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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 non-invasively 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 of the entire callosum but with sparing of the posterior third of the splenium show deficits in all modalities of interhemispheric transfer except for the transfer of visual information. Finally, disconnection of the splenium abolishes interhemispheric transfer of visual information (Gazzaniga and Freedman, 1973). The body of knowledge derived from the fully and partially disconnected patient is enormous (see Gazzaniga, 2000 for a review).

Today, we can use DTI tractography to subdivide the CC based on its cortical projection sites. This method is increasing our understanding of human brain function and interhemispheric integration. Several recent studies have used tractography to demonstrate the antero-posterior topographical arrangement of the CC in the human brain (Hofer and Frahm 2006; Huang et al., 2005; Park et al., 2006; Zarei et al., 2006). This topographical arrangement has previously been seen in radioactively labeled amino acid tract-tracing studies conducted in the non-human primate (Pandya et al., 1971). One recent study has revealed the cortical projection topographies of the human CC in exquisite detail (Park et al., 2006). Using grey matter and sulcal/gyral boundaries, the study demonstrates cortical projection targets of the CC and also gives an indication of the individual variability of connectivity. Research from our own lab gives further indication of the individual variability present in callosal connectivity when probabilistic tractography (Behrens et al., 2003) is conducted between the callosum and inferior parietal cortical areas (see Fig. 1). A finer grained study of topographical connectivity was recently reported (Dougherty et al., 2005). By combining visual field mapping fMRI data with fiber tracking between visual cortical areas and the callosum, it was found that extrastriate visual areas converge on the splenium. Additionally, these fibers were topographically organized by function, with representation from the fovea to the periphery proceeding in an anterior to posterior direction.

Tractography studies may help to shed new light on previously established behavioral experiments shown to reflect interhemispheric transfer time (IHTT). The classic Poffenberger paradigm (Poffenberger, 1912) is one such example. The paradigm tests the transfer of visuomotor information across the cerebral hemispheres by measuring reaction time differences to stimuli flashed directly one cerebral hemisphere or the other. When a participant reacts to stimuli presented to the same visual field as the responding hand, then a direct route between visual and motor cortical areas within the same hemisphere mediates the response. When responding with the hand opposite of the cerebral hemisphere stimulated, visual or motor signals must take an indirect route and cross the CC to initiate the response. By subtracting reaction times (RTs) in the crossed condition from RT in the uncrossed condition, the crossed–uncrossed difference (CUD) can be determined. The CUD is an indicator of IHTT and has been found to be on the order of 3–4 msec (Marzi et al., 1991). Interestingly, CUD is not a static figure in individuals; it may vary based on other functional or structural properties of the brain. For instance, attention seems to affect the CUD (Weber et al., 2005). Closer inspection of the underlying direct and indirect routes indicates that they may feature distinct patterns of connectivity. Indeed, the uncrossed route seems to involve anterior motor structures, namely premotor cortex, and the crossed route seems to involve transfer of perceptual information at the level of parietal cortex. The specific callosal channel involved may eventually be revealed by tractography, but for now, these results suggest that the CUD is not simply attributable to an extra step involving the callosum (Marzi et al., 1999).

Recent tractography work (Putnam et al., under revision) has revealed highly detailed properties of the human splenium, an area which when sectioned, abolishes the transfer of visual information (Fig. 2). Reaction time and electrophysiological studies (Barnett and Corballis, 2005; Bisiacchi et al., 1994; Marzi et al., 1991) demonstrate faster transfer of information from the right to the left hemisphere, and this may be mediated by fibers passing through the splenium. The differences in transfer time have been explained either in terms of an asymmetry of callosal fibers or as a result of hemispheric specialization. When performing probabilistic tractography (Behrens et al., 2003) from the callosum to left hemispheric cortical areas and separately from the callosum to right hemispheric cortical areas, results (Putnam et al., under revision) show a greater incidence of fibers in extrastriate visual areas connecting the splenium with the right hemisphere than with the left. This characteristic may be the anatomical underpinning of a speeded right to left transfer of visual information. More investigation is needed here, as observing more splenial fibers when tracking to the right hemisphere than when tracking to the left could be interpreted as there being more heterotopic connections passing through the splenium

