gentle loss of gray matter in adolescence (around 1% per year; Thompson et al., 2002). This tissue reduction is believed to reflect continued dendritic pruning and synaptic elimination.

The functional specialization of cortex also depends on experience. In visual cortex, the development of ocular dominance columns is dependent on exposure to appropriate stimuli at critical periods during development (Hubel and Wiesel, 1970). Once the cellular architecture of the brain is established, a lengthy process of myelination occurs. Myelin insulates axons and speeds up their conduction by a factor of up to 100 times. Myelination is only partially complete at birth and proceeds, in several growth spurts, until puberty and beyond (Thompson et al., 2000).

Abnormal Development. Disruption of any of these phases can lead to developmental disorders and subsequent mental retardation. Disorders of cortical development are often caused by aberrations in cell proliferation or migration. Abnormal cell proliferation can lead to focal cortical dysplasias or tuberous sclerosis, whose symptoms appear later in childhood in the form of seizures.

In some cases, genetic abnormalities disrupt neuronal migration. Studies of mutant mice are continuing to isolate genes whose mutations are known to derail cortical development. The *reeler* mutation, in mice, causes an abnormal laminar pattern to develop in the cerebral and cerebellar cortices. Normally, neuronal migration obeys an “inside-out” pattern. Later-generated neurons navigate past one born earlier, as they migrate to their final destination. In the *reeler* mouse, this normal migratory path is reversed. Signaling proteins such as *reelin*, whose structure is similar to extracellular matrix proteins, have been found to be critical in guiding neurons as they migrate through the central and peripheral nervous systems.

Other migration deficits lead to cortical malformations such as lissencephaly (smooth cortex), pachygyria (broad, flattened gyri), or heterotopias (normal neurons in abnormal locations). Some of these migrational disorders may result from damage to the radial glial fibers, such as their premature transformation into astrocytes, as well as other genetic, vascular, environmental causes. Patients with heterotopias have varying symptoms, including developmental delay, motor and sensory impairments, and in severe cases, seizures. Many people with intractable epilepsy also suffer from cortical dysgenesis. Perhaps surprisingly, epileptic symptoms may not appear until later in childhood or even adulthood. In these cases, aberrant synaptic connections between dysplastic and adjacent normal tissue are thought to contribute to hyperexcitable neural networks that increase seizure susceptibility.

Gyral Patterning. Lissencephaly is a malformation of the brain in which the cortex is smooth rather than convoluted. Infections during pregnancy can occasionally cause ischemia (diminished blood flow) or hypoxia (diminished oxygen availability) in the developing brain, and this may lead to cell death (necrosis) in the cortical layers. The cortex then fails to fold properly. Most of the cortex in lissencephalic children is only 4-layered, so laminar necrosis is thought to occur in specific cell layers, around 12-16 weeks of embryonic life. The prognosis for children with lissencephaly is poor: many show no significant cognitive development beyond a 3- to 5-month-old level. The opposite effect is seen in polymicrogyria, where an excess of small brain convolutions appear. Here ischemic lesions occur after the 20th fetal week, and induce mid-cortical laminar necrosis, mainly in cortical layer V. Differential growth in the surrounding cortical layers causes the cortex to buckle, producing too many convolutions. Such ischemic damage is thought to be due to perfusion failures, possibly provoked by cytomegalovirus (CMV), toxoplasmosis, or maternal trauma. CMV infection, which affects around 1% of newborns in the United States, is one of the ‘TORCH’ infections, an acronym that describes common perinatal infections: toxoplasmosis, other infections (e.g. syphilis), rubella, CMV, and herpes simplex virus. Early second trimester infections often lead to complete lissencephaly, while later second trimester infections cause polymicrogyria. With infections in the third trimester, gyral patterns may be normal or show focal areas of polymicrogyria. As with lissencephaly, the symptoms of polymicrogyria include seizures, deafness, motor disability and mental retardation.

Schizophrenia. Subtle disruptions of migration and neuronal connectivity, as well as imbalances in cortical neurotransmitters, have also been proposed for more common and complex disorders such as dyslexia and psychosis. Schizophrenia, for example, is a chronic, debilitating psychiatric disorder that affects 0.2-2% of the population. It often strikes without warning in the late teens or early twenties. Symptoms include auditory and visual hallucinations, psychotic outbreaks, bizarre or disordered thinking, depression and social withdrawal. Although its causes are unknown, it is increasingly considered a neurodevelopmental disorder affecting the cortical dopamine and serotonin systems. Symptoms are somewhat controlled by neuroleptic drugs, which block dopamine and serotonin receptors in the limbic and prefrontal cortices. Neurotransmitter metabolism is impaired in schizophrenia, and many studies also point to developmental risk factors for the disease. These include fetal malnutrition, extreme prematurity, hypoxia, and ischemia, as well as embryonic exposure to the flu virus. As with many cortical disorders, a key puzzle is why there is a long gap between an early cerebral insult and the emergence of symptoms twenty or more years later. To explain this, some favor a two-hit (or ‘diathesis-stress’) model, in which an early developmental or genetic anomaly must be compounded by psychological trauma, viral infection, or some currently unknown trigger later in life for the disease to be expressed. Renewed interest in this hypothesis comes from a recent wave of brain imaging studies identifying features of cortical maturation that occur well into adolescence and beyond. These brain imaging studies visualize a sequence of growth spurts in myelination through childhood, and dramatic waves of gray matter loss that are believed to reflect synapse production and pruning in the teen years. Schizophrenia typically strikes at a time when these developmental changes are still underway. In particular, a natural teenage process of synapse elimination, or pruning, may be accelerated or otherwise derailed in schizophrenia.

