5

Bridging Hemispheres

The experiments of Sperry, Gazzaniga, and collaborators with callosotomized patients shed profound light on the lateralization of human brain functions, but did not provide much additional insight into the functions normally subserved by the corpus callosum. Work on split brains in humans and animals had made it clear that the corpus callosum was essential for transferring information across the hemispheres when it was available to only one hemisphere. Although this process is relevant to our lateralized brain, it is not necessarily so in the brains of animals that show a much lower degree of functional laterality.

The functions of the corpus callosum have in fact been an enigma for many researchers over time. In the 1600s, Thomas Willis, of whom I spoke in Chapter 2, suggested that the callosum receives sensory input after it has been amplified by the lentiform body (i.e. the basal ganglia), much as a lens does, and projects this information to the gray matter of the cerebral cortex (Zimmer 2004). According to Willis, the corpus callosum was associated with imagination by connecting the different regions of the cerebral cortex. More modern interpretations have pointed to a role of the corpus callosum in coordinating sensory and motor information across the hemispheres, and some have argued that

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its emergence propelled further growth of the cerebral cortex by allowing more extensive and integrated neural networks to operate synchronically. However, there is an apparent contradiction between the evolutionary conservation of such a massive tract, and the relatively mild symptomatic effects produced by surgical callosotomy on human patients and animals, which can only be characterized in controlled laboratory conditions. In this chapter, I will attempt to explain the origin and functions of this massive tract, the largest of the human brain, and its relationship to brain lateralization and hand control, features that are relevant for speech and language origins.

Holding the Hemispheres Together

My Ph.D. thesis, with Eran Zaidel and Arne Scheibel as co-advisors, was initially aimed at understanding the relationship between callosal anatomy and anatomical brain asymmetry in postmortem brains. Earlier works, notably by Sandra Witelson, had reported sex and handedness differences in callosal size, with females and left-handers having larger callosums than right-handed males (Witelson 1985). This suggests that there is an inverse relationship between interhemispheric connectivity and brain lateralization. My interest was to make a direct anatomical-to-anatomical comparison, assessing the extent of morphological asymmetries, and to directly estimate fiber counts in the callosum instead of using cross-sections of the callosal area as had been done in previous studies.

Human postmortem and monkey tract-tracing studies suggested that different callosal regions bridge different cortical areas, such that the callosum contains a back-to-front topographic map of the cortical regions that project through it. Therefore, one could look for specific callosal sectors in relation to circumscribed anatomical asymmetries, like those of the planum temporale and the Sylvian fissure. Following Witelson, we cross-sectioned the callosum at the midline between the hemispheres, and parcellated it into a series of segments from back to front, each presumably connecting different cortical areas (Aboitiz et al. 1992a). Since there are no clear anatomical landmarks to parcel this tract, the standard procedure was to subdivide it geometrically into thirds according to its straight length (see Fig. 5.1). The anterior third is called the genu, and the mid-third the callosal body. The posterior third is subdivided into the posterior fifth, called the splenium, and the region between the posterior third and the posterior fifth is called the isthmus. The isthmus is usually the most slender callosal region, and there is postmortem evidence that fibers from the planum temporale and adjacent areas cross at this level to the other hemisphere. In my thesis, I found no relationship between the callosal cross-section area and callosal fiber density, supporting the notion that larger callosal sizes imply more fibers crossing through, although with substantial interindividual variance. In addition, I found partial support for my original hypothesis that asymmetries in the planum temporale are associated with a smaller isthmus area and fiber number, but only in males. However, the callosal region we were targeting for planum asymmetries may have been the wrong one, as recent studies by Giorgio Innocenti and collaborators

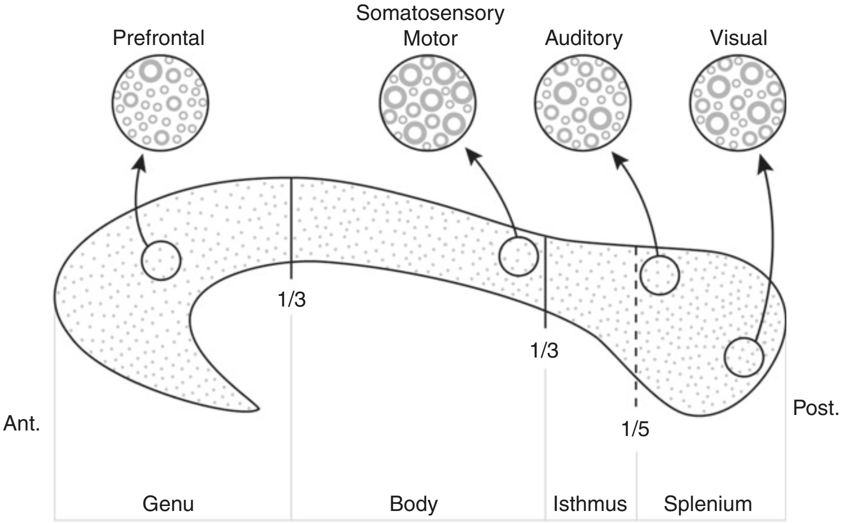

Fig. 5.1 A midsagittal section of the corpus callosum. This structure is geometrically subdivided into thirds, and in the posterior fifth. Insets show a schematic of the distribution of fiber diameters in callosal regions connecting different cortical areas

indicate that callosal fibers connecting the left and right planum temporales are located in the midportion of the callosal splenium (posterior fifth), rather than in the isthmus as we speculated (Caminiti et al. 2013; Innocenti et al. 2014). The relationship between callosal anatomy and brain lateralization is still unclear as there have been many discrepant reports, largely related to the different procedures used to determine callosal connectivity, anatomical asymmetries and functional lateralization (Dorion et al. 2000; Josse et al. 2008; Luders et al. 2010). Perhaps due to the lack of confirmatory findings, the subject has lost much of its initial impetus.

Nonetheless, there have been findings that support an association between callosal connectivity and interhemispheric coordination. A revealing study in this line was recently provided by Marcus Raichle's laboratory, the discoverer of the default-mode brain network (see Chapter 2). Using fMRI, Raichle and collaborators analyzed slow spontaneous fluctuations (more than 10 seconds per cycle) in cortical activity across the hemispheres in a child that had undergone a complete callosotomy (Johnston et al. 2008). After surgery, they found that while intrahemispheric correlations remained similar to condition before surgery, interhemispheric correlations were practically lost post-surgery, generating independent activity patterns in each hemisphere. In the previous chapter, I mentioned the fMRI study by Hesheng Liu and collaborators, in which interhemispheric correlations were higher in sensorimotor than in higher-order cortical areas, indicating that callosal connectivity is stronger for low-level processing regions; and that activity in higher-level ipsilateral networks is organized asymmetrically (Wang et al. 2014). In a more recent large-scale fMRI study, Kelly Shen and collaborators evaluated the strength of functional connectivity between homotopic regions across hemispheres, and compared these values with heterotopic functional connectivity in different resting state conditions (Shen et al. 2015). Heterotopic connectivity could be contralateral, that is, connecting different cortical regions in separate hemispheres, or ipsilateral, that is, connecting different cortical regions within a single hemisphere. Notably, they observed that functional connectivity between homotopic points in both hemispheres remained robust and stable across conditions, while contralateral, or ipsilateral heterotopic connectivity was less stable, depending on the resting condition. Furthermore, functional connectivity between homotopic regions depended on the specific connections through the corpus callosum, being stronger in sensory than association areas. This indicates that the integration of information is stronger between homotopic regions than between ipsilateral or contralateral heterotopic regions. Overall, this evidence points to callosal participation in the maintenance of interhemispheric integration. Nonetheless, in order to get more precise insight into the functions of this structure, we need to go into some anatomical detail about the microscopic structure of the callosum and its evolutionary and developmental underpinnings, which I will do in the rest of this chapter.

Mammals Are More Connected

Although it is the largest cerebral tract, the corpus callosum is not an ancient structure. It is present only in placental mammals (i.e. rats, cats, cows, monkeys, humans and many others), but is absent in marsupials (like opossums and kangaroos) and monotremes (echidnas and platypodes). However, marsupials and monotremes have abundant interhemispheric fibers, mainly running across the anterior commissure, a tract located in the deep forebrain, which is disproportionately large in these animals. A much smaller tract that also contributes to interhemispheric communication is the hippocampal commissure, which connects the two hippocampi in the dorsal hemisphere. In placental mammals, the corpus callosum probably served as a shortcut for interhemispheric fibers, as the pathway via the anterior commissure used by marsupials is quite long and tortuous. An alternative attempt to minimize interhemispheric axonal length is what is termed the fasciculus aberrans in large-brained marsupials like kangaroos, which somewhat shortens the distance traveled from the cerebral cortex to the anterior commissure (Aboitiz and Montiel 2003). In non-mammals (birds, reptiles and amphibians) there is a modest pallial commissure, homologous to the hippocampal commissure of mammals, and an anterior commissure connecting limbic regions like the amygdala. However, there are no reciprocal connections between the most expanding regions of the cerebral hemispheres, which are comparable to the cerebral cortex of mammals (Aboitiz and Montiel 2003). In addition, mammals are unique in the conspicuous laminar arrangement of the cerebral cortex, while the cerebral hemispheres of non-mammals have an overall globular shape, with no evident lamination (I will come back to this below, and in Chapter 9).

