



## Special issue: Review

## Frontal callosal disconnection syndromes

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## ARTICLE INFO

## Article history:

Received 18 November 2010

Reviewed 13 January 2011

Revised 17 January 2011

Accepted 18 April 2011

Published online 1 May 2011

## Keywords:

Corpus callosum

Frontal lobe

Interhemispheric disconnection

Callosal topography

## ABSTRACT

The interhemispheric connections of the cortical areas of the human brain are distributed within the corpus callosum according to a topographic order which is being studied in detail by novel imaging techniques. Total section of the corpus callosum is followed by a variety of interhemispheric disconnection symptoms each of which can be attributed to the interruption of fibers in a specific callosal sector. Disconnection symptoms deriving from posterior callosal sections, disconnecting parietal, temporal and occipital lobes across the midline, are more apparent than those following anterior callosal sections disconnecting the frontal lobes. In spite of the massive bulk of the frontal callosal connections in man, ascertained consequences of their interruption are limited to disorders of motor control, with particular regard to bimanual coordination. Technical advances in brain imaging and the design of appropriate tests are expected to reveal so far undetected deficits in the domain of executive and higher cognitive functions, resulting from callosal disconnection of the prefrontal cortices.

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## 1. Interhemispheric disconnection syndromes and callosal maps

Neurological disconnection symptoms and syndromes follow injuries to the brain connecting tracts (Catani and ffytche, 2005; Catani and Mesulam, 2008). Injuries to the forebrain commissures cause interhemispheric disconnections (Berlucchi and Aglioti, 1998; Glickstein and Berlucchi, 2008). The most conspicuous forebrain commissure, the corpus callosum, is the indispensable link for integrating the specialized functional activities of the right and left cortices (Sperry et al., 1969; Sperry, 1982). Depending on its location within the corpus callosum, focal callosal damage can cause unique combinations of functional impairments and spared functional capabilities. The impaired functions can thus be ascribed to the cortical regions disconnected by the callosal

damage, and the spared capabilities can thus be ascribed to the cortical regions with callosal connections spared by the damage (Gazzaniga, 2005).

By injecting radiolabeled aminoacids into various discrete regions of the cortex and by tracing the route taken by labeled fibers across the midline, Pandya and Seltzer (1986) obtained evidence for an orderly compartmentalization of the projections of different cortical areas within the corpus callosum of the rhesus monkeys (Fig. 1; see Schmahmann and Pandya, 2006).

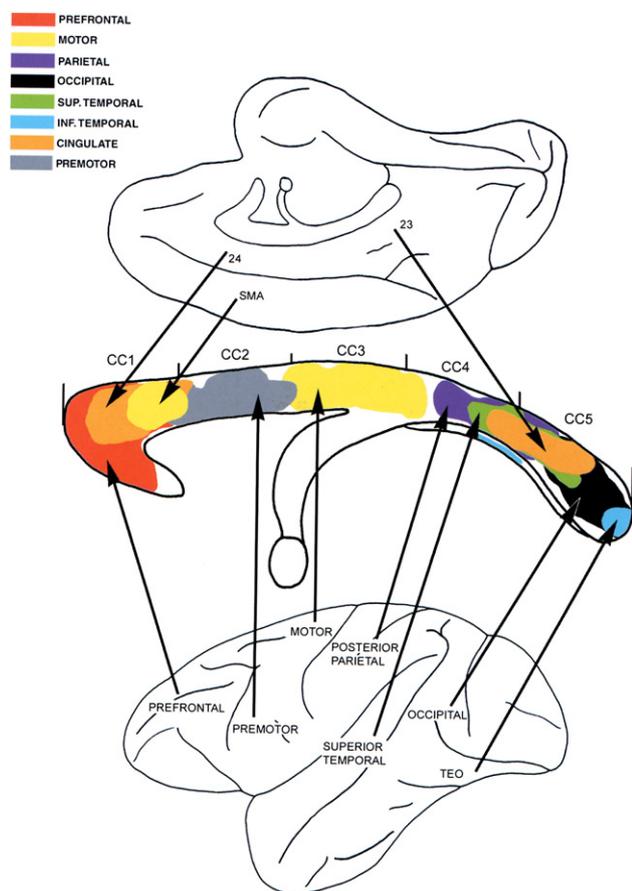
These findings have been extended with electron microscopic and immunocytochemical methods, allowing an analysis of the distribution of distinct morphological classes of axons within the corpus callosum of both rhesus monkeys (LaMantia and Rakic, 1990) and humans (Aboitiz and Montiel, 2003; Fig. 2). For many years evidence about the topographic

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doi:10.1016/j.cortex.2011.04.008



**Fig. 1 – Topography in the midsagittal plane of the corpus callosum of axons interconnecting the principal divisions of the cerebral cortex in the rhesus monkey. TEO is a temporo-occipital visual area; SMA is the supplementary motor area; 23 and 24 are Brodmann areas (from Schmahmann and Pandya, 2006). Callosal sectors can be compared with those delineated for humans by Witelson et al. (2003) in Fig. 3.**

organization of the human corpus callosum has been much less precise, insofar as it was largely based on correlations between the distribution of anterograde degenerations in the corpus callosum and the cortical sites of focal ischemic or traumatic cortical damage (De Lacoste et al., 1985). Such correlations have allowed the construction of a callosal map largely based on the extrapolation of the topography of the macaque's corpus callosum to that of man (Catani and Stuss, 2012, *this issue*). In an antero-posterior order the corpus callosum is anatomically divided into a genu, a body or trunk, an isthmus, and a splenium (Witelson et al., 2003; Fig. 3). The assumption of a similarity with the monkey callosal topography suggests that in humans the genu interconnects the prefrontal regions, the body or trunk interconnects the precentral and postcentral regions, the isthmus interconnects temporal and parietal regions, and the splenium interconnects mostly occipital regions (Aboitiz and Montiel, 2003; Fig. 4).

