

## 7 Asymmetry of White Matter Pathways

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Here are eight instances in which the lesion was in the posterior third of the third frontal convolution. This number seems to me to be sufficient to give strong presumptions. And the most remarkable thing is that in all the patients the lesion was on the left side. I do not dare draw conclusions from this.

—Paul Broca (1863)

With these words, from a short report of a series of patients with acquired speech deficits, begins the modern period of the study of cerebral asymmetry. Despite Broca's reticence to draw any conclusion from his clinical–anatomical observation, his words clearly allude to a concept that has stood the test of time: the asymmetrical distribution of functions in the human brain. In later writings, Broca not only vehemently defended his idea of left lateralization of speech but initiated the discussion on the anatomical correlates of cerebral dominance (Finger, 1994). This became an intensely growing field of research where anatomists focused their attention on either macroscopic (e.g., volume of gyri) or microscopic (e.g., cytoarchitectonic) differences between the two hemispheres. However, a handful of researchers faithful to their belief on the importance of brain connections have tried to explain cerebral dominance in terms of white matter asymmetry. Their efforts have often been limited to mere speculation, for the availability of reliable methods to trace connections in the human brain being lacking for decades. Recent developments in magnetic resonance imaging (MRI) have introduced new methods, based on diffusion imaging tractography that can reconstruct white matter trajectories in the living human brain (Basser et al., 2000; Le Bihan, 2003). The resultant influx of information on human connective anatomy derived from tractography is likely to fill the gap on our anatomical knowledge of human brain connections and reinvigorate models of cognition based on asymmetrical distribution of large-scale networks (Catani & Mesulam, 2008).

An overview of the hodological (pathway-based) approach to cerebral dominance and its historical context, with a special focus on the perisylvian networks, constitutes

the subject matter of this chapter. We first focus on the nineteenth-century postmortem studies of white matter tracts and the models of brain function and cerebral dominance based on those anatomical findings. We then survey twentieth-century studies derived from blunt dissections and neuroimaging and highlight their advantages and limitations. Finally, we present preliminary contributions from diffusion imaging tractography to the anatomy of the perisylvian networks, its heterogeneity in the normal population, and possible functional and behavioral correlates of different patterns of lateralization. Other tracts such as the uncinate, the cingulum, and the corticospinal and cerebellar tracts will also be discussed. One outcome of this review will be to underline the merits of the hodological approach to cerebral dominance and its modern pursuit with diffusion imaging tractography.

### **Early Hodological Approaches to Higher Cognitive Functions and Cerebral Dominance**

The seventeenth century was a time of great accomplishments in the brain sciences, where anatomists called for a more realistic model of brain function than one tied to the pineal gland and spirits flowing from the ventricles into the hollow nerves (Smith, 2007). For the first time, distinct anatomical features of the brain surface were highlighted (e.g., lateral fissure as the most prominent cleft of the cerebral hemisphere) and the anatomy of previously unknown structures described in some details (e.g., corpus striatus). Others, such as Nicolaus Steno (1669), began to draw attention to the complexity of the fiber system:

We need only view a dissection of that large mass, the brain, to have ground to bewail our ignorance. On the very surface you see varieties which deserve your admiration: but when you look into its inner substance you are utterly in the dark, being able to say nothing more than that there are two substances, one greyish and the other white, which last is continuous with the nerves distributed all over the body. [...] If this substance is everywhere fibrous, as it appears in many places to be, you must own that these fibres are disposed in the most artful manner; since all the diversity of our sensations and motions depend upon them. We admire the contrivance of the fibres of every muscle, and ought still more to admire their disposition in the brain, where an infinite number of them contained in a very small space, do each execute their particular offices without confusion or disorder. (Translated in Stirling, 1902, p. 32)

Despite these early anatomical achievements and insightful writings, new findings on the anatomy of white matter and novel ideas about the functional correlates of brain connections were not forthcoming. Throughout the eighteenth century, the development of physiological methods to study the nervous tissue allowed the formulation of theories of nerve conduction as scientists moved away from “fluidist” or “vibratory” explanations and began to experiment with electricity. This was an important development, although it resulted in the shifting of attention from human to animal anatomy and from the central nervous system to peripheral nerves.