The corpus callosum originated in evolution through a major developmental innovation. Some 30 years ago, Michael Katz and collaborators originally proposed that a “glial sling” bridging the two embryonic hemispheres appeared in early placental mammals, allowing axons to cross the midline (Katz et al. 1983). Subsequently, Linda Richards and her team described in more detail the generation of this interhemispheric bridge, which includes several glial specializations, and demonstrated that it serves as a substrate for growth of cortical axons across the midline between hemispheres (Lindwall et al. 2007; Suárez et al. 2014). As brains get larger, as in humans, the glial bridge becomes increasingly complex, with different cellular components involved.

As in other instances mentioned in this book, the genetic basis for the generation of commissural connections seems to be significantly conserved in evolution. There is a detailed molecular mechanism that allows axons to grow across the midline and invade the other side of the brain, which has been found at all levels in the nervous system of vertebrates, insects and worms. This is based on the interplay between three key proteins, called *Robo, Slit* and *Comm. Slit* is located in the midline and repels *Robo*, which is expressed in axons that are impeded from crossing to the other side. However, developing commissural axons stop expressing *Robo* at some point and join another midline molecule, *Comm*, which facilitates their growth across the midline (Dickson and Gilestro 2006). Notably, once axons have reached the other side, they start expressing *Robo* again at their tip, which makes them unable to cross back again. Richards and colleagues have found that different forms of *Slit* are indeed expressed in cells of the callosal glial wedge, and *Robo* is present in growing cortical axons. Likewise, mutant mice with inactivated *Slit* or *Robo* genes display severe malformations in the developing corpus callosum, as well as in many other fiber tracts. In addition to its axonal repellent function, *Slit* is required for the formation of the glial bridge that serves as a substrate for callosal axon growth (Richards 2002; Edwards et al. 2014; Unni et al. 2012). Thus, it appears that a major genetic rearrangement took place in placental mammals, involving the regulation of *Slit, Robo* and other genes, and the formation of a glial pathway that permitted the growth of callosal fibers across the midline. More recently, Richards and her team have reported a role of another protein, Netrin, in callosal axon guidance and regulating *Slit* expression during the formation of the corpus callosum (Fothergill et al. 2014).

There are rare genetic conditions in which the corpus callosum is not present in humans or selected rodent breeds (Edwards et al. 2014). In these cases, a robust longitudinal nerve tract called Probst's bundle develops on both sides of the brain, which may consist of prospective callosal fibers that turn back on the same hemisphere, or may simply reflect the compaction of a preexisting fiber tract (the cingulum bundle) that normally becomes disaggregated as callosal fibers cross through it to reach the midline (Stefanko 1980). Some genetic conditions, such as X-chromosome-linked lissencephaly (a type of cerebral malformation), Aicardi syndrome (also linked to the X chromosome), and ciliopathies, in which cellular cilia (tiny and movable "hairs" in the cells) are defective, have been associated with callosal agenesis. Callosal agenesis is also related to relatively severe cognitive impairments, including visual, motor and cognitive deficits and autistic behavior. Thirty percent of subjects with callosal agenesis have autistic symptomatology, and many individuals with autism spectrum disorder have congenital reduction of the callosal area. However, it is not known to what extent this correlation is due to the absence of the callosum *per se,* or to a more pervasive effect of the genetic disorder, affecting other neural and bodily systems. Many individuals with callosal agenesis have adequate intelligence levels and live relatively normal lives (if there is such a thing as a normal life).

Thus, interhemispheric connections are a new evolutionary acquisition, possibly associated with the origin of the mammalian cerebral cortex. However, its original functions are still somewhat of a mystery. As I have said, the interpretation of a role of the callosum in the integration of the cerebral hemispheres makes sense. However, this does not explain what its function was originally, when it was still a small tract (unless it appeared all at once, which I consider unlikely). It also leaves open the question of how birds have developed such sophisticated behavioral and cognitive skills without the help of interhemispheric connectivity. In order to understand this, we will need to delve into some anatomic and functional details that, although somewhat intricate, can be enlightening in these points.

160 Million Fibers

The corpus callosum is by far the largest fiber tract in the brain, which in humans contains some 160 million nerve fibers crossing the midline. This is a number I know quite well as it was perhaps the main result of my Ph.D. dissertation (Aboitiz et al. 1992b). I was not the first, however, to study this famous tract. At about the same time, Anthony LaMantia, working in his thesis with Pasko Rakic, was making an electron microscopy analysis of the fine callosal structure in the monkey brain (LaMantia and Rakic 1990a). Electron microscopy is a highly detailed technique that cannot be reliably used with humans because it requires pre-mortem preparation of tissue that cannot be performed on humans. But despite its elegance, LaMantia's work was with monkeys, not humans. However, in 1954, the anatomist Joseph Tomasch published a light-microscopy description of the fiber composition of four human callosums, a report that had gone largely unnoticed (Tomasch 1954). I decided to increase the sampling to 40 subjects, 20 males and 20 females. When I started my thesis I had no idea how painstaking a job this was going to be. At the time there were no adequate automatic counting procedures and I had to count fibers of different cross-section diameters for quite a long time. When I closed my eyes at night all I could see were the tiny circles and dots depicting the cross-sectioned myelinated and non-myelinated fibers under the intense light coming through the microscope lens. In a way, I felt reassured reading Ramón y Cajal's autobiography at the time, as he mentioned that when he went to sleep after a day of histological observations all the neuronal shapes he had seen in the day would come back to mind to produce a synthesis of the most important and relevant features among the effervescent diversity of neuronal types (Ramón y Cajal 2006).

One of the first relevant observations among this tedious work was that callosal fiber sizes are quite variable (Fig. 5.1). There are many small unmyelinated or slightly myelinated fibers, smaller than a micrometer in diameter. In addition, there are progressively smaller proportions of myelinated, medium-diameter (1 to 3 micrometers) and large-diameter fibers (larger than 3 micrometers) (myelin is a sheath that covers some axons to increase the propagation speed of nerve signals). Furthermore, different fiber types, particularly the large-diameter fibers, are not homogeneously distributed along the callosum. I first realized this when observing the posterior corpus callosum of a subject that showed a striking concentration of very large diameter fibers in the posteriormost region, where fibers connecting primary and secondary visual areas travel. This was a hint that fiber composition was indeed variable from subject to subject. However, looking at all the data in all callosal regions and across all subjects, a conserved pattern appeared, with two peaks of concentration of large diameter fibers. The first and largest is in the posterior part of the callosal body (the posterior middle third), and the second largest is located in the posterior most callosum (the back of the splenium). These are regions that connect primary and secondary somatosensory and motor areas (the posterior body), and visual areas (the posterior splenium). On the other hand, the callosal genu (the anterior third), which connects frontal and prefrontal areas, is characterized by high densities of small unmyelinated fibers. It was very stimulating to see that the findings by Tomasch with his small human sample, and by LaMantia with macaques were highly consistent with my own. These findings were not just an anatomical curiosity, as fiber diameter, together with myelin wrapping, determines the conduction velocity of nerve impulses. Therefore, they were of high functional relevance, meaning that these are fibers connecting primary or secondary sensory and motor areas that transmit their nerve impulses much faster than the average callosal fiber, while in higher order or association areas (particularly in the frontal region), callosal connectivity is generally slower. Subsequent MRI studies, again including Giorgio Innocenti's group, have assessed callosal fiber microstructure by fractional anisotropy, the basis for tractographic analyses that I mentioned in Chapter 2 (Caminiti et al. 2013). As I said, water diffusion is highly constrained by the orientation of axons and myelin sheaths, and is more constrained when the tract is highly packed and myelinated. Thus, a higher anisotropy value in a tract implies more myelination and increased packing. This technique is still in its beginnings, but in the future, it may provide a non-invasive assessment of callosal fiber variability across subjects.

The Zipper Hypothesis

Why would fibers connecting early stage sensory and motor areas be so fast-conducting? To get some insight into this question, we must first go into some details about the development of callosal connectivity in sensory and higher-order association areas. Innocenti, Caminiti and colleagues first showed in the cat that there is an initial excess of callosal fibers crossing the callosum, which decreases substantially soon after birth, with only about a quarter of the callosal fibers at birth being retained beyond the postnatal period (Innocenti et al. 1977; Innocenti 1981; Koppel and Innocenti 1983; Berbel and Innocenti 1988). These findings concurred with those of LaMantia and Rakic with monkeys (LaMantia and Rakic 1990b). Considering that I calculated 160 million callosal fibers in humans, this means that in the human newborn there could be as many as 640 million callosal fibers, with 480 million retracting shortly after birth. This retraction process can also be observed in gross morphology, as the cross-sectional area of the callosum transiently diminishes after birth, only to begin growing again due to increased fiber thickness, myelination and decreased fiber density. The number of callosal fibers stabilizes in later development and for most of adulthood, except with disease and advanced aging. Furthermore, this initial exuberance indicates that there is a strong intrinsic tendency of many fibers to cross the callosum, many more than are actually supported in adult life. Note that this process of terminal retraction is not exclusive for callosal connectivity, but has been found to be a major feature of the development of ipsilateral cortico-cortical connections as well, and may be related to the existence of critical periods for sensorimotor development, including language (see Chapter 10).