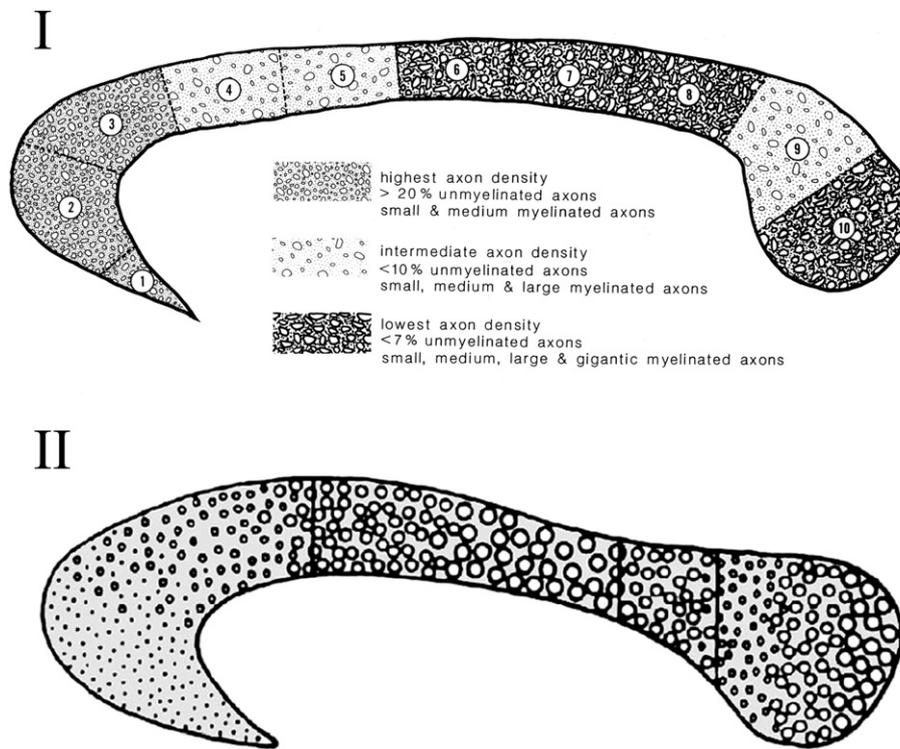
Recently, knowledge about the anatomo-functional topography of the human corpus callosum has been revolutionized by the technique called tractography by diffusion

tensor imaging (DTI). DTI tractography is based on the detection of the preferential (anisotropic) diffusion of water molecules along the main direction of parallel bundles of axons and their myelin sheaths. It allows one to measure the location, orientation, and anisotropy of particular tracts within the white matter, and to assess the presence of disconnections *in vivo* (Thiebaut de Schotten et al., 2008; Catani et al., *in press*). In particular, when coupled with structural imaging, tractography provides a visualization in the living brain of specific pathways within the corpus callosum and their relations with cortical areas (Doron and Gazzaniga, 2008). In addition to the demonstration of cortico-callosal topography, DTI tractography also has the potential of assessing the structural bases of efficiency of interhemispheric connectivity and to allow correlations between such assessments and behavioral measures of interhemispheric communication. Further, it can be used to study regional callosal degeneration and integrity in various neurological conditions involving damage to the white matter (Doron and Gazzaniga, 2008).

Hofer et al. (2008) have claimed that DTI tractography supports a substantial similarity in callosal topography between humans and macaque monkeys, but there appears to be a considerable discrepancy between the callosal map in monkeys and that in humans at least with regard to the callosal connections of the frontal cortex. DTI findings presented in Fig. 5 (Chao et al., 2009) show that in humans the genu and the anterior body of the callosum are fully occupied by the callosal connections of prefrontal areas (i.e., areas of the *Regio Frontalis* of Brodmann, 1909). As a result, the callosal connections of the premotor areas are pushed back, relative to the monkey, to the posterior callosal body, and those of the primary motor cortex are pushed back to the callosal isthmus (Hofer and Frahm, 2006; Zarei et al., 2006; Wahl et al., 2007; Park et al., 2008; Wahl and Ziemann, 2008; Chao et al., 2009). The occupation of more than half the corpus callosum by the interhemispheric connections of frontal cortical areas is in keeping with the conspicuous development of the frontal lobe in the human brain (Passingham, 2008).

## 2. Frontal callosal disconnections

Pure interhemispheric disconnection symptoms and syndromes, uncomplicated by associated gray matter damage, occur most often after surgical sections of the corpus callosum, either total or partial, carried out in order to control drug-refractory epileptic conditions. Much of the scientific evidence on the effects of interhemispheric disconnection of the frontal lobes as well as of other cerebral lobes have been made available by studies of these patients (Glickstein and Berlucchi, 2008). Additional limited evidence has been furnished by studies of non-epileptic patients submitted to removals of deeply located tumors and cysts using a trans-callosal approach. Recently, novel electrophysiological and brain imaging techniques have permitted the correlation of size, microstructural properties and functional connectivity of specific sectors of the corpus callosum with specific abilities and performances in neurologically intact and injured individuals. Patients with ischemic or tumoral lesions of the



**Fig. 2 – Midsagittal sections of the rhesus monkey (I) and human corpus callosum (II) showing regional differences in fiber composition along the corpus callosum. Larger circles indicate larger fiber diameters; small dots indicate unmyelinated fibers. Note the predominance of small and unmyelinated fibers in both simian and human anterior corpus callosum (I is from LaMantia and Rakic, 1990, and II is from Aboitiz and Montiel, 2003).**

corpus callosum can also provide information about interhemispheric disconnections, but the frequent coexistence of damage to one or both hemispheres complicates the attribution of the deficits to interruption of callosal fibers per se. The following is a non-exhaustive review of the evidence which has accumulated on the effects of frontal callosal disconnections in humans.

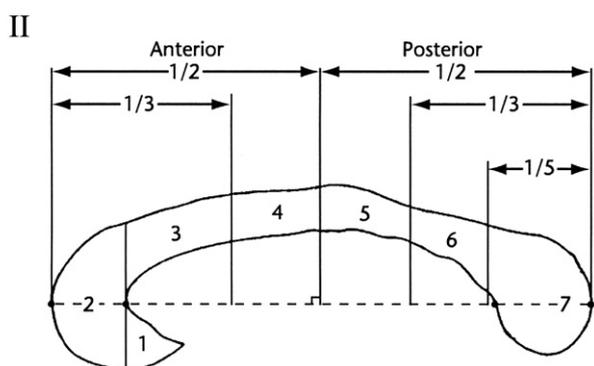
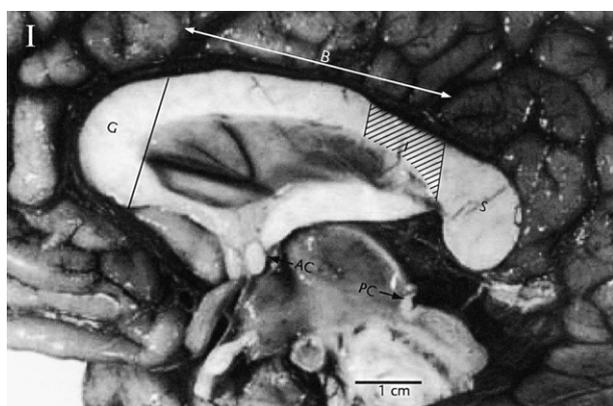
In view of this extensive development of the frontal lobe and its interhemispheric connections, it is quite surprising that section of the human anterior callosum seems to cause considerably fewer or less apparent effects compared to total or posterior callosotomy. In neurological patients, old studies did not reveal symptoms that could be attributed with certainty to an interhemispheric disconnection of the frontal lobes in cases of a post-mortem ascertained softening of the genu of the corpus callosum (e.g., Giannelli, 1907; Mingazzini, 1922; Berlucchi and Aglioti, 1998; see Fig. 6).