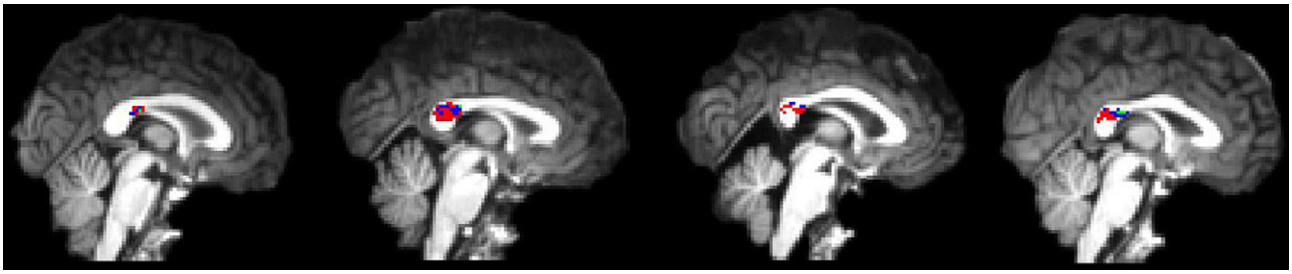

Fig. 1 – Probabilistic tractography from the callosum to three inferior parietal regions. The entire CC was seeded and connected to each region independently (green = supramarginal gyrus, anterior; blue = supramarginal gyrus, posterior; red = angular gyrus). The connectivity reveals substantial individual variability in the area and location within the CC upon which cortical areas converge.

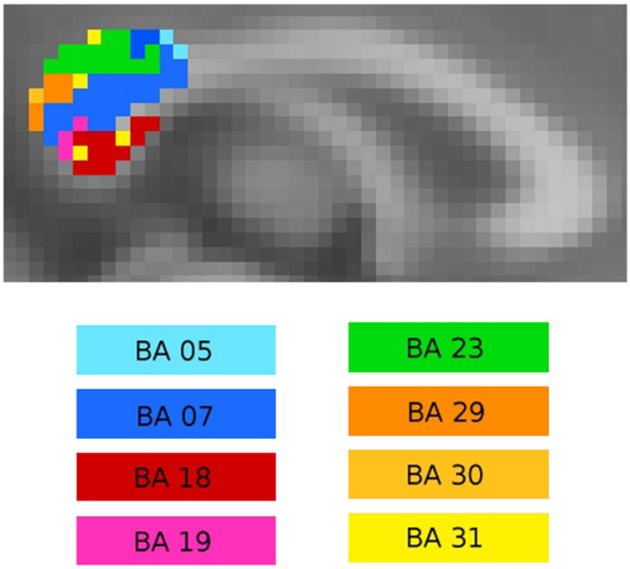

Fig. 2 – Topographical organization of splenial projections in 21 right handed subjects. The CC section shown represents the splenium with the posterior-most section starting on the left side of the image. Each voxel in the splenium shows the cortical region (represented by Brodmann's Areas, BA) with which it shows the highest probability of connection. Among these areas, extrastriate visual cortices BA 18 and BA 19 showed a greater probability of connection across subjects when tracking from the splenium to the right hemisphere than from the splenium to the left hemisphere.

either to or from the left hemisphere (Dougherty et al., 2005). These results represent only the beginning of what will be learned from an increasingly detailed knowledge of topography of the human CC.