The studies by Innocenti's group showed that concomitant with major fiber loss, there is a drastic rearrangement of callosal projections around birth, when initially callosal fibers evenly innervate all cortical regions (Innocenti et al. 1977; Innocenti 1981, 1986; Innocenti Bressoud 2003; Koppel and Innocenti 1983; Berbel and Innocenti 1988; Aggoun-Zouaoui and Innocenti 1994). From then on, callosal development differs between fibers connecting primary and secondary sensorimotor areas on the one hand, and higher order cortical areas on the other. Only in primary and secondary sensory (visual, somatosensory and auditory) and motor areas, is there a topographic map of the sensory or motor surface. This is the "homunculus" in sensory and motor cortices, and the representation of the visual field in visual areas. You will recall that these maps only correspond to the opposite part of the sensory surface. In auditory areas, the situation is slightly different, as there is a "tonotopic" representation, corresponding to different auditory tones that are segregated in the cochlea of the inner ear. Moving to higher order cortical areas, the sensory or motor topography becomes diffuse, as these regions are involved in more abstract processing mechanisms. Notably, the process of callosal terminal retraction is much more pronounced in the primary and secondary areas than in higher order areas of the cortex. In the former, callosal projections become restricted to a strip located in the borders between adjacent sensory (or motor) areas, while fibers connecting higher order areas are evenly eliminated across the surface (Fig. 5.2). Still, many more fibers may remain connecting higher order areas than sensorimotor regions. The projecting callosal strip that remains in sensory and motor cortices is the representation of the sensory or motor midline of the adjacent areas, so that the only sensorimotor regions connected through the callosum are those corresponding to the medial part of the body and the sensory field, like the visual midline, or the midline of the body surface. Since each hemisphere only receives input from the contralateral side, callosal fibers in these regions serve to connect the two hemi-representations in the midline, forming a continuous sensory and motor field across the hemispheres. In the regions of sensory or motor areas that are far from the midline, representing say the periphery of the visual field,

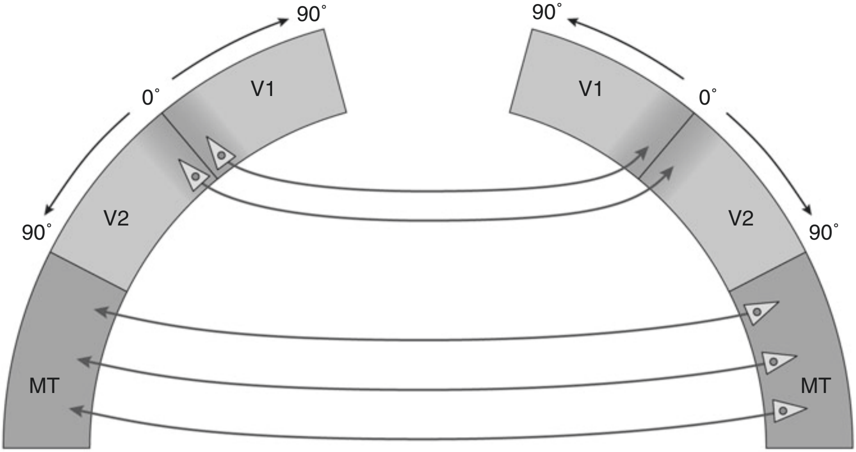

Fig. 5.2 The anatomical arrangement of adult callosal connections. Although in the newborn, neurons project to the corpus callosum throughout the sensory areas (in this case, V1 and V2), these projections undergo severe retraction after birth and only those that connect regions related to the sensory midline remain (0°), while those that represent peripheral regions of the visual field (→90°) are lost. In higher-order areas, there is also profound retraction, but evenly distributed across the respective areas (in this case, area MT). The remaining neurons in adults continue projecting to and from all parts of the respective areas, as well as projecting to additional areas. For simplicity, connections between primary and secondary sensory areas are depicted only from left to right, and in area MT, these are shown from right to left. In fact, all these projections are bidirectional.

there are very few callosal fibers, if any. Likewise, callosal fibers connecting the hand region of motor or somatosensory cortex are negligible, as in these areas most callosal fibers connect midline body regions. Therefore, tasks that are learned with one hand need to be transferred to the other hemisphere via the higher-order areas that are intensively connected via the callosum, and not by primary/secondary areas. Audition is in a way an exception to this rule, as the surface of the cochlea does not map space locations of sounds but rather different tones, with high tones at one extreme and low tones at the other. Callosal projections in auditory areas of the cortex cover different tonalities, but are still restricted to the edges of auditory regions.

The uneven distribution of fiber sizes in the callosum now makes some sense. In the first steps of visual or somatosensory processing, the events that occur around the midline are usually the most relevant, and must be rapidly processed in order for there to be continuous perception across the two hemispheres. Ramón y Canal first proposed the midline rule, asserting that callosal and other commissural connections establish the continuity of the two halves of the sensory map across the hemispheres (Ramón y Cajal 1898). Further studies, including those by the Nobel Prize winners David Hubel and Torsten Wiesel, supported the notion that callosal fibers extend the visual network across hemispheres (Hubel 1988). More specifically, Jean-Christophe Houzel and others have proposed that callosal fibers participate in the process of adaptation to and prediction of a moving object, that passes in front of an observer from one visual field to the other by crossing the vertical midline (Houzel et al. 2002). A beautiful experiment in this line was recently made by Kerstin Schmidt and collaborators, who lightly anesthetized the right visual cortex of a cat by lowering its temperature, and recorded neurons in the left hemisphere while presenting moving stimuli in the contralateral visual field (i.e. right) (Peiker et al. 2013). They found that these neurons activated more strongly when stimuli entered the midline, predictably to cross to the opposite visual field, as opposed to activation with movement toward the periphery of the visual field. Thus, visual neurons may anticipate the movement of objects across the midline, perhaps in addition to other functions involved in fusing the two visual images. This may require very rapid communication across the callosum, and a similar situation may hold for motor and somatosensory areas (both regions displaying the highest concentration of large diameter fibers through the callosum).

Moving Maps to the Cortex

The fine anatomy of callosal fibers and its variability among species give some hints about the original function of interhemispheric connections, and may explain why other large-brained animals like birds never developed this arrangement. We know that embryonic specialization in early placental mammals permitted fiber growth across the midline, and that the callosum was advantageous because it provided a shortcut to the other side of the brain. Nonetheless, we still have no clues about what processing benefits they provided when they first appeared given there must have been selective pressure favoring their development.

To clarify this point, let me remind the reader that the mammalian cerebral cortex is quite different in shape from that of other vertebrates. It is organized as a bidimensional sheet or lamina consisting of several layers, as opposed to the brain of birds, which develops as a well-packed three-dimensional neuronal network. The bidimensional arrangement of the sensory cerebral cortex of mammals is particularly suited for the development of topographically arranged maps of the sensory surfaces, like the somatosensory homunculus or the representation of the visual field (see above). Conversely, in reptiles, birds and other vertebrates, spatial information about the environment is not processed in the cerebral hemispheres, but in a laminar brainstem structure called the optic tectum (see Fig. 5.3). In these animals, the cerebral hemispheres behave like higher-order cortical areas, with no clear topographic sensory or motor organization (Aboitiz and Montiel 2003). These differences are reflected in the relatively small size of the mammalian superior colliculus, the structure homologous to the bird's tectum, an example supporting Robert Barton's hypothesis of evolutionary independence of different neural processing systems (see Chapter 3).

Thus, in mammals there has been a shift in the early sites of spatial processing from the brainstem to the cerebral cortex. As I discussed above, spatial processing poses the problem of midline fusion as each side of the brain receives input from only half of the sensory surface. Non-mammals have solved this problem by developing a tectal commissure that connects the two halves of the sensory field in the midbrain. But as spatial maps moved to the cerebral hemispheres of mammals, the problem of midline fusion became an issue, and interhemispheric connections came as a solution. In the beginning, as in monotremes and marsupials, the only available path for these fibers was through the anterior commissure, which was still a long way but was perhaps better than nothing. The corpus callosum came as an improvement that permitted a shorter travelling distance. One could even stretch this hypothesis and say that without interhemispheric connectivity mammals