In keeping with the old evidence, a pioneering study by Gordon et al. (1971) reported that two epileptic patients submitted to section of the anterior two-thirds of the corpus callosum, thus deprived of their frontal interhemispheric connections, did not present with any of the interhemispheric disconnection deficits exhibited by epileptic patients with complete callosal sections. More specifically, anterior callosotomy patients did not show any of the signs of alexia in the left visual field and anomia for objects felt with the left hand that are so evident in patients with complete callosotomies

(Sperry et al., 1969). While highlighting the importance of the posterior callosum and especially the splenium for interhemispheric communication, at the same time the results of Gordon et al. (1971) raised the problem of what functions are mediated by the large frontal sector of the corpus callosum.

Knowledge of the premotor and motor functions of the frontal lobe suggests that frontal callosal connections may serve (1) to mediate interhemispheric sensory guidance of unilateral movements, (2) to help bilateral coordination during associated synchronous and symmetric movements of corresponding effectors on the two sides of the body, and (3) to allow an orderly dissociation between corresponding left–right effectors during bilateral actions that require coordinated but different movements on the two sides. Experiments on monkeys have confirmed these expectations (e.g., Brinkman and Kuypers, 1973; Brinkman, 1984; Berlucchi, 1990; Wiesendanger and Serrien, 2004).

Modern studies have proven beyond a doubt that frontal callosal disconnection causes the inability to learn movement patterns that require simultaneous, mutually adjusted movements of both upper limbs, such that in the movement of each limb the action of the contralateral limb has to be continuously taken into account. Preilowski (1973) tested two epileptic patients with a section of the anterior two-thirds of the corpus callosum plus the anterior commissure on a difficult bilateral coordination task. On this task neurologically intact persons achieve a smooth performance



**Fig. 3 – Divisions of the human corpus callosum and their sizes according to Witelson et al. (2003). G = Genu; B = Body; I = Isthmus; S = Splenium. According to other authors the Isthmus is not included in the body.**

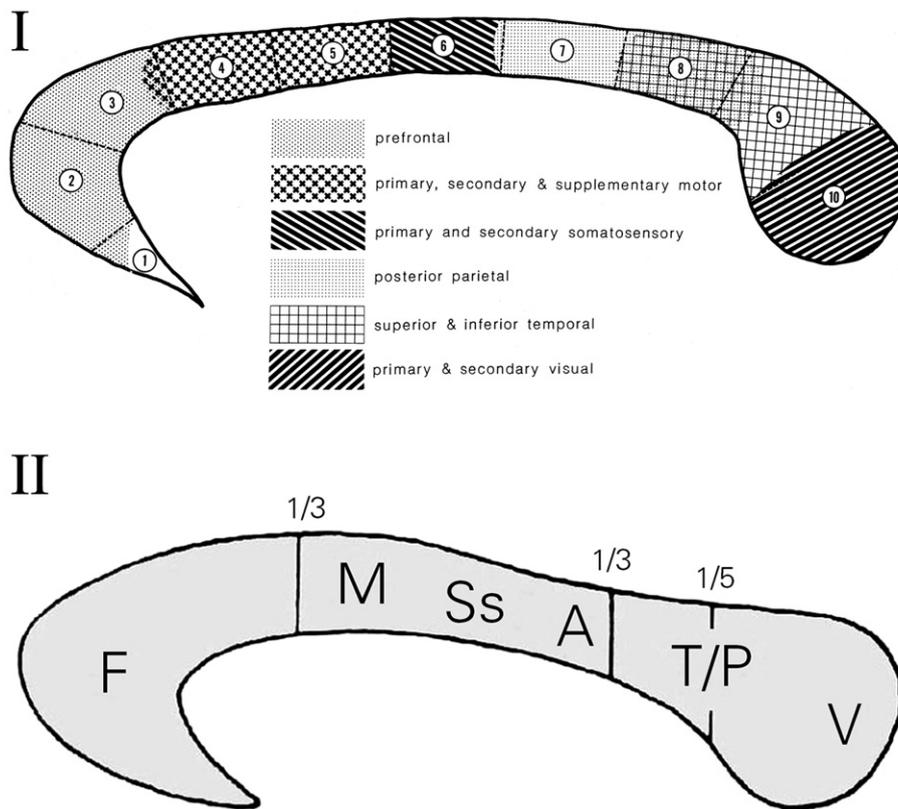
through a multistage learning practice, initially involving visual and proprioceptive feedback but ultimately becoming so rapid that motor control seems to be provided not by sensory feedback, but rather by an interhemispheric exchange of information directly related to motor commands. Unlike healthy controls and epileptic patients with intact forebrain commissures, and despite extensive and protracted practice, the two anterior callosotomy patients failed to reach such stage of smooth control and their performance remained dependent on visual and proprioceptive feedback. According to Preilowski (1973), the anterior callosotomy interferes with learning by eliminating the interhemispheric exchange of motor corollary outflows normally occurring between premotor and motor areas of the frontal lobes. The Preilowski task can be considered to be difficult, but the same anterior callosotomy patients performed very poorly in much simpler bimanual coordination tasks that required asynchronous and asymmetric movements of the two hands, including an out-of-phase bilateral tapping test (Zaidel and Sperry, 1977).

Jeeves et al. (1988) found that individuals with callosal agenesis performed the Preilowski task as poorly as anterior callosotomy patients, while a normal performance was exhibited by a girl in whom the central one-third of the corpus callosum had been sectioned for removing an underlying cyst. According to current callosal maps (e.g., Wahl and

Ziemann, 2008) it is likely that the latter section removed the callosal connections of the primary motor cortex, such that deficits on the Preilowski task can be attributed solely to disconnection of the premotor and possibly prefrontal cortex. This possibility is supported by a more recent study in which Caillé et al. (2005) tested on various motor tasks, including the Preilowski task, four non-epileptic patients submitted to section of different portions of the genu and/or the body of the CC for the removal of cysts in the third ventricle. One patient, whose section included the middle and posterior two-thirds of the genu, i.e., premotor and supplementary motor interhemispheric connections according to current callosal maps, was able to perform the task perfectly before the operation but had great difficulty afterwards, strongly implicating those connections in this kind of bimanual coordination. Two other patients, one with a section of the anterior and middle genu, and the other with a section of the middle and posterior genu, were also impaired on the Preilowski task. A fourth patient, with a more posterior section of the genu extending into the anterior body, exhibited deficits in interhemispheric tactile transfer but performed normally on the Preilowski task.