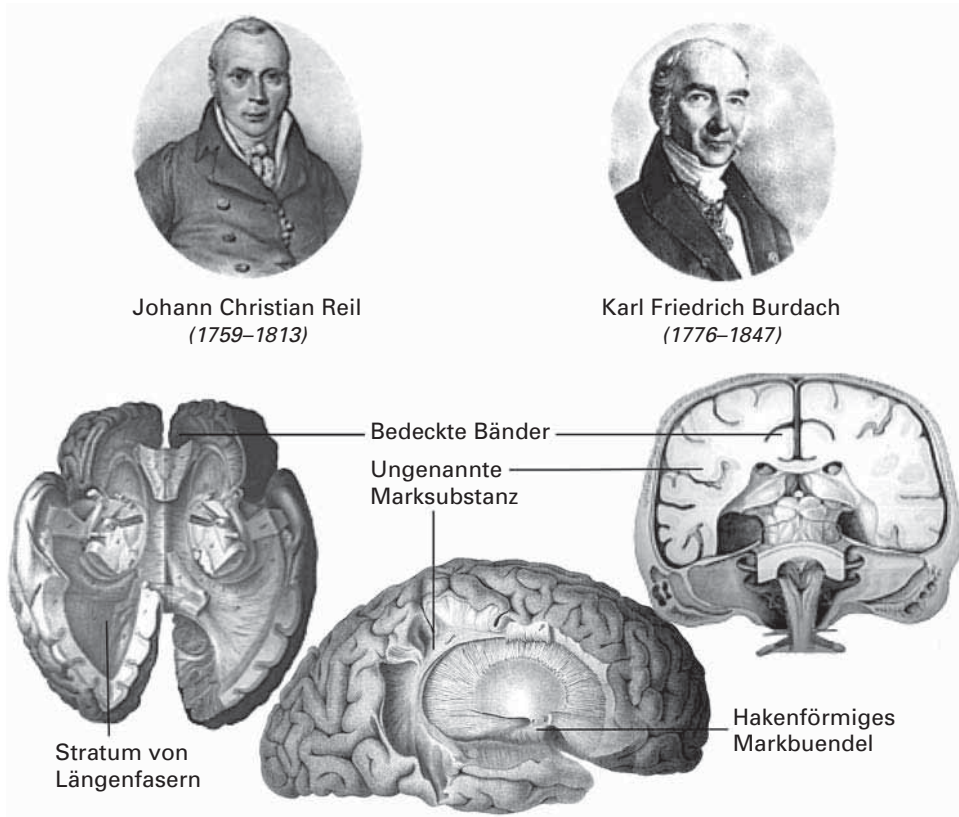
The emergence of the hodological theme as a central component of neurological and psychiatric thinking took place in the nineteenth century and can be attributed to the confluence of two developments: the extension of neuroanatomical research from a description of surface morphology to the dissections of the subcortical tracts, and the spread of “associationist” models of cognitive functions from the realm of psychology to that of neurology and psychiatry (Catani & Mesulam, 2008). An obvious conduit for this convergence was the identification of white matter pathways. Below, we review the pioneering anatomical work of Johann Christian Reil and Karl Friedrich Burdach, which led to the discovery of most association tracts of the human brain. We then introduce the work of Theodor Hermann Meynert and his associationist school, which had a profound influence across countries, continents, and centuries. In the final section of this first part, we discuss the disconnection paradigm derived from associationist theory and Hugo Liepmann’s model of cerebral dominance based on the asymmetry of large-scale sensory-motor networks for praxis.

### **The Discovery of the Association White Matter Tracts**

The first development pivotal to the emergence of the hodological approach to brain function was the identification of the association tracts connecting distant regions within the same cerebral hemisphere. Several anatomists made important contributions to this field, but Johann Christian Reil and Karl Friedrich Burdach (see figure 7.1) stand out for the originality of their findings and the far-reaching influence of their writings.

