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Neuroimaging techniques offer new perspectives on callosal transfer and interhemispheric communication

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ABSTRACT

The brain relies on interhemispheric communication for coherent integration of cognition and behavior. Surgical disconnection of the two cerebral hemispheres has granted numerous insights into the functional organization of the corpus callosum (CC) and its relationship to hemispheric specialization. Today, technologies exist that allow us to examine the healthy, intact brain to explore the ways in which callosal organization relates to normal cognitive functioning and cerebral lateralization. The CC is organized in a topographical manner along its antero-posterior axis. Evidence from neuroimaging studies is revealing with greater specificity the function and the cortical projection targets of the topographically organized callosal subregions. The size, myelination and density of fibers in callosal subregions are related to function of the brain regions they connect: smaller fibers are slow-conducting and connect higher-order association areas; larger fibers are fast-conducting and connect visual, motor and secondary somotosensory areas. A decrease in fiber size and transcallosal connectivity might be related to a reduced need for interhemispheric communication due, in part, to increased intrahemispheric connectivity and specialization. Additionally, it has been suggested that lateralization of function seen in the human brain lies along an evolutionary continuum. Hemispheric specialization reduces duplication of function between the hemispheres. The microstructure and connectivity patterns of the CC provide a window for understanding the evolution of hemispheric asymmetries and lateralization of function. Here, we review the ways in which converging methodologies are advancing our understanding of interhemispheric communication in the normal human brain.

1. Introduction

In the 1950s, Roger Sperry and Ronald Myers (Myers, 1956) discovered that cutting the corpus callosum (CC) in animals interrupted the transfer of information between the two cerebral hemispheres. Shortly thereafter, split-brain studies were implemented in humans (Gazzaniga et al., 1962), ultimately revealing most of our understanding of hemispheric specialization and lateralization (for a historical account see Glickstein and Berlucchi, 2008, this issue). In the fully disconnected human brain, callosal function has been inferred. By using eye tracking equipment to conduct split visual field

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studies, the specialized functions of each hemisphere were illuminated through behavioral research. By studying partially callosotomized patients, functional subregions of the callosum became apparent. Behavioral studies of split-brain patients indicated that partial resection of the CC affected some behaviors more than others (Fabri et al., 2001; Funnell et al., 2000; Gazzaniga, 2000). There have been a number of attempts to segment the CC into functional or geometric subregions (Witelson, 1985, 1989; Denenberg et al., 1991; Clarke and Zaidel, 1994). The problem with these arrangements is the assumption that function and topography are related to gross callosal shape. This may not be the case. A large amount of inter-individual morphological variation is present in the normal callosum, though much of it is entirely unrelated to function.

Today we are in a unique position to examine the CC and interhemispheric connections in the human brain noninvasively through combinations of functional and anatomical imaging techniques. Using new imaging technologies, the CC has been divided into its cortical projection targets, which appear relatively topographical in arrangement (Hofer and Frahm, 2006; Huang et al., 2005; Zarei et al., 2006; Park et al., 2006). However, there may be exceptions to the topographical arrangement as well as tremendous overlap of fibers in a given callosal subregion (Park et al., 2006). Additionally, there appears to be both homotopical and heterotopical arrangement of interhemispheric connections (Clarke, 1999). A cortical area of one hemisphere may show homotopical connectivity, or it may connect with several cortical areas of the opposite hemisphere. Understanding the complexity of the arrangement of callosal fibers and interhemispheric connectivity gives anatomical specificity to subregions of the callosum and eliminates the arbitrary nature of the previous morphology-based parcellation schemes. New functional parcellation methods may also benefit from earlier work that has identified the structure as relatively heterogeneous in its microstructural properties. It has been shown, using light-microscopy in post-mortem brains (Aboitiz et al., 1992a, 1992b), that regional differences in myelination, fiber size and density correspond to callosal topography.

Connectivity and microstructure provide for a better understanding of callosal function than does sectioning the structure based on gross morphology. Imaging methods performed *in vivo*, such as diffusion-weighted imaging, are paving the way to a new understanding of the topographical connectivity patterns of the callosum. The regional microstructural differences across the CC may relate to the evolution of interhemispheric communication and functional lateralization. Current magnetic resonance imaging (MRI) methods will yield further insights into the evolution and function of the human CC and its role in interhemispheric integration.

2. Imaging white matter pathways

Diffusion tensor imaging (DTI) is an MRI technique used to measure the motion of water molecules in and around nerve fibers *in vivo*. Diffusion is a three-dimensional process, and in gases and liquids, molecules move freely and randomly. However, when constrained, mobility is not the same in all directions. This is the case in the brain; water molecules in brain tissue do not diffuse equally in all directions. When molecular motion is limited by axonal fiber bundles, water diffusion is highly anisotropic, meaning that diffusion occurs along a particular axis. Water molecules travel roughly six times faster along the length of a fiber process than when perpendicular to it, thus directionality can be inferred by measuring the attenuation in MR signal on diffusion-weighted spin-echo sequences (Le Bihan, 2003). Several mathematical models for characterizing diffusion are commonly used in the research literature. Mean diffusivity (MD) quantifies the amount of diffusion within a brain voxel but it lacks directional information. To measure unequal, or anisotropic diffusion, a model of the diffusion tensor has been proposed, which gives a scalar quantity known as fractional anisotropy (FA) (Basser et al., 1994). The values of FA range from 0 to 1. Values approaching 1 indicate the water molecules in a voxel are diffusing nearly entirely along one particular axis. Values approaching 0 indicate nearly equal diffusion in all directions. When combined with directional information, the diffusion tensor at each voxel can be thought of as either a sphere or an ellipsoid, with the former representing equal diffusion and the latter representing the preference for diffusion in one direction. By using computer algorithms to link together contiguous voxels in white matter, it is possible to reconstruct major fiber pathways in the brain, such as those coursing through the CC. This technique is known as DTI tractography, or fiber tracking. Both deterministic and probabilistic algorithms have been proposed (Behrens et al., 2003; Dougherty et al., 2005) (see also Jones, 2008, this issue). Combined with an understanding of the relationship between topography and regional microstructural differences, DTI tractography provides a window through which to view the evolution of cerebral lateralization (see also Catani and Mesulam, 2008, this issue) and interhemispheric integration in the normal human brain.

3. Callosal and commissural projection topographies

We now have the ability to explore, using DTI, the callosal topographies of the human brain (see also Catani and Thiebaut de Schotten, 2008, this issue). Despite the size and importance of the CC, little is known about the functional roles of specific callosal subregions. Much of our knowledge about the functional specificity of the CC has come from testing patients who have undergone a callosotomy. Studies of patients who have undergone partial or staged resection of the CC have yielded insights into the function of callosal subregions (Fabri et al., 2001; Gazzaniga and Freedman, 1973; Risse et al., 1989). During staged resections, the function of callosal subregions can be determined with neuropsychological testing. Disconnected cortical regions fail to transfer information thus allowing for inference as to which areas of the CC transfer visual, somatosensory, tactile, or motor information. Patients having disconnection of the anterior and body of the CC but sparing of the splenium showed interhemispheric transfer deficits only in dichotic listening and some somatosensory tasks (Risse et al., 1989). Patients with disconnection