Conclusion

In summary, we have reviewed some key developments in brain research that have advanced our understanding of the cerebral cortex. We described how the cortex develops, how it is organized structurally and functionally, and how several diseases affect it. Recent discoveries are now making it clearer how these diseases emerge in development and old age. The resulting knowledge is likely to accelerate the development of strategies to combat them.

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(Table and Figures are on the following pages...)

Table 1. *Some Neurological Conditions Resulting from Diseases and Lesions of the Cerebral Cortex.*

Disorder	Pathology and Region Affected	Symptoms
I. Degenerative		
Alzheimer's Disease	Amyloid protein deposits and neurofibrillary tangles (NFTs) in entorhinal, temporo-parietal, and ultimately frontal cortices; progressive neuronal loss	Memory loss, mood disturbances, emotional lability, impulsivity; progressive cognitive decline
Frontotemporal Dementia	Atrophy of frontal and anterior temporal lobes; pathology may include swollen chromatolytic neurons (SCN), Pick bodies	Abulia, disinhibition and emotional lability; impaired memory and language; possible spasticity, non-fluent aphasia
II. Developmental		
Cortical Malformations	Abnormal proliferation or migration of neurons during embryonic development; abnormal cortical folding (lissencephaly; polymicrogyria)	Mental retardation, motor and sensory impairment; developmental delay; seizures
III. Neuropsychiatric		
Schizophrenia	Abnormal dopamine and serotonin transmission; cortical gray matter loss, progressive in childhood-onset cases	Psychosis, hallucinations, bizarre thoughts delusions, sensory disturbances; depression, asociality
IV. Focal Lesions (e.g. stroke)		
Perisylvian aphasias		
Broca's	Lesions in Broca's speech area (inferior frontal gyrus, left hemisphere) and adjacent cortex.	Impaired speech production; relatively spared language comprehension
Wernicke's	Lesions in Wernicke's language comprehension area (left posterior temporal lobe)	Flowing, but nonsensical speech; impaired language comprehension