Several other investigations have shown that some tests of bilateral motor coordination are performed normally or near-normally by callosotomy patients while other tasks are not (e.g., Tuller and Kelso, 1989; Franz et al., 1996; Eliassen et al., 2000; Serrien et al., 2001; Kennerley et al., 2002; Sternad et al., 2007). Normal or near-normal performance after callosotomy relates to the production of repetitive in-phase symmetric movements, whereas performance deteriorates when the task demands the establishment and maintenance of precise asynchronies between symmetric or asymmetric movements of the two sides. The general message from these studies is that callosal connections are not required for synchronizing symmetric bilateral movements, but rather for allowing a relatively separate and independent motor control by either hemisphere through a reciprocal interhemispheric inhibition. DTI analyses of differences in functional callosal connectivity among healthy individuals (e.g., Johansen-Berg et al., 2007; Fling et al., 2010), as well as a localized change of callosal microstructural properties in multiple sclerosis (e.g., Bonzano et al., 2008) and lateral amyotrophic sclerosis (e.g., Bartels et al., 2008), all strongly implicate frontal callosal connections, including those of supplementary motor cortex, cingulate motor cortex and primary motor cortex, in disorders of bilateral motor coordination. Posterior callosal connections related to parietal cortex may also be implicated in bilateral movement timing in reaction to an external stimulus (Eliassen et al., 2000) or in particular discrete or continuous movements (Kennerley et al., 2002; Sternad et al., 2007).

In patients with multiple sclerosis, small but significant alterations in the intermanual transfer of learning in a reaction time task, involving a visually guided thumb-finger opposition, were found by Bonzano et al. (2011) to correlate with a DTI-assessed alteration of microstructural properties of the corpus callosum. The correlation was significant only for the middle callosal sector which is now thought to correspond to the interhemispheric connections of the primary motor cortex (Wahl and Ziemann, 2008).



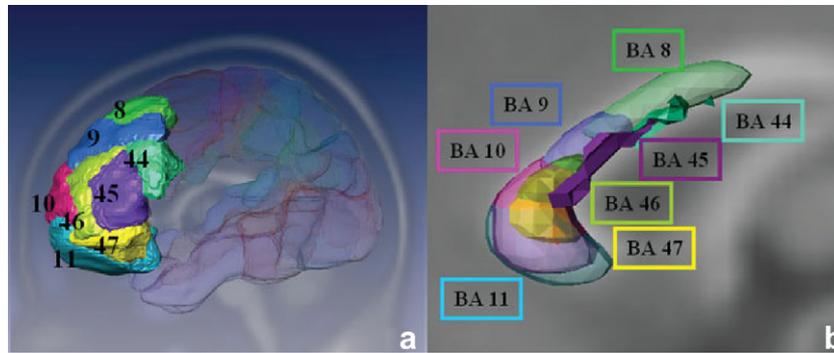
**Fig. 4 – Midsagittal sections of the rhesus monkey (I) and human corpus callosum (II) showing similarities in the topographic distribution of fibers from different cortical sectors. F = frontal; M = motor; Ss = somatosensory; A = auditory; T/P = temporo-parietal; V = visual (I is from LaMantia and Rakic, 1990, and II is from Aboitiz and Montiel, 2003).**

### 3. The case of apraxia

A long-entertained hypothesis of classical neurology associated ideomotor apraxia of the non-dominant hand with a frontal interhemispheric disconnection from a lesion of the anterior corpus callosum. Such a lesion was supposed to separate the motor center of the non-dominant hand from the praxic control center lateralized to the dominant hemisphere (see Catani and ffytche, 2005). Strong evidence against this hypothesis was provided already by the results of the early surgical attempts to treat epilepsy with callosotomy. In 18 epileptic patients with complete or partial callosal section involving the anterior callosum, apraxia occurred only when damage to one or the other hemisphere coexisted with callosal damage (Akelaitis et al., 1942). In keeping with this early conclusion, Gazzaniga et al. (1967), Volpe et al. (1982) and Zaidel and Sperry (1977) showed that each hemisphere possesses independent mechanisms for the praxic control of the contralateral hand. There are dyspraxic or apraxic symptoms after callosal sections, but these are either short-lasting and ascribable to pre-existing or surgical damage rather than to hemispheric disconnection. Long standing apraxic deficits are different from classic ideomotor apraxia, which affects all sensory modalities, and are caused by posterior rather than frontal callosal disconnections. In total or posterior callosotomy patients, the apraxia of the non-dominant hand is

specific for the verbal modality and consists in the inability to perform movements specified by verbal commands, coupled with a perfect ability to use the same hand for imitating those movements when they are demonstrated by the examiner or are executed with one's own dominant hand. This dyspraxic deficits probably reflects the incapacity of the non-dominant hemisphere to decode the verbal command, or the impossibility for verbal but not visual commands to access the praxic center of that hemisphere (Zaidel and Sperry, 1977; Aglioti et al., 1998). Other dyspraxic or apraxic disorders which may or may not depend on callosal disconnection, whether frontal or parietal, have recently been reviewed by Heilman and Watson (2008).

The term *diagonistic dyspraxia* was coined by Akelaitis (1945) to describe a behavioral pattern of involuntary competition between the two hands which occasionally appeared to interfere with the correct execution of unimanual or coordinated bimanual actions in callosotomy patients. For example, a patient with an anterior section of the corpus callosum sometimes could not drink because one hand emptied the glass that the other hand had just filled, and another total callosotomy patient returned with one hand to the baker the bread he had just bought with the other hand. In many subsequent publications the adjective *diagonistic*, which denotes a fight between two contestants, was misspelled *diagnostic*, which of course has a very different meaning. To be sure, for Akelaitis (1945) *diagonistic dyspraxia* was by no



**Fig. 5 – Topographic distribution within the anterior corpus callosum of the interhemispheric connections of the various areas of human prefrontal cortex as identified by Brodmann (1909) in his *Regio Frontalis* (from Chao et al., 2009). BA = Brodmann Area. Note that the part of the anterior corpus callosum occupied by prefrontal axons is comparatively larger than in monkeys (Figs. 1 and 4).**

means diagnostic of a callosal disconnection, because he attributed the intermanual conflict of the first patient (a rather sophisticated “spinster”) to a hysterical and schizoid personality, and that of the second patient (a much simpler “married man”) to subtle epileptic fits. Scepkowski and Cronin-Golomb (2003) have extensively reviewed many forms of intermanual conflict, or lack of control over the movements of one hand (the anarchic hand), or the denial of ownership of one hand (the alien hand) which have been reported after Akelaitis

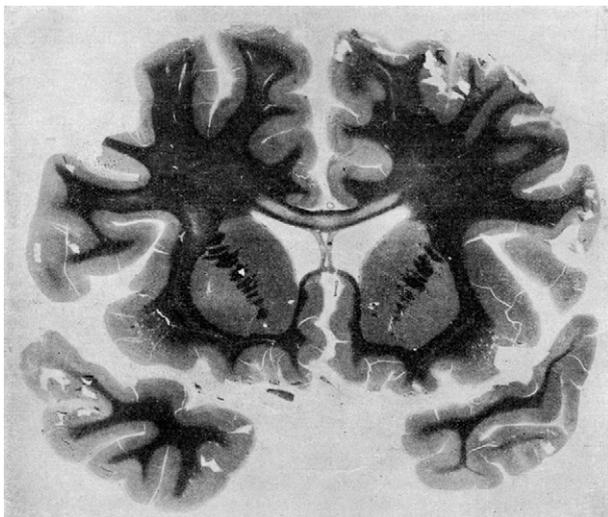
(1945). Although damage to the supplementary motor cortex is often involved in these disorders, there is little evidence, if any, that they are due to frontal callosal disconnection.