4. Microstructure and callosal channels

Beyond improving our understanding of the topographical arrangement of the CC, DTI is allowing researchers to investigate the functional role of callosal microstructure (Boorman et al., 2007; Dougherty et al., 2005; Johansen-Berg et al., 2007). In the past, light-microscopy investigations of the post-mortem human CC revealed regional differences in fiber densities and axon diameters (Aboitiz et al., 1992a, 1992b). In addition to recognizing that over 200,000,000 axons pass through the CC, it was discovered that the axon diameter map of the CC had a topographical pattern that roughly matched the presumed functional topology. The fiber types seem to be arranged in an orderly manner, with smaller diameter axons connecting higher-order processing areas and larger diameter axons connecting visual and somatosensory cortices. Small, slow-conducting fibers (smaller than 2 μm in diameter) were most populous in the genu of the CC and relatively reduced in the posterior body and isthmus. Large, fast-conducting fibers (larger than 3 μm in diameter) were found to be most populous in the mid and posterior body of the CC. Overall, small fibers seem to connect prefrontal and higher-order processing areas of the temporal and parietal lobes (Fig. 3). A reduced conduction velocity is evident in smaller fibers relative to larger diameter and more heavily myelinated fibers. Larger fibers connecting somatosensory, auditory and visual areas need fast conduction velocities because they are believed to be involved in mid-line fusion (Aboitiz et al., 1992a, 1992b).

As the understanding of the relationship between tractography (e.g., probability of a connection, volume of a tract, FA along a tract) and the underlying biological factors improves, we are beginning to identify some of the functional effects of microstructural differences in the CC. Through neuroimaging and electrophysiological techniques, researchers are beginning isolate specific callosal channels and relate them to cognitive and behavioral measures. Recent reports are showing a relationship between individual differences in brain microstructure (FA) and behavior or physiological measurements from transcranial magnetic stimulation (Boorman et al., 2007; Johansen-Berg et al., 2007). At the current state of the art, it is possible to locate the function of a callosal channel down to an area smaller than 2 mm^2 on a mid-sagittal slice of the CC.

Recent DTI studies point to functional relevance of callosal microstructure. Several lines of research suggest that normal aging and certain disease states may affect IHTT and that this is mediated by the microscopic properties of the CC (Pfefferbaum et al., 2005; Schulte et al., 2005; Westerhausen et al., 2006). The microstructural properties of the white matter in the CC seem to be relevant to normal function. Tissue microstructure may also reveal disorders of white matter that are not evident on standard T1-weighted MRI scans. One study (Schulte et al., 2005) reported differences in callosal FA and MD between alcoholics and controls on tests of parallel processing and transfer of visuomotor information. Another study (Westerhausen et al., 2006) found significant negative correlations between MD and IHTT estimates obtained from electrophysiological measures. The results showed that electrophysiological measures obtained from occipital electrode positions were associated with

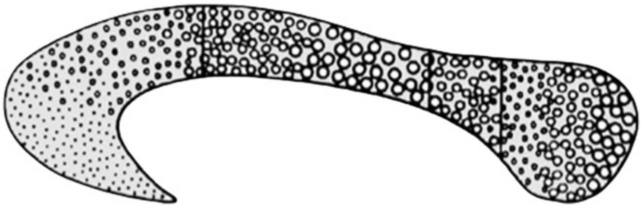

Fig. 3 – Schematic of the mid-sagittal CC indicating the regional distributions of callosal fiber diameters as determined from light-microscopy studies on post-mortem brains. Areas requiring fast conduction, the auditory, motor and visual areas, are connected by larger, more myelinated fibers. Alternatively, specialized cognitive regions are connected by smaller, less myelinated fibers. Image reprinted from Aboitiz et al., 2003.

higher MD. Essentially, faster interhemispheric transfer was correlated with greater mean diffusion in areas of the posterior CC. They interpret this result as there being an increasing proportion of axons with higher density of membrane and myelin that resulted in a reduced average conduction time through the posterior CC. Since axons in the mid-sagittal slice of the CC are oriented exclusively in the left–right axis, increases in mean diffusion are believed to represent larger diameter, and faster conducting axons. These studies indicate that even while current imaging resolution is unable to resolve the true diameter of an axon, measures available with current scanning parameters may hint at the function of callosal microstructure.