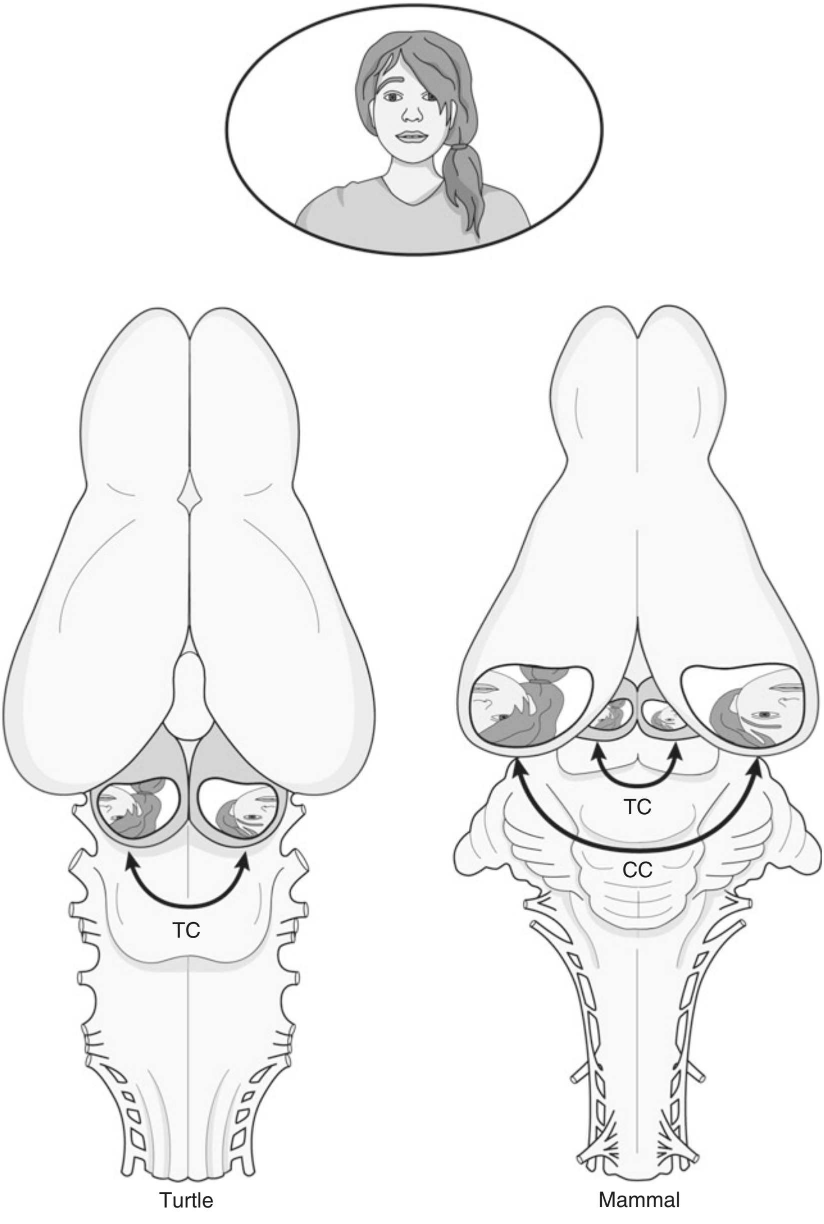

Fig. 5.3 The topographic representation of visual inputs in a reptile and a mammal. In reptiles, the visual map is established in the optic tectum (gray),

would never have generated or at least expanded the cerebral cortex as we know it, not because of developmental but rather functional limitations.

Despite the attractiveness of the hypothesis of midline fusion, the great majority of callosal fibers connects areas other than the sensory or motor regions and is directed mainly to higher-order and association areas involved in higher cognitive processes. It is likely that when this pathway became available, first via the anterior commissure and then through the corpus callosum, not only sensory and motor but also many other fibers were able to traverse to the other hemisphere. As a side effect of the initial benefit of midline fusion, fibers from other cortical regions also made their way across the hemispheres, contributing to other aspects of interhemispheric integration. This may have had the benefit of generating more interconnected networks, but it still remains to be proven that this design is any better than that of other animals without interhemispheric connections, such as birds.

Robin Mihrshahi proposed that besides perceptual midline fusion, interhemispheric integration of motor areas played a key role in the evolution of the callosum (Mihrshahi 2006). In fact, some behavioral functions may have strongly benefited from the development of cross-hemispheric communication, such as bimanual coordination, a mammal-specific behavioral pattern that relies on interhemispheric axons connecting higher-order cortical areas. Bimanual coordination is observed in most mammals, excepting those that have undergone anatomical specializations for walking, swimming or digging; and is pretty much absent in other vertebrates. Moreover, bimanual coordination depends on hand dexterity, which is supported by the cortico-spinal tract, another invention of the mammalian brain. Thus, bimanual coordination is a result of the interplay between these two tracts, the callosum and the cortico-spinal tract, and is extremely useful for beha-

Fig.5.3 (Continued)
and there is a tectal commissure (TC) that fuses both halves of visual representation. In mammals, in addition to the optic tectum (in mammals this structure is called superior colliculus), the visual map is also generated in the visual cortex, where the corpus callosum serves to fuse the two representations at the midline.

viors like nest building and especially food manipulation, features that may have been very important in early mammalian evolution. Bimanual coordination and hand dexterity are especially important in primates, and foreshadowed the capacity for toolmaking and communication in our immediate ancestors. William Hopkins and colleagues observed chimpanzees fishing for termites with sticks, as they do in the wild. They assessed the degree of hand preference and performance in this task, and took tractographic measures of the fiber integrity of the corpus callosum of all individuals (Phillips et al. 2013). They found increasing connectivity through the corpus callosum in individuals with stronger hand preference and performance, regardless of direction (left- or right-handers), which supports the concept of an increasing sensorimotor (but not necessarily higher-level) communication between hemispheres in association with hand specialization. The authors also measured the regional size of the corpus callosum and found no differences in relation to handedness, which emphasizes the use of tractographic instead of area analysis to study callosal connectivity.

There is ample evidence that the corpus callosum in humans is required for everyday bimanual coordination tasks, like typing or eating with a knife and fork, and of course toolmaking in our ancestors. Most of us learn these tasks easily and they become daily routines, but acallosal patients have difficulty with them, especially when these tasks are new and subjects have to learn them. You will recall the alien hand syndrome I mentioned in the previous chapter. While patients who underwent callosal surgery tend to do badly in bimanual coordination tasks, subjects with callosal agenesis (who are born without a corpus callosum) do much better in such tasks, showing some compensatory capacity during development. Gazzaniga and collaborators recently studied a patient undergoing callosotomy in successive stages, where the anterior corpus callosum was sectioned in an initial operation, and the posterior part was resected in a second procedure (Eliassen et al. 2000). With each hand, the patient had to simultaneously draw either mirror image or non-mirror image figures following a model presented to her. Mirror image drawings require tight bimanual coordination, for which an intact corpus callosum may be needed. The patient was evaluated before and after the first operation and after the second. Before surgery, the non-mirror images were drawn poorly, but mirror images were drawn reasonably well. Sectioning the anterior callosum in the first operation had little effect on either the mirror image or non-mirror image drawings. Nonetheless, after sectioning the posterior callosum in the second operation, mirror image drawing deteriorated, while non-mirror drawings improved, presumably because there was less interference between the two hands. The authors concluded that bimanual spatial coordination in visuomotor tasks is significantly impaired by the absence of the corpus callosum, and considering the critical role of the posterior callosum in this task bimanual integration is likely conveyed by the parietal cortex.

Helene Sisti and collaborators used a bimanual task in which healthy subjects had to move a cursor on a computer screen using two dials, with different levels of difficulty during a learning period (Sisti et al. 2012). The researchers studied the callosal regions of the subjects tractographically and found a positive correlation between fractional anisotropy and behavioral performance, but only in regions connecting prefrontal areas. This was found only after a period of training, as the correlation was not significant during early training sessions. In motor regions, the group led by Ulf Ziemann assessed callosal fractional anisotropy and a functional measure of interhemispheric connectivity using TMS with normal subjects and neurologic patients that performed a bimanual finger-tapping task (Wahl et al. 2015). They found that both structural and functional parameters correlated with task performance. Thus, the callosal region, through which bimanual coordination is executed, may depend on the specific task being assessed. As I said above, callosal fibers from primary and secondary motor areas are unlikely to participate in this task as these fibers are concentrated in the body midline rather than in the hand or arm representation.

Transferring Sounds

The above holds well for visual, somatosensory and motor transfer, but not so much for audition. We have seen that the auditory cortex is different from the somatosensory or visual areas, as it has no spatial representation of the auditory scene. Likewise, it appears that auditory callosal fibers do not fit the pattern of visual and somatosensory fibers, as they tend to be located in the anterior part of the splenium, which has an association area-like fiber composition. This may make sense because in audition, much side-to-side information transfer already takes place at very early neural processing levels in the brainstem. In the visual pathway of mammals, brainstem side-to-side connectivity is very limited, and is mainly performed via the tectal or collicular commissure. Thus, cortico-cortical interhemispheric transfer may not need to be as rapid for audition as it does for vision and touch. This has been shown by a series of studies that measure interhemispheric transfer in the visual and the auditory modalities that are based on a simple neuropsychological procedure called the simple reaction time task.