#### **4. Frontal callosal disconnection does not underpin interhemispheric deficits seemingly related to frontal functions**

Cortical terminal stations for olfaction and taste are in the frontal lobe, yet signs of interhemispheric disconnection in these modalities appear unrelated to frontal callosal connections. One of the anterior callosotomy patients of Gordon et al. (1971) could name olfactory stimuli presented to either nostril, whereas in patients with complete callosotomy this ability was limited to the nostril projecting to the speaking left hemisphere. More recently, a similar lateralization of taste perception to one side has been found in total and posterior callosotomy patients, but not in anterior callosotomy patients where laterality of taste perception is unaffected (Berlucchi, 2004).

The speed of reaction of total callosotomy subjects to light stimuli presented in the two visual fields exhibits a super-normal gain over single stimuli which is attributable to neural summation. Such neural summation is absent in neurally intact subjects arguably because it is inhibited by the intact corpus callosum (Corballis, 1998; Savazzi and Marzi, 2004). In view of the already described inhibitory interactions between the motor cortex of the two sides, suppression of neural summation by the corpus callosum is likely to be determined by frontal interhemispheric connections. Yet, as with healthy controls, anterior callosotomy patients do not show the enhanced redundancy gain resulting from suppression of neural summation. Therefore the suppression seen after total callosotomy should be ascribed to the posterior corpus callosum (Corballis et al., 2004; Ouimet et al., 2009).

In auditory language comprehension, the left hemisphere is specialized in the processing of syntactic and lexical semantic information, whereas the right hemisphere is specialized in the processing of prosodic information. Interactions between the two hemispheres are expected to be



**Fig. 6 – A frontal brain section passing through the anterior third of the genu of the corpus callosum (from Mingazzini, 1922). The Marchi stain for myelin shows a clear loss of fibers in a central lamina of the corpus callosum interposed between two apparently spared laminae. The patient died after an epileptic seizure. He was a heavy smoker and drinker given to frequent excesses of violence, but a neurological examination had shown no specific symptoms. From this and other cases of frontal callosal degenerations (e.g., Giannelli, 1907), Mingazzini (1922) was led to conclude that there was as yet no proof that anterior callosal lesions caused specific motor or psychic symptoms.**

necessary for the coordination of the two types of processing, and given that in both hemispheres language functions are subserved by distributed fronto-temporal networks (Thiebaut de Schotten et al., 2012; Yeterian et al., 2012, *this issue*), frontal callosal connections can be expected to participate in syntax–prosody coordination. Yet, the event-related potential technique has shown that as with healthy individuals, patients with lesions in the anterior two-thirds of the corpus callosum react to heard sentences mismatched for syntax–prosody interaction with an anterior negativity. This electrical response is lacking in patients with lesions in the posterior corpus callosum, demonstrating that this callosal sector, rather than the frontal sector, is the crucial neuroanatomical basis for the interhemispheric integration of prosodic and syntactic information (Friederici et al., 2007; Sammler et al., 2010).

Miller et al. (2010) have examined three anterior callosotomy patients and three posterior callosotomy patients on a reasoning task that required verbal moral judgments. Unlike neurally intact subjects, who base their judgments on both the outcome of an action and the beliefs of the agent, all callosotomy patients based their judgments primarily on the outcome of the actions, disregarding the beliefs of the agent. Miller et al. (2010) attribute a crucial role to the right temporoparietal junction in ordinary moral judgments and postulate that in the intact brain such judgments require complex interhemispheric interactions between both anterior and posterior cortical areas.

## 5. Future directions for the search of effects of frontal callosal disconnections

All or most of the interhemispheric effects so far attributable with certainty to frontal callosal disconnections pertain, as expected on anatomical grounds, to motor control. In view of the large size of the frontal lobes and the occupation of more than half of the corpus callosum by their interhemispheric connections, the relative paucity of frontal callosal disconnection symptoms and their restriction to the motor domain call for more extended search for non-motor symptoms related to the prefrontal components of the frontal lobes. Prefrontal functions include executive functions such as planning, temporal integration, decision making, monitoring, inhibitory control, social cognition and moral judgment, along with a general regulation of mood, attention, perception and action. Callosal connections serving these functions are tentatively assigned to the genu, which according to both old and new callosal maps is the sector containing the prefrontal interhemispheric connections. Prefrontal deficits after lesions of the genu have not been studied systematically in view of the difficulty to devise appropriate tests that can be performed by brain injured patients. However recent investigations correlating functional callosal connectivity and integrity point to the functional domains where tests appropriate to the testing of patients with callosal lesions can be developed. A few instances of such investigations are summarized in what follows.

In both monkeys (Peters and Sethares, 2003) and humans (Schulte et al., 2005; Hasan et al., 2009; Sullivan et al., 2010)

features of the microstructure of the corpus callosum can be shown to correlate with cognitive functions in development, aging and disease. The massive post-natal myelination process of the human brain, involving an increase in thickness of myelin sheaths as well as of axonal diameters, extends into late childhood and adolescence for motor and sensory cortical areas, and into late adulthood for higher-order cortical areas (Giedd et al., 1999). The protracted growth of white matter in the first decades of life can be affected by experience, as documented by a significant increase in size of a premotor-related portion of the corpus callosum following a prolonged (29 months) and highly intensive practice with a musical instrument in children aged 5–7 (Schlaug et al., 2009). The well established finding of a larger anterior corpus callosum in professional adult musicians compared to non-musicians (Schlaug et al., 1995) is therefore likely to depend on experience rather than on genetically determined individual differences. Evidence on effects of frontal callosal disconnections on the acquisition of musical abilities is lacking.

Individual differences in callosal microstructure may reflect variation in functional callosal connectivity, as shown for the effectiveness of interhemispheric transfer of auditory information (Westerhausen et al., 2009). The ability to introspect about self-performance in a visual judgment task was found to correlate positively with both gray matter volume in the anterior prefrontal cortex and white matter integrity in the genu of the corpus callosum, the callosal sector occupied by the interhemispheric connections of the anterior and orbital prefrontal cortex (Fleming et al., 2010). If the metacognitive ability to introspect about one's own performance depends to some extent on the callosal connections of the anterior prefrontal cortex, then individuals with selective lesions of the genu should be tested on tasks of this kind to reveal a possible specific sign of interhemispheric disconnection.