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Figures and Legends

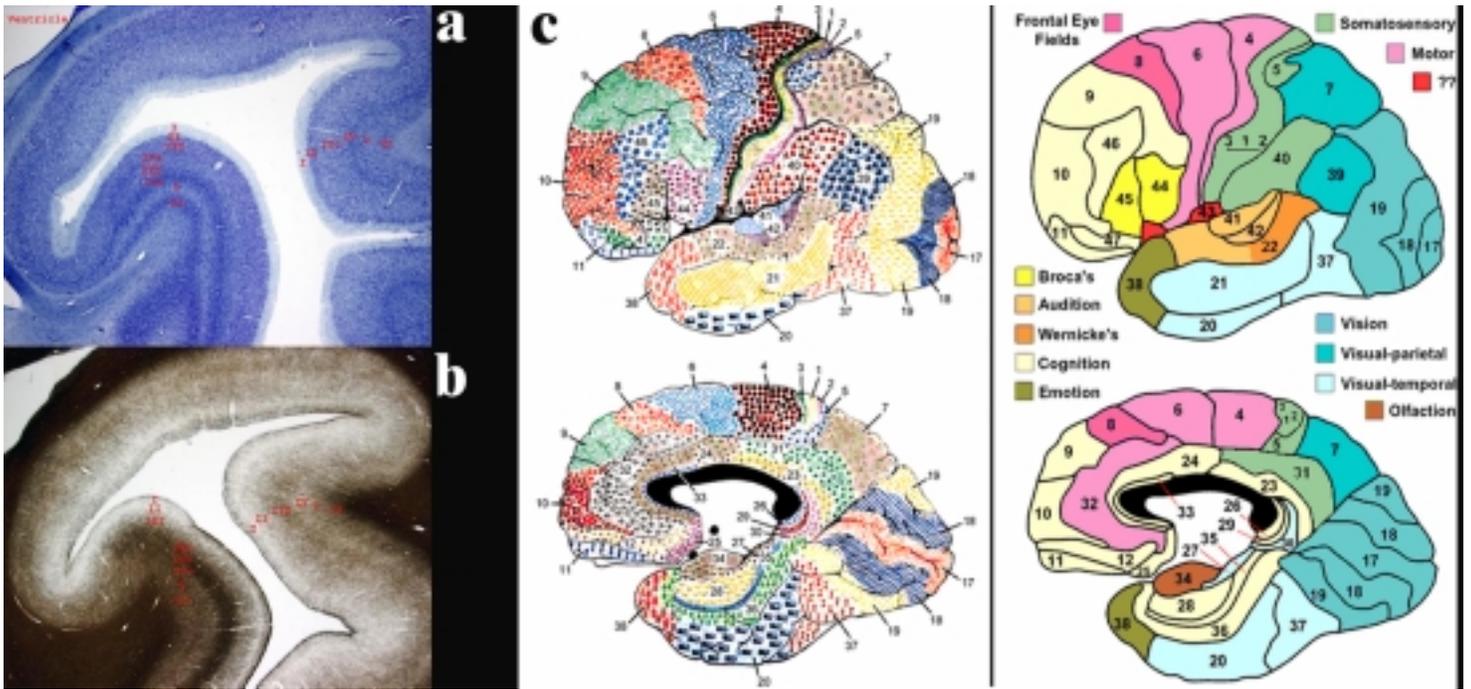


Figure 1. *Cortical Layers and Brodmann Areas.* Histologic staining reveals the different cellular layers in the human cerebral cortex: (a) Nissl stain; (b) myelin stain. (c): The German anatomist Korbinian Brodmann divided the cortex into 52 regions, based on their cellular content. Each region contains distinct patterns of cells, and has a different function. The key (right panels) describes some of these functions. [Images in (a) and (b) courtesy of Dr. Jacopo Annese, Laboratory of Neuro Imaging, University of California, Los Angeles; Images in (c) reproduced, with permission, courtesy of Prof. Mark Dubin, University of Colorado, Boulder].

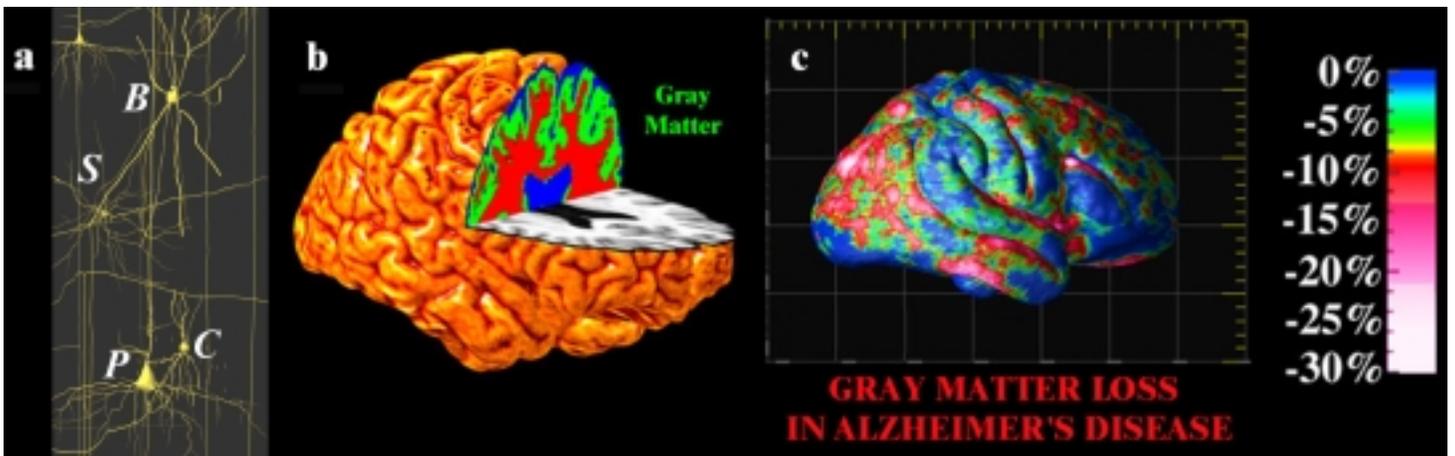


Figure 2. *Cortical Cells and Cortical Deficits in Alzheimer's Disease.* (a) shows four major classes of brain cell found in the cerebral cortex: pyramidal cells (P), spiny stellate cells (S), basket cells (B), and chandelier cells (C). (b). In Alzheimer's

disease, patients lose cortical gray matter (*labeled in green, panel (b)*). A color-coded map (c) shows the average pattern of gray matter loss in 26 Alzheimer's patients. Red colors show regions with greatest deficits (10-30% tissue loss) relative to healthy elderly normal subjects. These disease-specific differences are initially greatest in temporal and parietal association areas, and spread to engulf the rest of the cortex. [*Image (a) courtesy of John Bacheiler, Laboratory of Neuro Imaging, University of California, Los Angeles*].

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