In the 1800s, Franciscus Donders designed the reaction time task to measure the time required to perform a given computation (Newell 1989). In this task, subjects had to respond automatically to a visual or auditory stimulus by pressing a button. The time taken to press this button is the result of the sum of perceptual, motor and cognitive processes. By manipulating the cognitive task and keeping the perceptual and motor components constant Donders estimated the time the brain takes to perform a specific cognitive process. Thus, he compared the response time for automatic tasks and tasks that required a perceptual choice, and found that the latter involved more time. A variant of this task was used by John Stroop in the 1920s, in which subjects were shown the names of colors (red, blue, green) written in different colored ink, so that, for example, the word “red” was written in the same color or a different color (Stroop 1935; MacLeod 1992). Subjects had to respond to the color of the ink and not to the word. For example, if the word “red” was written in blue, the correct answer was “blue”. Subjects took longer to respond when the word was different from the color of the ink. Around the same time, psychologist Albert T. Poffenberger designed an experimental paradigm to measure the time needed for interhemispheric transfer of sensory information, consisting of pressing a button with one hand (left or right) as fast as possible after the appearance of a lateralized stimulus in one visual field (left or right) (Poffenberger 1912). When the stimulus was presented in the same visual field as the responding hand (left visual field and left hand, or right visual field and right hand), the response times were shorter than when the stimulus was presented to the visual field opposite to the responding hand (left visual field and right hand, or right visual field and left hand). The difference was about 5 milliseconds, depending on the specific task. When the visual field and responding hand were on the same side, the stimulus reached the contralateral hemisphere, which also commands the contralateral hand (see previous Chapter). However, if visual field presentation and responding hand were crossed, the stimulus had to be transferred to the opposite hemisphere to perform the manual response. This time difference is considered an estimate of sensory interhemispheric transfer through the corpus callosum.

However, Marco Iacoboni and Eran Zaidel showed that visual interhemispheric transfer is quite different from auditory transfer. They analyzed the crossed-uncrossed reaction time difference for auditory and visual stimuli with a patient that had undergone a complete callosotomy (Iacoboni and Zaidel 1999; Zaidel and Iacoboni 2003). They found that the auditory crossed-uncrossed difference was rather small and highly variable (less than 5 milliseconds), while the visual crossed-uncrossed difference was much greater (between 25 and 45 milliseconds), indicating that the auditory crossed-uncrossed difference is not a reliable estimate of callosal interhemispheric transfer. Rebecca Woelfle and Jessica Grahn also found in normal humans that interhemispheric transfer took less time when auditory rather than visual cues were used (Woelfle and Grahn 2013). The subjects, who were trained musicians and non-musicians, performed a simple reaction task of pressing in button in response to a visual or auditory stimulus. The crossed-uncrossed difference was less for auditory than for visual stimuli, and was slightly greater in musicians than non-musicians. As I have mentioned, the smaller crossed-uncrossed difference for auditory stimuli may be explained by the fact that acoustic information can cross the midline already in the brainstem, while in the visual system this occurs mostly at cortical levels; or, in the case of normal subjects, because visual callosal connections require longer axons than auditory connections due to the anatomy of the neural pathways (see below). A recent and intriguing finding in this line by Giorgio Innocenti and collaborators is a callosal projection to the corpus striatum in monkeys and humans (Innocenti et al. 2016) that is carried by thin fibers, with an estimated interhemispheric transfer time of about 2 and 4 milliseconds in monkeys and humans, respectively, which fits with the results of standard neuropsychological studies of interhemispheric transfer. Furthermore, callosal corticostriatal axons originate mainly from sensory, motor and premotor cortices (with an important exception in humans, which I will discuss below), suggesting that simple sensorimotor interhemispheric transfer is mediated by crossed cortico striatal projections through the corpus callosum.

Time is of the Essence

Different species have different brain sizes and consequently interhemispheric distance varies accordingly, such that in large-brained species like us, callosal fibers are much longer than in mice. Furthermore, interhemispheric delay may be especially detrimental when information has to cross back and forth between the hemispheres, as happens with more complex processing. In this line, James Ringo, Robert Doty, Steve Demeter and Patrice Simard conjectured in 1994 that more time is required to transmit information across the hemispheres in species with larger brains as they have on average a longer interhemispheric distance (Ringo et al. 1994). This imposes an additional delay that they argued is detrimental for fine time-critical neural computations in which multiple passes across the callosum would make processing prohibitively slow. A simple solution is to keep high-resolution processing, or reciprocal neural loops involved in higher processing, restricted to a single hemisphere, leading to hemispheric specialization. A not yet confirmed prediction from their hypothesis was that all large-brained species like elephants and cetaceans would also show a high degree of hemispheric specialization (interestingly, elephants and cetaceans are also good vocal learners; see Chapter 10).

Partly motivated by the above conjecture, my student Ricardo Olivares made a comparative analysis of fiber composition in the posterior corpus callosum of several domestic species of different brain sizes (mouse, rabbit, cat, cow and horse) (Olivares et al. 2001). Ricardo noticed that in each species, fiber sizes are distributed in an asymmetric bell-like curve in which one side of the bell (the left, closer to zero) is very short and the other (the right), containing higher values, has a very long tail. The peak of the curve includes the large majority of fibers and reflects the most common diameter, or modal value. This shape is similar to probability functions like Poisson's or ex-Gaussian distribution. What is more striking is that the modal value changes little across species regardless of brain size. Following Ringo and his colleagues, this implies that interhemispheric transfer is in fact delayed in larger brained species, as most callosal fibers do not significantly increase conduction velocity concomitant with the physical separation of the two hemispheres. On the other hand, the few largest-diameter fibers (the long tail at the right of the bell) noticeably increased in diameter and consequently in conduction velocity in larger brains. This strongly suggests that some kinds of information can be rapidly transferred even in big brains. As we saw earlier, many (but not all) of these large fibers correspond to sensory and motor regions and may participate in midline fusion. Nonetheless, provided that nerve fiber conduction velocity increases linearly with fiber diameter, and scales directly with increasing interhemispheric distance, we calculated the expected increases in fiber caliber required for interhemispheric delay to remain constant, regardless of brain size. We found that the increased size of the largest fibers is not sufficient to maintain a constant interhemispheric delay as brains get bigger, so that there is a toll on interhemispheric transmission.

Furthermore, we searched the literature for information about interhemispheric transfer velocity and transmission times of visual fibers in different animals, and found that species with laterally-directed eyes like rabbits have very long transfer times as opposed to cats, with frontally-directed eyes and shorter interhemispheric transfer times. The laterally placed eyes of rabbits cover a visual field of almost 360 degrees around their heads to maximize detection of predators, while carnivores like cats and dogs depend strongly on frontal vision, and visual midline fusion may be important for them to catch prey. Likewise, Olivares showed that cats and dogs have a higher proportion of large or very large splenial fibers than would be expected in ungulates, rabbits or rodents of the same brain size, all of the latter having laterally placed eyes to different degrees (Olivares et al. 2001). In addition to these findings, we found a significant difference in the relative size of the posterior callosum in relation to total callosal area in frontal-looking species like carnivores and humans, compared to laterally-looking species (mostly herbivores), suggesting that these species devote a higher proportion of visual fibers to the callosum, or have larger visual fibers (Olivares et al. 2000).

After our report, two laboratory groups published similar findings, but with different samples of species. The first was led by Samuel Wang, and included Patrick Hof as one of their collaborators. Wang's group has for some time been interested in describing scaling regularities among different cellular brain components and brain size. Shortly after our publication, these authors published preliminary findings with a small sample of species similar to ours (adding a primate, the macaque), and confirmed an increase in the diameter of the large fibers in species with larger brains (Harrison et al. 2002). They later confirmed these findings in a broader sample of species from shrews to whales, and measured fibers in the posterior and anterior portions of the callosal body (Wang et al. 2008). In line with our conclusions, they showed that while modal fiber diameter remained relatively constant across species, maximal fiber diameters and the degree of myelination of these fibers rose steeply with increasing brain size. Nonetheless, the associated increase in conduction velocity was not sufficient to maintain a constant interhemispheric transmission time, which ranged from one to two milliseconds in the smallest species to about 5 milliseconds in whales (in humans, this value was calculated to be about 4 milliseconds). Wang explains these findings in terms of a functional tradeoff between the need to increase conduction velocity in larger brains on the one hand, and the energy cost and the anatomical difficulty of packing larger axonal volumes on the other, which is a reasonable hypothesis that has to be tested.

The second finding was made by Giorgio Innocenti, Roberto Caminiti, Patrick Hof and others, who analyzed the diameter and anatomic position of callosal fibers originating from specific cortical regions in different primate species (Caminiti et al. 2009). In a series of important articles, they confirmed the previous findings of anterior to posterior distribution of callosal fibers according to cortical topography, and the distribution of fiber diameters described before. The shortest interhemispheric delays were found in areas connecting motor and sensory regions, consistent with previous findings. Moreover, comparing the sizes of axons from motor regions in the macaque, chimpanzee and human, they reported conservatism in modal fiber diameter, and progressively greater maximal axon diameters in relation to increased brain size. Again, the largest axons were not sufficiently fast to render a constant interhemispheric delay. Moreover, differences in maximal axon diameter were not evident from chimp to human. Notably, although frontal regions have very thin callosal fibers, their interhemispheric delays are rather short, because the distance traveled by axons is shorter than in more posterior regions. On the other hand, fibers connecting visual regions have to travel a long distance to the midline, and consequently the interhemispheric delay is relatively high despite there being a high proportion of coarse diameter fibers connecting these areas. Another important point made by Innocenti's group was that there is greater intrinsic variability of fiber sizes and transmission times in species with larger brains. Here, humans ranked higher than chimps. Greater intrinsic variability was observed across callosal regions, but also among fibers connecting specific brain regions. They concluded that there tends to be a wider range of conduction velocities in species with larger brains, which implies that there is a wider time frame for segregating neuronal circuits, particularly considering oscillatory activity. More recently, Kimberley Phillips, Chet Sherwood, Patrick Hof and others described the fiber composition of the corpus callosum in 14 primate species, including humans, again confirming the same essential findings (Phillips et al. 2015).