The possible involvement of abnormalities in prefrontal callosal connections in inheritable or acquired disorders of the nervous system is a topic of growing interest. Regional atrophy of transcallosal prefrontal connections has been reported in cognitively normal carriers of the  $\epsilon 4$  allele for the Apolipoprotein E, which is known as a risk factor for Alzheimer's disease (Filippini et al., 2009). Ultrastructural disruption of myelinated axons in the white matter underlying anterior cingulate cortex, lateral prefrontal cortex and orbitofrontal cortex has been observed in post-mortem analyses of brains of adults with the autistic spectrum disorders (Zikopoulos and Barbas, 2010). A diffuse degradation of callosal microstructural properties obtains in HIV-1 infection (Towgood et al., *in press*), with different effects on component processes of visual attention and perception relevant for local–global feature integration. Anterior callosal microstructural degradation, presumably disconnecting prefrontal regions, reduces the sensitivity to interfering global targets, while altered microstructure of posterior callosal sectors is associated with enhanced response facilitation from additional global targets (Müller-Oehring et al., 2010). Again, this suggested anterior–posterior differentiation within the corpus callosum could be checked in individuals with lesions in different callosal sectors.

Functional magnetic resonance imaging (fMRI) of the human corpus callosum can also help to investigate activation

of the interhemispheric connections of the frontal lobe during the performance of cognitive and motor tasks. Surprisingly, fMRI activations signals can be detected in the white matter, suggesting that transit of action potentials along callosal fibers can be accompanied by a local change in blood flow. There is already evidence for selective activation of callosal sectors in relation to interhemispheric transfer tasks, such as the crossed versus uncrossed visuo-motor control of the hand (see *Berlucchi et al., 1995*), and some research has already implicated the genu and the splenium of the corpus callosum in this and other tasks (*Tettamanti et al., 2002; Weber et al., 2005; Omura et al., 2004; Mazerolle et al., 2010; Gawryluk et al., 2011*). Perhaps this method will prove to be appropriate for a most direct approach to the construction of functional maps of the corpus callosum.

## Acknowledgments

I thank Dr. Marco Catani for suggesting the inclusion of figures and for providing some of them, and Marco Veronese for his help with the preparation of the illustrations.

## REFERENCES

- Aboitiz F and Montiel J. One hundred million years of interhemispheric communication: The history of the corpus callosum. *Brazilian Journal of Medical and Biological Research*, 36(4): 409–420, 2003.
- Aglioti S, Beltramello A, Tassinari G, and Berlucchi G. Paradoxically greater interhemispheric transfer deficits in partial than complete callosal agenesis. *Neuropsychologia*, 36(10): 1015–1024, 1998.
- Akelaitis AJ. Studies on the corpus callosum. IV. Diagonistic dyspraxia in epileptics following partial and complete section of the corpus callosum. *American Journal of Psychiatry*, 101(5): 594–599, 1945.
- Akelaitis AJ, Risteen WA, Herren RY, and Van Wagenen WP. Studies on the corpus callosum. III. A contribution to the study of dyspraxia and apraxia following partial and complete section of the corpus callosum. *Archives of Neurology and Psychiatry*, 47(6): 971–1008, 1942.
- Bartels C, Mertens N, Hofer S, Merboldt KD, Dietrich J, Frahm J, et al. Callosal dysfunction in amyotrophic lateral sclerosis correlates with diffusion tensor imaging of the central motor system. *Neuromuscular Disorders*, 18(5): 398–407, 2008.
- Berlucchi G. Commissurotomy studies in animals. In Boller F and Grafman J (Eds), *Handbook of Neuropsychology*, vol. 4. Amsterdam: Elsevier, 1990: 9–47.
- Berlucchi G. Some effects of cortical and callosal damage on conscious and unconscious processing of visual information and other sensory inputs. *Progress in Brain Research*, 144: 79–93, 2004.
- Berlucchi G and Aglioti S. Interhemispheric disconnection syndromes. In Pizzamiglio L and Denes G (Eds), *Handbook of Clinical and Experimental Psychology*. Hove, U.K.: Psychology Press, 1998: 635–670.
- Berlucchi G, Aglioti S, Marzi CA, and Tassinari G. Corpus callosum and simple visuomotor integration. *Neuropsychologia*, 33(8): 923–936, 1995.
- Bonzano L, Tacchino A, Roccatagliata L, Abbruzzese G, Mancardi GL, and Bove M. Callosal contributions to simultaneous bimanual finger movements. *Journal of Neuroscience*, 28(12): 3227–3233, 2008.
- Bonzano L, Tacchino A, Roccatagliata L, Mancardi GL, Abbruzzese G, and Bove M. Structural integrity of callosal midbody influences intermanual transfer in a motor reaction-time task. *Human Brain Mapping*, 32(2): 218–228, 2011.
- Brinkman C. Supplementary motor area of the monkey's cerebral cortex: Short- and long-term deficits after unilateral ablation and the effects of subsequent callosal section. *Journal of Neuroscience*, 4(4): 918–929, 1984.
- Brinkman J and Kuypers HGJM. Cerebral control of contralateral and ipsilateral arm, hand and finger movements in the split-brain rhesus monkey. *Brain*, 96(4): 653–674, 1973.
- Brodman K. *Vergleichende Lokalisationlehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues*. Leipzig: Verlag von Johann Ambrosius Barth, 1909.
- Caillé S, Sauerwein HC, Schiavetto A, Villemure JG, and Lassonde M. Sensory and motor interhemispheric integration after section of different portions of the anterior corpus callosum in nonepileptic patients. *Neurosurgery*, 57(1): 50–59, 2005.
- Catani M and Stuss DT. At the forefront of clinical neuroscience. *Cortex*, 48(1): 1–6, 2012.
- Catani M, Dell'Acqua F, Vergani F, Malik F, Hodge H, Roy P, et al. Short frontal lobe connections of the human brain. *Cortex*, 48(2): doi:10.1016/j.cortex.2011.12.001.
- Catani M and ffytche DH. The rises and falls of disconnection syndromes. *Brain*, 128(10): 2224–2239, 2005.
- Catani M and Mesulam M. What is a disconnection syndrome? *Cortex*, 44: 911–913, 2008.
- Chao Y, Cho K, Yeh C, Chou K, Chen J, and Lin C. Probabilistic topography of human corpus callosum using cytoarchitectural parcellation and high angular resolution diffusion imaging tractography. *Human Brain Mapping*, 30(10): 3172–3187, 2009.
- Corballis MC. Interhemispheric neural summation in the absence of the corpus callosum. *Brain*, 121(9): 1795–1807, 1998.
- Corballis MC, Corballis PM, and Fabri M. Redundancy gain in simple reaction time following partial and complete callosotomy. *Neuropsychologia*, 42(1): 71–81, 2004.
- De Lacoste MC, Kirkpatrick JB, and Ross ED. Topography of the human corpus callosum. *Journal of Neuropathology and Experimental Neurology*, 44(6): 578–591, 1985.
- Doron KW and Gazzaniga MS. Neuroimaging techniques offer new perspectives on callosal transfer and interhemispheric communication. *Cortex*, 44(8): 1023–1029, 2008.
- Eliassen JC, Baynes K, and Gazzaniga MS. Anterior and posterior callosal contributions to simultaneous bimanual movements of the hands and fingers. *Brain*, 123(12): 2501–2511, 2000.
- Filippini N, Zarei M, Beckmann CF, Galluzzi S, Borsci G, Testa C, et al. Regional atrophy of transcallosal prefrontal connections in cognitively normal APOE ε4 carriers. *Journal of Magnetic Resonance Imaging*, 29(5): 1021–1026, 2009.
- Fleming SM, Weil RS, Nagy Z, Dolan RJ, and Rees G. Relating introspective accuracy to individual differences in brain structure. *Science*, 329(5998): 1541–1543, 2010.
- Fling BW, Walsh CM, Bangert AS, Reuter-Lorenz PA, Welsh RC, and Seidler RD. Differential callosal contributions to bimanual control in young and older adults. *Journal of Cognitive Neuroscience*, posted online on 18 Oct 2010.
- Franz EA, Eliassen JC, Ivry RB, and Gazzaniga MS. Dissociation of spatial and temporal coupling in the bimanual movements of callosotomy patients. *Psychological Science*, 7(5): 306–310, 1996.
- Friederici AD, von Cramon DY, and Kotz SA. Role of the corpus callosum in speech comprehension: Interfacing syntax and prosody. *Neuron*, 53(1): 135–145, 2007.
- Gawryluk JR, D'Arcy RCN, Mazerolle EL, Brewer, and Beyea SD. Functional mapping in the corpus callosum: A 4 T fMRI study of white matter. *NeuroImage*, 54(1): 10–15, 2011.

