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Unfolding the mysteries of the brain

Researchers are learning to map the wrinkled landscape of the cerebral cortex for clues to how the mind develops

by EMILY ANTHES • August 3, 2009

The surface of the brain is a complex landscape, featuring endless peaks and valleys. This intricately folded outer layer, known as the cerebral cortex, is one of the brain's most noticeable features. But it's also one of the least well understood.

“There's this large expanse of cortex, much of which is like South America to a 17th century cartographer,” said David Van Essen, a neurobiologist at Washington University in St. Louis. “It's this big mass of land, and we know what the outlines are, but no one's been able to chart the intricacies.”

That's beginning to change. Technological and computational advances have enabled researchers to image the brain's wrinkled exterior in stunning detail, mapping the size and shape of each fold. Scientists pursuing this new discipline of “cortical cartography” expect it to yield insights into how the brain develops and what happens when things go awry. Researchers have already discovered that the cerebral cortex - which controls higher-level functions, including thought, emotion, and perception - is folded abnormally in disorders ranging from autism to depression. Such insights could lead to better and earlier diagnoses and perhaps even new clues to treatment.

When the human brain develops in the womb, the outer surface is initially almost entirely smooth. But during the last few months of fetal development, the cortex begins to fold and wrinkle; by the time a full-term infant is delivered, most of the folding has been completed, though subtle refinements continue through early childhood. The folds create more surface area, increasing the size of the cerebral cortex that can fit in our skulls, and, it's believed, partly accounting for the greater cognitive powers of humans compared with species with smoother brains.

“There are some basic principles of folding, but the topology varies quite a bit” from person to person, said Ellen Grant, a radiologist at Massachusetts General Hospital who specializes in imaging young brains. “There's tuning that's due to someone's genes and environment.”

That means that everyone's folding pattern is unique.

“The difference between your cortex and mine are even greater than the differences between our fingerprints,” Van Essen said. And these differences can reveal how our brains work. “The cortical folds are meaningful because they tell us, albeit indirectly, about the wiring of the brain.”

Van Essen has created a cortical atlas, which compiles brain-imaging data to reveal variations in the topography of the cortex. Because even normal brains vary in the precise folding patterns, Van Essen's atlas combines data from many individuals to create representations of what folding looks like in an average brain at various stages of development. And as the atlas evolves, it's beginning to include images of what can happen when the surface of the cortex doesn't develop as expected.

For example, because so much of the folding takes place during the latter weeks of fetal development, premature infants arrive with much of their cortical development yet to be completed. And the folding patterns of preemies relegated to the neonatal intensive care unit don't match those of their counterparts who spend their full nine months in the womb. New research from Van Essen's lab shows that even when preemies reach their originally forecasted due dates, their brains are not as large or as folded as those of full-term newborns.

“That means there's something different in how those brains are organized and in the connections that have formed,” Grant said. Perhaps some extra environmental influence in the hospital is disrupting folding or preemies are missing out on some vital influence that their counterparts get in the uterus, though researchers haven't yet narrowed down what these influences may be.

Scientists have also found evidence of abnormal folding in a variety of mental and neurodevelopmental conditions, including depression, epilepsy, and the rare Williams Syndrome. These irregularities take a variety of forms - some regions of the brain may be overfolded, others underfolded, some folds may be too deep, others too shallow, and so on.

Some intriguing work has been done examining schizophrenia. In a 2004 study, researchers discovered that schizophrenics have different folding patterns in one particular region: Broca's area, which is involved in language processing and production, mental tasks that are disrupted in schizophrenia.

“It was one of those rare findings that made perfect sense,” said Bruce Fischl, a neuroscientist at Massachusetts General Hospital and coauthor of the study. Additional studies have found further irregularities in the folding of schizophrenics' frontal lobes, the seat of high-level cognitive functions.

Other research has shown that autistic children seem to have overly folded brains. This extra folding is significant enough that it actually increases the surface area of the cortex, said Antonio Hardan, a child psychiatrist at Lucile Packard Children's Hospital at Stanford in Palo Alto, Calif., who conducted the research.

The finding is consistent with earlier discoveries that children with autism have bigger brains than their peers.

Researchers are still trying to work out just what all these findings mean. They speculate that irregularities in folding indicate other problems - perhaps abnormal connections between various brain areas - or result from other destructive processes going on in the brain.

“I think right now it's just at the point of being descriptive,’" said Martha Shenton, director of the Psychiatry Neuroimaging Laboratory at Brigham and Women's Hospital. “This is an indicator that something happened during neurodevelopment.”

Perhaps some of the genetic abnormalities or environmental factors that contribute to autism, schizophrenia, and other disorders can also disrupt folding.

But even if the folding problems aren't the cause of disorders, they're still clinically significant. The hope is that they'll allow noninvasive imaging to be used to screen high-risk patients - teens, for example, with a family history of schizophrenia - to predict who will develop full-blown disorders and the type, severity, and course of the disease.

What's more, since there are still refinements in the cortical surface through early childhood, if you catch signs of altered folding in infancy, “it's possible that you can modify it,” Grant said. “If you can detect abnormalities and deficiencies early, that has all sorts of implications for interventions.”