Finally on this point, Innocenti, Caminiti and Hof extended their previous findings to language-related regions, finding cross-species conservatism in the size of callosal fibers originating from the planum temporale in humans and chimpanzees (Innocenti et al. 2010). In addition, William Hopkins, Chet Sherwood and colleagues found that planum temporale asymmetries in the chimpanzee were associated with a smaller proportion of large diameter fibers in the posterior corpus callosum (Hopkins et al. 2012), which in a way is reminiscent of my early results described at the beginning of this chapter (Aboitiz et al.

1992b). Although in principle this is an interesting finding, in my opinion this data needs to be consistently replicated before it can be considered a fact.

Travelling Waves

As I said in Chapter 2, oscillatory activity is a hallmark of brain function, speech and language being no exceptions to this. As David Poeppel and colleagues have evidenced, speech processing takes place in a nested symphony of neuronal oscillations in a wide but continuous frequency range, from high frequency gamma activity involved in phoneme perception to low-frequency delta oscillations related to large-scale language processing like complex grammar and semantic associations (Chait et al. 2015). We also saw in Chapter 4 that speech perception and production may involve complex bilateral interactions, therefore the question of how these oscillations are coordinated across the hemispheres is crucial. To achieve cross-hemispheric coordination information must be rapidly transmitted across the hemispheres, very likely conveyed by high oscillatory frequency codes. Motor and somatosensory cortices contain the largest axons in the corpus callosum, and are concentrated in the representation of the sensorimotor midline, which includes the organs of speech: the tongue, larynx and lips. However, we know little about interhemispheric transmission during vocalizations. The study of interhemispheric synchronization during normal and pathological speech production may prove a valuable field of study that could be of clinical relevance when considering neural plasticity mechanisms and compensatory effects in speech-impaired individuals.

In Chapter 3, I mentioned an article by György Buzsáki, Nikos Logothetis and Wolf Singer that highlighted the conservation of oscillatory brain activity across a wide variety of mammals from bats and mice to humans, from very high frequencies at 100 or more cycles per second that take place in the hippocampus, to very slow frequencies of about 10 seconds per cycle (Buzsáki et al. 2013). Just to remind the reader classical human electroencephalographic waves are found in most mammals and other vertebrates, including gamma, alpha, beta and theta waves, and have been associated with similar functions in all species. High-frequency oscillations like gamma (at 40 cycles per second or more) are considered to reflect local processing and cognitive contents, and are distinguished from low-frequency oscillations (theta or slower waves) that underlie the workings of large-scale networks that integrate different local processes and contextual elements. The rainbow of oscillatory brain frequencies is thus a highly preserved character across species regardless of brain size, and probably reflects aspects of neuronal network dynamics that are essential for local-global integration and self-organization. A critical requirement for oscillatory dynamics is that stimuli or signals are delivered at appropriate times in the respective neuronal groups, which must be achieved by several physiological processes including synaptic activity, dendritic integration, inhibitory processes and, especially important for our concerns, close regulation of axonal conduction velocity in the different circuits. Thus, in the same line as Ringo and colleagues, Buzsáki, Logothetis and Singer claim that with increasing brain size, time constraints become especially important for oscillatory activity, which is partly compensated for by increasing conduction velocity in a small group of axons. Our work and Innocenti's on the corpus callosum have shown that the range of axonal conduction velocities amplifies as brains grow larger, which may have important consequences for the dynamics of local-global processing in larger brains.

Interhemispheric distance is no more than 1 cm in the mouse brain, but can reach 10–14 cm or more in the human brain, depending on the regions being connected. Conduction velocity of the most abundant, relatively small fibers (about 0.8 microns in diameter) is calculated to be 5–8 meters per second, producing an interhemispheric delay of about 2 milliseconds in the mouse, and 15 and 25 milliseconds in the human. Low oscillatory frequencies like theta have periods of 100–250 milliseconds per cycle, so a delay of 2 milliseconds (mouse) or 20 milliseconds (human) makes up a small proportion of the oscillatory cycle in both species. In other words, these delays may do no harm to low-frequency coordinated activity across the hemispheres. Even in humans, the transmission delay takes about a tenth of the entire cycle, a variability that is within the expected range. On the other hand, at higher frequencies like gamma (40 cycles per second), with cycles lasting only 25 milliseconds, the situation becomes more complicated for the human brain. While in the mouse, 2 milliseconds of delay may not affect high-frequency interhemispheric synchrony, the resulting delay in humans is impossibly long to maintain accurate synchrony if callosal connections are made via the average fibers. Larger callosal fibers, say more than 3 microns in diameter, transmit impulses at about 40 meters per second, while the largest 0.1% of fibers, with axons 10 micrometers in diameter or more, can transmit at 120 meters per second. This yields interhemispheric delays of about 3 milliseconds for fibers 3 micrometers in diameter, and close to 1 millisecond for the largest fibers, which may fit within a 10% tolerance in the variability of gamma oscillatory gamma cycles. These large fibers could allow high-frequency interhemispheric synchrony in the human and other big brains (Aboitiz et al. 2003).

But is there any high frequency synchrony between hemispheres after all? In the visual system, there are fast-conducting callosal fibers, but the longer interhemispheric distance results in increased transmission delay. With single cell recording techniques, Andreas Engel, Wolf Singer and collaborators were the first to observe interhemispheric synchrony in pairs of neurons of the primary visual area of the cat. Synchrony became disrupted after sectioning the corpus callosum (Engel et al. 1991). Later, Engel, Ina Peiker and colleagues moved to humans, using magnetoencephalography, a technique that records magnetic field variations in the skull surface (as opposed to recording electric fields in the EEG) (Peiker et al. 2015). They assessed visual integration deficits in autistic subjects performing an object discrimination task with partially occluded figures. While controls showed increased gamma coherence (a measure indicative of synchronic activity) in visual temporal areas during tasks that require information from both hemispheres, autistic subjects failed to show this increase in such tasks. But high frequency interhemispheric communication may be more complex than a straightforward fit in the phase of the fast cycles. Rafael Malach and his group used electrodes located directly on the cortical surface of five individuals suffering pharmacologically intractable epilepsy, while monitoring brain activity during surgery (Nir et al. 2008). They observed strong, spontaneous slow-frequency cross-hemispheric fluctuations in the activity of high-frequency oscillations, particularly gamma (above 40 cycles per second). That is, the intensity of rapid oscillations fluctuate slowly, and these fluctuations are synchronized in both cerebral hemispheres, a finding that is reminiscent of the low-frequency interhemispheric synchrony reported with fMRI by Marcus Raichle and collaborators (see above in this chapter).

On the other hand, callosal fibers connecting auditory regions usually do not reach diameters as large as those of visual or somatosensory or motor fibers, and consequently there is likely a smaller fiber contingent able to support high frequency interhemispheric synchrony. However, interhemispheric distance is shorter for auditory than for visual fibers, which works in their favor. Saskia Steinmann, Christoph Mulert, Angela Friederici, and other authors conducted a high-density EEG study with healthy subjects participating in a dichotic listening task (Steinmann et al. 2014). Besides analyzing the synchrony, the authors employed a source estimation algorithm that, in combination with tridimensional MRI brain reconstructions, allowed for reconstructing the deep location of surface activity recorded on the scalp with EEG. Notably, the authors found a specific increase in gamma synchrony between the right and left auditory cortices, when subjects consciously perceived the syllable presented to the non-dominant ear (the left ear, projecting principally to the right hemisphere). This is taken as evidence for high-frequency interhemispheric transfer of auditory linguistic information. Considering the close interhemispheric coupling that takes place with speech perception and production, it is likely that cross-hemispheric, high-frequency synchronic ensembles are relevant for speech perception and production, and perhaps for bimanual motor tasks, a process that must depend on a small contingent of fast-conducting fibers.