- Gazzaniga MS. Forty-five years of split-brain research and still going strong. *Nature Reviews Neuroscience*, 6(8): 653–659, 2005.
- Gazzaniga MS, Bogen JE, and Sperry RW. Dyspraxia following division of the cerebral hemispheres. *Archives of Neurology*, 16(6): 606–612, 1967.
- Giannelli A. Softening of the genu of the corpus callosum. *Journal of Mental Pathology*, 8(2): 49–62, 1907.
- Giedd JN, Blumenthal J, Jeffries NO, Rajapakse JC, Vaituzis AC, Liu H, et al. Development of the human corpus callosum during childhood and adolescence: A longitudinal MRI study. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 23(4): 571–588, 1999.
- Glickstein M and Berlucchi G. Classical disconnection studies of the corpus callosum. *Cortex*, 44(8): 914–927, 2008.
- Gordon HW, Bogen JE, and Sperry RW. Absence of deconnection syndrome in two patients with partial section of the neocommissures. *Brain*, 94(2): 327–336, 1971.
- Hasan KM, Kamalia A, Iftikhar A, Kramer LA, Papanicolaou AC, Fletcher JM, et al. Diffusion tensor tractography quantification of the human corpus callosum fiber pathways across the lifespan. *Brain Research*, 1249: 91–100, 2009.
- Heilman KM and Watson RT. The disconnection apraxias. *Cortex*, 44(8): 975–982, 2008.
- Hofer S and Frahm J. Topography of the human corpus callosum revisited-comprehensive fiber tractography using diffusion tensor magnetic resonance imaging. *NeuroImage*, 32(3): 989–994, 2006.
- Hofer S, Merboldt KD, Tammer R, and Frahm J. Rhesus monkey and human share a similar topography of the corpus callosum as revealed by diffusion tensor MRI in vivo. *Cerebral Cortex*, 18(5): 1079–1084, 2008.
- Jeeves MA, Silver PH, and Jacobson I. Bimanual co-ordination in callosal agenesis and partial commissurotomy. *Neuropsychologia*, 26(6): 833–850, 1988.
- Johansen-Berg H, Della-Maggiore V, Behrens TEJ, Smith SM, and Paus T. Integrity of white matter in the corpus callosum correlates with bimanual co-ordination skills. *NeuroImage*, 36(Suppl. 2): T16–T21, 2007.
- Kennerley SW, Diedrichsen J, Hazeltine E, Semjen A, and Ivry RB. Callosotomy patients exhibit temporal uncoupling during continuous bimanual movements. *Nature Neuroscience*, 5(4): 376–381, 2002.
- LaMantia AS and Rakic P. Cytological and quantitative characteristics of four cerebral commissures in the rhesus monkey. *Journal of Comparative Neurology*, 291(4): 520–537, 1990.
- Mazerolle EL, Beyea SD, Gawryluk JR, Brewer KD, Bowen CV, and D'Arcy RC. Confirming white matter fMRI activation in the corpus callosum: Co-localization with DTI tractography. *NeuroImage*, 50(2): 616–621, 2010.
- Miller MB, Sinnott-Armstrong W, Young L, King D, Paggi A, Fabri M, et al. Abnormal moral reasoning in complete and partial callosotomy patients. *Neuropsychologia*, 48(7): 2215–2220, 2010.
- Mingazzini G. *Der Balken. Eine anatomische, physiopathologische und klinische Studie*. Berlin: Springer, 1922.
- Müller-Oehring EM, Schulte T, Rosenbloom MJ, Pfefferbaum A, and Sullivan EV. Callosal degradation in HIV-1 infection predicts hierarchical perception: A DTI study. *Neuropsychologia*, 48(4): 1133–1143, 2010.
- Omura K, Tsukamoto T, Kotani Y, Ohgami Y, Minami M, and Inoue Y. Different mechanisms involved in interhemispheric transfer of visuomotor information. *NeuroReport*, 15(18): 2707–2711, 2004.
- Ouimet C, Jolicœur P, Miller J, Ptito A, Paggi A, Foschi N, et al. Sensory and motor involvement in the enhanced redundant target effect: A study comparing anterior- and totally split-brain individuals. *Neuropsychologia*, 47(3): 684–692, 2009.
- Pandya DP and Seltzer B. The topography of commissural fibres. In Lepore F, Ptito M, and Jasper HH (Eds), *Two Hemispheres – One Brain: Functions of the Corpus Callosum*. New York: Alan R. Liss, 1986: 47–73.
- Park H, Kim JJ, Lee S, Seok JH, Chun J, Kim DJ, et al. Corpus callosal connection mapping using cortical gray matter parcellation and DT-MRI. *Human Brain Mapping*, 29(5): 503–516, 2008.
- Passingham R. *What is Special About the Human Brain?* Oxford: Oxford University Press, 2008.
- Peters A and Sethares C. Is there remyelination during aging of the primate central nervous system? *Journal of Comparative Neurology*, 460(2): 238–254, 2003.
- Preilowski BFB. Possible contribution of the anterior forebrain commissures to bilateral motor coordination. *Neuropsychologia*, 10(3): 267–277, 1973.
- Sammler D, Kotz SA, Eckstein K, Ott DV, and Friederici AD. Prosody meets syntax: The role of the corpus callosum. *Brain*, 133(9): 2643–2655, 2010.
- Savazzi S and Marzi CA. The superior colliculus subserves interhemispheric neural summation in both normals and patients with a total section or agenesis of the corpus callosum. *Neuropsychologia*, 42(12): 1608–1618, 2004.
- Scepkowski LA and Cronin-Golomb A. The alien hand: Cases, categorizations, and anatomical correlates. *Behavioral and Cognitive Neuroscience Reviews*, 2(4): 261–277, 2003.
- Schlaug G, Forgeard M, Zhu L, Norton A, Norton A, and Winner E. Training-induced neuroplasticity in young children. *Annals of the New York Academy of Sciences*, 1169: 205–208, 2009.
- Schlaug G, Jäncke L, Huang Y, Staiger JF, and Steinmetz H. Increased corpus callosum size in musicians. *Neuropsychologia*, 33(8): 1047–1055, 1995.
- Schmahmann JD and Pandya DN. *Fiber Pathways of the Brain*. New York: Oxford University Press, 2006.
- Schulte T, Sullivan EV, Müller-Oehring EM, Adalsteinsson E, and Pfefferbaum A. Corpus callosal microstructural integrity influences interhemispheric processing: A diffusion tensor imaging study. *Cerebral Cortex*, 15(9): 1384–1392, 2005.
- Serrien DJ, Nirkko AC, and Wiesendanger M. Role of the corpus callosum in bimanual coordination: A comparison of patients with congenital and acquired callosal damage. *European Journal of Neuroscience*, 14(11): 1897–1905, 2001.
- Sperry R. Some effects of disconnecting the cerebral hemispheres. *Science*, 217(4566): 1223–1226, 1982.
- Sperry RW, Gazzaniga MS, and Bogen JE. Interhemispheric relationships: The neocortical commissures; syndromes of hemispheric disconnection. In Vinken PJ and Bruyn GW (Eds), *Handbook of Clinical Neurology. Disorders of Speech, Perception, and Symbolic Behaviour*, vol. 4. Amsterdam: Elsevier, 1969: 273–290.
- Sternad D, Wei K, Diedrichsen J, and Ivry RB. Intermanual interactions during initiation and production of rhythmic and discrete movements in individuals lacking a corpus callosum. *Experimental Brain Research*, 176(4): 559–574, 2007.
- Sullivan EV, Rohlfing T, and Pfefferbaum A. Longitudinal study of callosal microstructure in the normal adult aging brain using quantitative DTI fiber tracking. *Developmental Neuropsychology*, 35(3): 233–256, 2010.
- Tettamanti M, Paulesu E, Scifo P, Maravita A, Fazio F, Perani D, et al. Interhemispheric transmission of visuomotor information in humans: fMRI evidence. *Journal of Neurophysiology*, 88(2): 1051–1058, 2002.
- Thiebaut de Schotten M, Kinkingnéhun S, Delmaire C, Lehericy S, Duffau H, Thivard L, et al. Visualization of disconnections syndromes in humans. *Cortex*, 44(8): 1097–1103, 2008.
- Thiebaut de Schotten M, Dell'Acqua F, Valabregue R, and Catani M. Monkey to human comparative anatomy of the frontal lobe association tracts. *Cortex*, 48(1): 81–95, 2012.
- Towgood KJ, Pitkanen M, Kulasegaram R, Fradera A, Kumar A, Soni S, et al. Mapping the brain in younger and older

