The convolutions of human cerebral cortex are remarkable for their sheer complexity and their variability across individuals and even between hemispheres of the same individual. A number of recent studies demonstrate abnormalities in cortical folding in different diseases and disorders. This lecture will demonstrate the methods used to analyze and characterize cortical folding patterns in healthy adults and in disease conditions. It will also frame the issues in a broader developmental and mechanistic context.

Mechanistic basis of cortical folding. Cortical convolutions emerge mainly during the third trimester, around the time that long-distance cortico-cortical connections are established. This observation, coupled with numerous complementary lines of evidence, suggest that mechanical tension along long-distance axons is a primary driving force that gives rise to cortical folds (Van Essen, 1997). This attractive hypothesis can explain the consistency as well as the variability of cortical convolutions. Additionally, it predicts that disease-related abnormalities in cortico-cortical long-distance circuitry may actually give rise to folding abnormalities. Alternative hypotheses that emphasize differential growth within the cortex have been proposed (Richman et al., 1975; Xu et al., 2010; Lefèvre and Mangin, 2010); definitive evidence for either mechanism is lacking.

Surface-based analyses of cortical folding. Surface-based methods provide a powerful way to visualize and analyze cortical folding patterns in individuals and populations. A critical initial stage involves cortical segmentation and surface generation from MR scans. In adults, automated segmentation can be carried using freely available software platforms (e.g., FreeSurfer), whereas prenatal and early postnatal ages entail segmentation using customized software and extensive manual editing. Once reconstructed, cortical shape can be characterized quantitatively using objective measures such as sulcal depth and cortical folding indices (Van Essen, 2005). Comparisons across individuals can be most accurately carried out using surface-based registration to a population-average atlas surface. This lecture will focus on two widely used surface-based atlases (PALS-B12 and fsaverage, plus recent refinements). This approach has revealed striking symmetries in the average pattern of folding in the two hemispheres (despite the dramatic individual differences), and also a novel perspective on shape-based hemispheric asymmetries.

Cortical folding abnormalities have been revealed in a number of disease conditions. The most striking example is in Williams Syndrome, where a complex but bilaterally symmetrical pattern of folding abnormalities is distributed across all cortical lobes (Van Essen et al., 2006; see also Kippenhan et al., 2005). Some of the folding abnormalities occur in regions that are also associated with functional MRI abnormalities and are implicated in functions characteristic of the Williams Syndrome behavioral syndrome.

Cortical folding abnormalities have also been reported in autism (Nordahl et al., 2007), with a pattern that differs for different autism subtypes, and in schizophrenia (Csernansky et al., 2008) and ADHD. In these other disorders, the number of abnormalities is fewer than in Williams Syndrome.
Syndrome and their magnitude is modest. One explanation is that the underlying connectional
disorder is more subtle. Alternatively, greater diversity in the phenotype of these complex
disorders and inadequate stratification of subjects may adversely impact the sensitivity to
characterizing folding abnormalities.

Surface-based morphometry also reveals important changes that occur during development and
aging. One illustration of this involves an analysis of healthy term infants, which reveals that
postnatal cortical expansion is notably non-uniform, with regions involved in higher cognitive
functions expanding about two-fold more than early sensory and motor regions (Hill et al.,
2010a,b). Another example reveals important, spatially non-uniform differences term-born infants
vs premature infants scanned at term equivalent.

The hypothesis that cortical folding abnormalities reflect abnormal connectivity can in principle be
tested experimentally, but incisive tests will require methods for connectivity analysis that exceed
existing technology. Substantial improvements in the methods for acquiring and analyzing
connectivity data are likely to emerge through the Human Connectome Project
(http://www.humanconnectome.org/) and related endeavors. Hence, there are encouraging
prospects for major advances in characterizing human brain connectivity, its normal variability
and the abnormalities associated with disease and disorders.

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