Integrating Speech, Emotion and Meaning

Callosal fibers may also play a role at higher levels of speech and language processing in the temporal coordination of different speech processes, especially the exchange of information between right-dominant and left-dominant streams. A widely used strategy to study language and semantic processing is the N400 event-related potential, a negative voltage deflection occurring about 400 milliseconds after stimulus presentation (see Chapter 2). N400 and other similar potentials have been associated with cognitive incongruencies in which two or more stimuli are contradictory to each other. In the early eighties, Marta Kutas discovered the N400 in a semantic congruence/incongruence task where she presented phrases word-by-word on a screen that had expected endings like "The coffee was too hot to . . . ". In this sentence, the last word is expected to be "drink" (Kutas and Hillyard 1980). Kutas presented different ending words, the expected one ("drink"), and unexpected ones (say, "eat", or even more unexpected, "walk"). Comparing the event-related EEG curves for the expected and unexpected ending words, there was an evident negative deflection occurring at some 400 milliseconds for the incongruous words, which was more pronounced the more incongruous the word was with the content of the sentence. This was termed the semantic incongruency effect, and was marked by N400 potential. Angela Friederici took advantage of this technique to study interhemispheric processing in partially callosotomized patients. Since syntax is represented mainly on the left hemisphere, and prosody is right-hemisphere dominant, the corpus callosum might be important to integrate the two processing streams. Instead of semantic incongruency, Friederici's group presented incongeuncies between the prosodic contour of a phrase and its syntactic structure (Sammler et al. 2010). Notably, while normal subjects developed a good N400 effect after prosodic-semantic incongruencies, patients with lesions in the posterior third of the corpus callosum failed to show this effect. However, patients did show a normal semantic N400 effect, indicating that the deficit was specific for tasks being processed in different hemispheres. In a subsequent study, Friederici's team also showed that patients with anterior callosal lesions displayed a normal prosodic-syntactic N400 incongruency effect, supporting the participation of parieto-temporal interhemispheric connections in the integration between intonation and phrase structure. This evidence is in line with studies showing that patients with callosal agenesis perform poorly in tasks requiring affective or nonliteral sentence understanding, like metaphors or proverbs (Paul et al. 2003; Rehmel et al. 2016). Analyzing the callosal projection to the corpus striatum that I mentioned above, Innocenti found that only in humans does this projection originate in temporoparietal areas that fit Geschwind's area in the language network of the left hemisphere (Innocenti et al. 2016). Furthermore, this projection crosses through the callosal isthmus, and is proposed by Innocenti's group to participate in syntactic-prosodic integration.

There have been findings supporting interhemispheric interplay in semantic processing. In an early study, Eran Zaidel and collaborators presented subjects with words belonging to different semantic categories (say, content words vs. action words) either in the left or the right visual fields, or presented the same word simultaneously in both visual fields (Mohr et al. 1994). Bilateral presentation improved recognition, but this did not occur when pseudo words (phonetically correct, but meaningless sequences of letters) were used as stimuli. This indicates that cross-hemispheric interactions are in fact relevant for processing semantic information. Warren Brown and his team also showed that subjects with agenesis of the corpus callosum display poorer narrative contents compared to IQ-matched controls, and have specific difficulties in semantic and pragmatic interpretations of the discourse (Turk et al. 2010).

Large-scale processes involved in semantic and higher syntactic analysis might relate to lower frequency neuronal oscillations that are more likely associated with contextual information. In this line, my student Enzo Brunetti conducted a variant of a lexical decision task in which words belonging to different semantic categories (animals, man-made objects, abstract nouns) and pseudo words were binaurally presented to subjects that had to say whether or not the word they heard corresponded to one of the pre-defined semantic categories, say animals (Brunetti et al. 2013). Enzo observed overall phase synchronization increments at low frequencies that were specific for the semantic category that was being used at the moment, whichever it was as there were no differences among semantic categories. However, the average topography of the synchronic networks was specific for each category, despite there being significant individual variability. Enzo also showed early increases in gamma synchrony associated with semantic relevance for the task. Source analysis of this data suggests that the synchronic networks at work are bilateral, at least for low-frequency oscillations. This finding underscores the role of callosal communication in higher aspects of speech and language processing. Overall, these findings are consistent with the recent report by Alexander Huth and collaborators, who identified a widespread semantic representation across the cerebral cortex, whose anatomical organization seems to be conserved across subjects (Huth et al. 2016).

All in all, the corpus callosum provides a massive pathway for cross-hemispheric integration, and despite time constraints, synchronic oscillatory activity can be performed in our large brains at relatively high frequencies, although through a limited contingent of large and very large diameter fibers. Its role in midline control, providing continuity across the sensorimotor representations, may represent one of the most basic and earliest functions of interhemispheric fibers, while processes like bimanual coordination and some aspects of speech perception and production (the corpus callosum may participate, but is not essential for speech processes), may have appeared as late acquisitions. Another question that remains is whether having such abundant interhemispheric connectivity provides any processing advantage to the mammalian brain over that of birds, some of which have shown cognitive capacities as elaborate as those of many mammals, or even more so. Comparative research in the organization of large-scale networks in mammals and birds is needed to provide insight into this issue.

References

Aboitiz F, Montiel J (2003) One hundred million years of interhemispheric communication: the history of the corpus callosum. Braz J Med Biol Res 36:409–420

Aboitiz F, López J, Montiel J (2003) Long distance communication in the human brain: timing constraints for inter-hemispheric synchrony and the origin of brain lateralization. Biol Res 36:89–99

Aboitiz F, Scheibel AB, Zaidel E (1992a) Morphometry of the Sylvian fissure and the corpus callosum, with emphasis on sex differences. Brain 115:1521–1541

Aboitiz F, Scheibel AB, Fisher RS, Zaidel E (1992b) Fiber composition of the human corpus callosum. Brain Res 598:143–153

Aggoun-Zouaoui D, Innocenti GM (1994) Juvenile visual callosal axons in kittens display origin- and fate-related morphology and distribution of arbors. Eur J Neurosci 6:1846–1863

Berbel P, Innocenti GM (1988) The development of the corpus callosum in cats: a light- and electron-microscopic study. J Comp Neurol 276:132–156

Brunetti E, Maldonado PE, Aboitiz F (2013) Phase synchronization of delta and theta oscillations increase during the detection of relevant lexical information. Front Psychol 4:308

Buzsáki G, Logothetis N, Singer W (2013) Scaling brain size, keeping timing: evolutionary preservation of brain rhythms. Neuron 80:751–764

Caminiti R, Ghaziri H, Galuske R, Hof PR, Innocenti GM (2009) Evolution amplified processing with temporally dispersed slow neuronal connectivity in primates. Proc Natl Acad Sci U S A 106:19551–19556

Caminiti R, Carducci F, Piervincenzi C, Battaglia-Mayer A, Confalone G, Visco-Comandini F, Pantano P, Innocenti GM (2013) Diameter, length, speed, and conduction delay of callosal axons in macaque monkeys and humans: comparing data from histology and magnetic resonance imaging diffusion tractography. J Neurosci 33:14501–1411

Chait M, Greenberg S, Arai T, Simon JZ, Poeppel D (2015) Multi-time resolution analysis of speech: evidence from psychophysics. Front Neurosci 9:214

Dickson BJ, Gilestro GF (2006) Regulation of commissural axon pathfinding by slit and its Robo receptors. Annu Rev Cell Dev Biol 22:651–675

Dorion AA, Chantôme M, Hasboun D, Zouaoui A, Marsault C, Capron C, Duyme M (2000) Hemispheric asymmetry and corpus callosum morphometry: a magnetic resonance imaging study. Neurosci Res 36:9–13

Edwards TJ, Sherr EH, Barkovich AJ, Richards LJ (2014) Clinical, genetic and imaging findings identify new causes for corpus callosum development syndromes. Brain 137:1579–1613

Eliassen JC, Baynes K, Gazzaniga MS (2000) Anterior and posterior callosal contributions to simultaneous bimanual movements of the hands and fingers. Brain 123:2501–2511

Engel AK, König P, Kreiter AK, Singer W (1991) Interhemispheric synchronization of oscillatory neuronal responses in cat visual cortex. Science 252:1177–1179

Fothergill T, Donahoo AL, Douglass A, Zalucki O, Yuan J, Shu T, Goodhill GJ, Richards LJ (2014) Netrin-DCC signaling regulates corpus callosum formation through attraction of pioneering axons and by modulating Slit2-mediated repulsion. Cereb Cortex 24:1138–1151

Harrison KH, Hof PR, Wang SS (2002) Scaling laws in the mammalian neocortex: does form provide clues to function. J Neurocytol 31:289–298

Hopkins WD, Pilger JF, Storz R, Ambrose A, Hof PR, Sherwood CC (2012) Planum temporale asymmetries correlate with corpus callosum axon fiber density in chimpanzees (Pan troglodytes). Behav Brain Res 234:248–254

Houzel JC, Carvalho ML, Lent R (2002) Interhemispheric connections between primary visual areas: beyond the midline rule. Braz J Med Biol Res 35:1441–1453

Hubel DH (1988) Eye, Brain and Vision. Scientific American Library, New York

Huth AG, de Heer WA, Griffiths TL, Theunissen FE, Gallant JL (2016) Natural speech reveals the semantic maps that tile human cerebral cortex. Nature 532:453–458

Iacoboni M, Zaidel E (1999) The crossed-uncrossed difference in simple reaction times to lateralized auditory stimuli is not a measure of interhemispheric transmission time: evidence from the split brain. Exp Brain Res 128:421–424

Innocenti GM (1981) Growth and reshaping of axons in the establishment of visual callosal connections. Science 212:824–827

Innocenti GM (1986) General organization of callosal connections in the cerebral cortex. In: Jones EG, Peters A (eds) Cerebral Cortex. Volume 5. Sensory Motor Areas and Aspects of Cortical Connectivity. Plenum Press, New York, p 291–354

Innocenti GM, Bressoud R (2003) Callosal axons and their development. In: Zaidel E, Iacoboni M (eds) The Parallel Brain. Cognitive Neuroscience of the Corpus Callosum. MIT Press, Cambridge, p 11–26