In a recent experiment that integrated fMRI and DTI (Baird et al., 2005), the effects of callosal microstructure were correlated with task performance in an object-naming task. The results suggest a relationship between callosal microstructure and task performance. In the study, objects were presented from unusual and canonical perspectives. Objects presented at unusual perspectives would require interhemispheric integration, as the right parietal cortex is specialized for recognizing objects from unusual perspectives. The information would need to be transferred to the left inferior frontal cortex, which is specialized for object naming. Experimental results indicate that shorter reaction times were associated with higher FA values in the splenium, whereas longer reaction times were associated with higher FA values in the genu. These results can be taken to reveal individual differences in task performance based on the microstructural of the CC. How the brain solves a behavioral task may depend upon the integrity of the white matter in the CC and the regional differences among individuals. Future studies should seek to determine the causal relationship. Is the callosal microstructure shaped by the strategies of the brain, vice-versa, or does it result from interplay of the two?

5. Evolution of specialization and asymmetry

Evidence suggests that evolutionary pressures guiding brain size are accompanied by reduced interhemispheric connectivity and greater intrahemispheric connectivity. This is especially evident in the human and is likely related to cerebral lateralization (Rilling and Insel, 1999). Detailed connection topographies of the anterior commissure and CC have been performed in the macaque using tract-tracing techniques (Schmahmann and Pandya, 2006; Schmahmann et al., 2007). The commissural connections include orbitofrontal cortex, superior temporal cortex, along with inferior temporal and parahippocampal gyrus. The callosal connections include prefrontal, premotor, motor, posterior parietal, superior temporal occipital and area inferior temporal cortical area (TEO). Notably reduced or absent from both the commissural and callosal connections in the monkey are direct connections between ventral prefrontal cortex and connections with ventral temporal cortex. These may reveal the beginnings of reduced interhemispheric connectivity seen in humans. Additionally, these connections are also absent from recent diffusion tensor tractography work into the connection topographies and parcellations of the human CC (Hofer and Frahm, 2006; Huang et al., 2005; Zarei et al., 2006; Park et al., 2006). Interestingly, the absence of direct commissural and callosal connections might be explained by the fact that both ventral prefrontal cortex and ventral temporal/fusiform gyrus areas show selectivity for highly specialized and lateralized functions. The ventral occipito-temporal/fusiform areas have been demonstrated to be selective for faces in the right hemisphere (Gauthier et al., 1999; Kanwisher et al., 1997; Fox et al., 2008, this issue) and selective for visual words in the left hemisphere (Cohen et al., 2003; Epelbaum et al., 2008, this issue).

In the past (Gazzaniga, 2000; Corballis et al., 2000; Rilling and Insel, 1999), lateralization of function in the human brain has been explained through evolutionary terms as a way to extend a new function to the opposite hemisphere while still retaining the old function in the original one. For example, to make room for specialized left hemisphere functions, the left hemisphere may have lost visuo-spatial functions retained by the right hemisphere. While this means new and different capacity can be added in the same amount of neural space, it does increase the risk that a unilateral lesion may completely impair a specific cognitive function. Other theoretical mechanisms for such an extension relate back to axon diameter and conduction velocities (Aboitiz et al., 1992a, 1992b; Zaidel and Iacoboni, 2003). These notions suggest that areas receiving reduced input from a homologous cortical area would become specialized by virtue of being deprived of transcallosal connections. By being connected through smaller diameter, slower-conducting transcallosal fibers, specialized areas do not rely on fast interhemispheric communication and in fact, fast connections may induce noise in separate processing systems due to unnecessary crosstalk. Research that seeks to combine callosal microstructure with cortical projection topographies will advance our understanding of human interhemispheric integration. The combination of these characteristics may have been an integral component in the lateralization of function.

6. Conclusion

We have examined the ways in which converging technologies are increasing our understanding of interhemispheric communication. New imaging technologies such as DTI have been used to identify the topographical arrangement of the human CC in increasingly impressive detail. The CC is not simply a large pathway connecting the two cerebral hemispheres in a uniform manner; it seems to serve differential functions based on the cortical areas connected through it. The future of research into the CC will seek to combine measures from behavioral experiments with the regional variations in callosal axonal diameters. As the understanding of relationships between cortical projections topographies and microstructural properties of the CC increase, we may begin to understand how the timing of interhemispheric communication is important for higher-order cognitive processes. Indeed, the manner in which different individuals approach everyday cognitive tasks may in part be explained by differences in the microstructural properties underlying brain connectivity.

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