- asymptomatic HIV-1 men: Frontal volume changes in the absence of other cortical or diffusion tensor abnormalities. *Cortex*, doi:10.1016/j.cortex.2011.03.006.
- Tuller B and Kelso JAS. Environmentally-specified patterns of movement coordination in normal and split-brain subjects. *Experimental Brain Research*, 75(2): 306–316, 1989.
- Volpe BT, Sidtis JJ, Holtzman JD, Wilson DH, and Gazzaniga MS. Cortical mechanisms involved in praxis: Observations following partial and complete section of the corpus callosum in man. *Neurology*, 32(6): 646–650, 1982.
- Wahl M, Lauterbach-Soon B, Hattingen E, Jung P, Singer O, Volz S, et al. Human motor corpus callosum: Topography, somatotopy, and link between microstructure and function. *Journal of Neuroscience*, 27(45): 12132–12138, 2007.
- Wahl M and Ziemann U. The human motor corpus callosum. *Reviews in the Neurosciences*, 19(6): 451–466, 2008.
- Weber B, Treyer V, Oberholzer N, Jaermann T, Boesiger P, Brugger P, et al. Attention and interhemispheric transfer: A behavioral and fMRI study. *Journal of Cognitive Neuroscience*, 17(1): 113–123, 2005.
- Westerhausen R, Grüner R, Specht K, and Hugdahl K. Functional relevance of interindividual differences in temporal lobe callosal pathways: A DTI tractography study. *Cerebral Cortex*, 19(6): 1322–1329, 2009.
- Wiesendanger M and Serrien DJ. The quest to understand bimanual coordination. *Progress in Brain Research*, 143: 491–505, 2004.
- Witelson SF, Kigar DL, and Walter A. Cerebral commissures. In Nadel L (Ed), *Encyclopedia of Cognitive Science*, vol. 1. London: Nature Publishing Group, 2003: 476–485.
- Yeterian EH, Pandya DN, Tomaiuolo F, and Petrides M. The cortical connectivity of the prefrontal cortex in the monkey brain. *Cortex*, 48(1): 57–80, 2012.
- Zaidel D and Sperry RW. Some long-term motor effects of cerebral commissurotomy in man. *Neuropsychologia*, 15(2): 193–204, 1977.
- Zarei M, Johansen-Berg H, Smith S, Ciccarelli O, Thompson AJ, and Matthews PM. Functional anatomy of interhemispheric cortical connections in the human brain. *Journal of Anatomy*, 209(3): 311–320, 2006.
- Zikopoulos B and Barbas H. Changes in prefrontal axons may disrupt the network in autism. *Journal of Neuroscience*, 30(44): 14595–14609, 2010.