Innocenti GM, Fiore L, Caminiti R (1977) Exuberant projection into the corpus callosum from the visual cortex of newborn cats. Neurosci Lett 4:237–242

Innocenti GM, Caminiti R, Hof PR (2010) Fiber composition in the planum temporale sector of the corpus callosum in chimpanzee and human. Brain Struct Funct 215:123–128

Innocenti GM, Vercelli A, Caminiti R (2014) The diameter of cortical axons depends both on the area of origin and target. Cereb Cortex 24:2178–2188

Innocenti GM, Dyrby TB, Andersen KW, Rouiller EM, Caminiti R (2016) The crossed projection to the striatum in two species of Monkey and in

Humans: behavioral and evolutionary significance. Cereb Cortex pii: bhw161 [EPub ahead of Print]

Johnston JM, Vaishnavi SN, Smyth MD, Zhang D, He BJ, Zempel JM, Shimony JS, Snyder AZ, Raichle ME (2008) Loss of resting interhemispheric functional connectivity after complete section of the corpus callosum. J Neurosci 28:6453–6458

Josse G, Seghier ML, Kherif F, Price CJ (2008) Explaining function with anatomy: language lateralization and corpus callosum size. J Neurosci 28:14132–14139

Katz MJ, Lasek RJ, Silver J (1983) Ontophyletics of the nervous system: development of the corpus callosum and evolution of axon tracts. Proc Natl Acad Sci U S A 80:5936–5940

Koppel H, Innocenti GM (1983) Is there a genuine exuberancy of callosal projections in development? A quantitative electron microscopic study in the cat. Neurosci Lett 41:33–40

Kutas M, Hillyard SA (1980) Reading senseless sentences: brain potentials reflect semantic incongruity. Science 207:203–205

LaMantia AS, Rakic P (1990a) Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. J Comp Neurol 291:520–537

LaMantia AS, Rakic P (1990b) Axon overproduction and elimination in the corpus callosum of the developing rhesus monkey. J Neurosci 10:2156–2175

Lindwall C, Fothergill T, Richards LJ (2007) Commissure formation in the mammalian forebrain. Curr Opin Neurobiol 17:3–14

Luders E, Cherbuin N, Thompson PM, Gutman B, Anstey KJ, Sachdev P, Toga AW (2010) When more is less: associations between corpus callosum size and handedness lateralization. Neuroimage 52:43–49

Macleod *CM* (1992) The Stroop task: the "gold standard" of attentional measures. J Exp Psychol: General 121:*12–14*

Mihrshahi R (2006) The corpus callosum as an evolutionary innovation. J Exp Zool B Mol Dev Evol 306:8–17

Mohr B, Pulvermüller F, Zaidel E (1994) Lexical decision after left, right and bilateral presentation of function words, content words and non-words: evidence for interhemispheric interaction. Neuropsychologia 32:105–124

Newell *FW* (1989) Franciscus Cornelis Donders (1818–1889). Am J Ophthalm 107:691–693

Nir Y, Mukamel R, Dinstein I, Privman E, Harel M, Fisch L, Gelbard-Sagiv H, Kipervasser S, Andelman F, Neufeld MY, Kramer U, Arieli A, Fried I, Malach R (2008) Interhemispheric correlations of slow spontaneous neuronal fluctuations revealed in human sensory cortex. Nat Neurosci 11:1100–1108

Olivares R, Michalland S, Aboitiz F (2000) Cross-species and intraspecies morphometric analysis of the corpus callosum. Brain Behav Evol 55:37–43

Olivares R, Montiel J, Aboitiz F (2001) Species differences and similarities in the fine structure of the mammalian corpus callosum. Brain Behav Evol 57:98–105

Paul LK, Van Lancker-Sidtis D, Schieffer B, Dietrich R, Brown WS (2003) Communicative deficits in agenesis of the corpus callosum: nonliteral language and affective prosody. Brain Lang 85:313–324

Peiker C, Wunderle T, Eriksson D, Schmidt A, Schmidt KE (2013) An updated midline rule: visual callosal connections anticipate shape and motion in ongoing activity across the hemispheres. J Neurosci 33:18036–18046

Peiker I, David N, Schneider TR, Nolte G, Schöttle D, Engel AK (2015) Perceptual integration deficits in autism spectrum disorders are associated with reduced interhemispheric gamma-band coherence. J Neurosci 35:16352–16361

Phillips KA, Schaeffer JA, Hopkins WD (2013) Corpus callosal microstructure influences intermanual transfer in chimpanzees. Front Syst Neurosci 7:125

Phillips KA, Stimpson CD, Smaers JB, Raghanti MA, Jacobs B, Popratiloff A, Hof PR, Sherwood CC. (2015) The corpus callosum in primates: processing speed of axons and the evolution of hemispheric asymmetry. Proc Biol Sci 282:20151535. Erratum in: Proc Biol Sci. 2016, 283:1826. Proc Biol Sci. 2015, 282:1819

Poffenberger AT (1912) Reaction time to retinal stimulation with special reference to the time lost in conduction through nerve centers. Arch Psychol 23:1–73

Ramón y Cajal S (1898) Estructura del quiasma óptico y teoria general de los entrecruzamientos nerviosos. Rev Trim Micrograf 3:2–18

Ramón y Cajal S (2006) Recuerdos de mi Vida. Crítica Editorial, Barcelona

Rehmel JL, Brown WS, Paul LK (2016) Proverb comprehension in individuals with agenesis of the corpus callosum. Brain Lang 160:21–29

Richards LJ (2002) Surrounded by Slit–how forebrain commissural axons can be led astray. Neuron 33:153–155

Ringo JL, Doty RW, Demeter S, Simard PY (1994) Time is of the essence: a conjecture that hemispheric specialization arises from interhemispheric conduction delay. Cereb Cortex 4:331–343

Sammler D, Kotz SA, Eckstein K, Ott DV, Friederici AD (2010) Prosody meets syntax: the role of the corpus callosum. Brain 133:2643–2655

Shen K, Mišić B, Cipollini BN, Bezgin G, Buschkuehl M, Hutchison RM, Jaeggi SM, Kross E, Peltier SJ, Everling S, Jonides J, McIntosh AR, Berman MG (2015) Stable long-range interhemispheric coordination is supported by direct anatomical projections. Proc Natl Acad Sci U S A 112:6473–6478

Sisti HM, Geurts M, Gooijers J, Heitger MH, Caeyenberghs K, Beets IA, Serbruyns L, Leemans A, Swinnen SP (2012) Microstructural organization of corpus callosum projections to prefrontal cortex predicts bimanual motor learning. Learn Mem 19:351–357

Stefanko SZ (1980) Fasciculus callosus longitudinalis (bundle of Probst) and its relation to the corpus callosum. Patol Pol 31:263–272

Steinmann S, Leicht G, Ertl M, Andreou C, Polomac N, Westerhausen R, Friederici AD, Mulert C (2014) Conscious auditory perception related to long-range synchrony of gamma oscillations. Neuroimage 100:435–443

Stroop JR (1935) Studies of interference in serial verbal reactions. J Exp Psychol 18:643–662

Suárez R, Gobius I, Richards LJ (2014) Evolution and development of interhemispheric connections in the vertebrate forebrain. Front Hum Neurosci 8:497

Tomasch J (1954) Size, distribution, and number of fibres in the human corpus callosum. Anat Rec 119:119–135

Turk AA, Brown WS, Symington M, Paul LK (2010) Social narratives in agenesis of the corpus callosum: linguistic analysis of the Thematic Apperception Test. Neuropsychologia 48:43–50

Unni DK, Piper M, Moldrich RX, Gobius I, Liu S, Fothergill T, Donahoo AL, Baisden JM, Cooper HM, Richards LJ (2012) Multiple Slits regulate the development of midline glial populations and the corpus callosum. Dev Biol 365:36–49

Wahl M, Lauterbach-Soon B, Hattingen E, Hübers A, Ziemann U (2015) Callosal anatomical and effective connectivity between primary motor cortices predicts visually cued bimanual temporal coordination performance. Brain Struct Funct 221:3427–3443

Wang SS, Shultz JR, Burish MJ, Harrison KH, Hof PR, Towns LC, Wagers MW, Wyatt KD (2008) Functional trade-offs in white matter axonal scaling. J Neurosci 28:4047–4056

Wang D, Buckner RL, Liu H (2014) Functional specialization in the human brain estimated by intrinsic hemispheric interaction. J Neurosci 34:12341–12352

Witelson SF (1985) The brain connection: the corpus callosum is larger in left-handers. Science 229:665–668

Woelfle R, Grahn JA (2013) Auditory and visual interhemispheric communication in musicians and non-musicians. PLoS One 8:e84446

Zaidel E, Iacoboni M (2003) Introduction: Poffenberger's simple reaction time paradigm for measuring interhemispheric transfer time. In: Zaidel E, Iacoboni M (eds) The Parallel Brain. Cognitive Neuroscience of the Corpus Callosum. MIT Press, Cambridge, p 1–7

Zimmer C (2004) Soul Made Flesh. The Discovery of the Brain – and How it Changed the World. Free Press, New York