In 1788 Johann Christian Reil became professor at the University of Halle and director of the Clinical Institute at the age of 29 (Scharf, 1960). In 1795 he founded the first physiology journal in Germany, the *Archiv für die Physiologie*, which he used as a vehicle for many publications about anatomy and physiology, including his own description of cortical and subcortical brain structures (Reil, 1809a, 1812b). His anatomical discoveries derived from the development of a method based on the soaking of the brain in alcohol (initially he used brandy) that made it more suitable for dissection (Reil, 1808). This method allowed him to reveal the course of the white matter bundles running beneath the major convolutions of the human brain (see figure 7.1). Among the tracts that he identified were the medial curving fibers within the cingulate gyrus (i.e., *Bedeckte Bänder* or *Längenbänder*; Reil, 1812b) and the lateral arching connections coursing beneath the perisylvian fronto-parieto-temporal gyri that he described as the unnamed white matter substance (i.e., *Ungenannte Marksubstanz*; Reil, 1812a). Other tracts that he identified on the most ventral part of the brain are the hooked-shaped fibers behind the insula (i.e., *Hakenförmiges Markbuendel*; Reil, 1809b) and a longitudinal bundle between the occipital and temporal lobes (i.e., *Stratum von Längenfasern*; Reil, 1812b).

Reil illustrated and commented on the presence of these tracts on both hemispheres and their possible role:

**Figure 7.1**

Johann Christian Reil and Karl Friedrich Burdach described for the first time the association tracts of the human brain. Here the original drawings from their work are shown (the figures on the left and in the middle are from Reil).

**Table 7.1**

Nomenclatures for the association tracts

Reil (1809b, 1812a, 1812b)	Burdach (1822)	<i>Nomina Anatomica</i> (1989)
<i>Ungenannte Marksubstanz</i>	<i>Bogenbündel (arcuatus)</i>	Arcuate fasciculus
<i>Hakenförmiges Markbündel</i>	<i>Hakenbündel (unciformes)</i>	Uncinate fasciculus
<i>Stratum von Längenfaseren</i>	<i>Längenbündel (longitudinalis inferior)</i>	Inferior longitudinal fasciculus
<i>Bedeckte Bänder</i>	<i>Zwingen (cingula)</i>	Cingulum

Each hemisphere is an independent organ and forms a closed loop in its own; both loops flow into each other through the mentioned structures [arcuate and uncinata]. (Reil, 1809b)

Reil's findings were confirmed a decade later by Karl Friedrich Burdach. Burdach was conferred doctor in medicine at Leipzig in 1799 and received a professorship for anatomy, physiology, and forensic medicine in Dorpat in 1811 (Meyer, 1970). Here he commenced his anatomical dissections of the brain that he continued after moving to Königsberg as director of the Anatomical Institute. His studies culminated in the *Vom Baue und Leben des Gehirns*. This is a three-volume textbook containing confirmatory dissections of Reil's findings and his own original descriptions of some previously unidentified tracts (Burdach, 1822), including the fibers connecting the occipital to the frontal lobe, later identified as part of the inferior fronto-occipital fasciculus (Curran, 1909). He also used Latin names for the major tracts, which became widely adopted and still remain almost unchanged in the current international anatomical nomenclature (see table 7.1; Committee, 1989).

Both Reil and Burdach were fascinated by Schelling's natural philosophy, which inspired their functional interpretations and speculative reflections (Meyer, 1970). However their functional inferences were either dismissive of the role of the association tracts (e.g., Reil) or based on erroneous physiological speculations (e.g., Burdach):

The core [of the brain] is constituted by the organizations of the crus cerebri [*Hirnschenkel*] and the corpus callosum [*Balken*]. These together with the gyri and the grey matter seem to be the fundamental component of the brain, everything else seems to be just connection and transduction apparatus. (Reil, 1809c)

Fantasy is warm and lively; organically linked to blood circulation and can therefore be excited by the fast change of blood, resulting in a stronger tension in the brain. Reason in contrast is cold and cautious; any tempestuous movement is hostile to it [...]. The longitudinal system [association fibers] is more closely linked to the blood vessels [...] its alert activation causes more blood to be drawn to the vascular plexus [...]. The transverse [commissural] system on the contrary is in no special relation to the vascular system. (Burdach, 1826)

This theoretical vacuum left the field open to the triumph of cortical localizationist theories and the fierce antilocalizationist opposition based on holistic stances. One would have to wait until the second half of the century for the emergence of the hodological theme following the spread of "associationist" models of cognitive functions from the realm of psychology to that of neurology and psychiatry (James, 1890; Meynert, 1885; Wundt, 1904). According to the associationist doctrine, the formation of concepts, the recall of memories, the naming of objects, and even the spontaneous and voluntary initiation of movement, required the associative convergence (or integration) of information from multiple sources. The association tracts seemed to be the ideal anatomical substrate for such a theory.

### Meynert's Associationist Theory of Brain Function

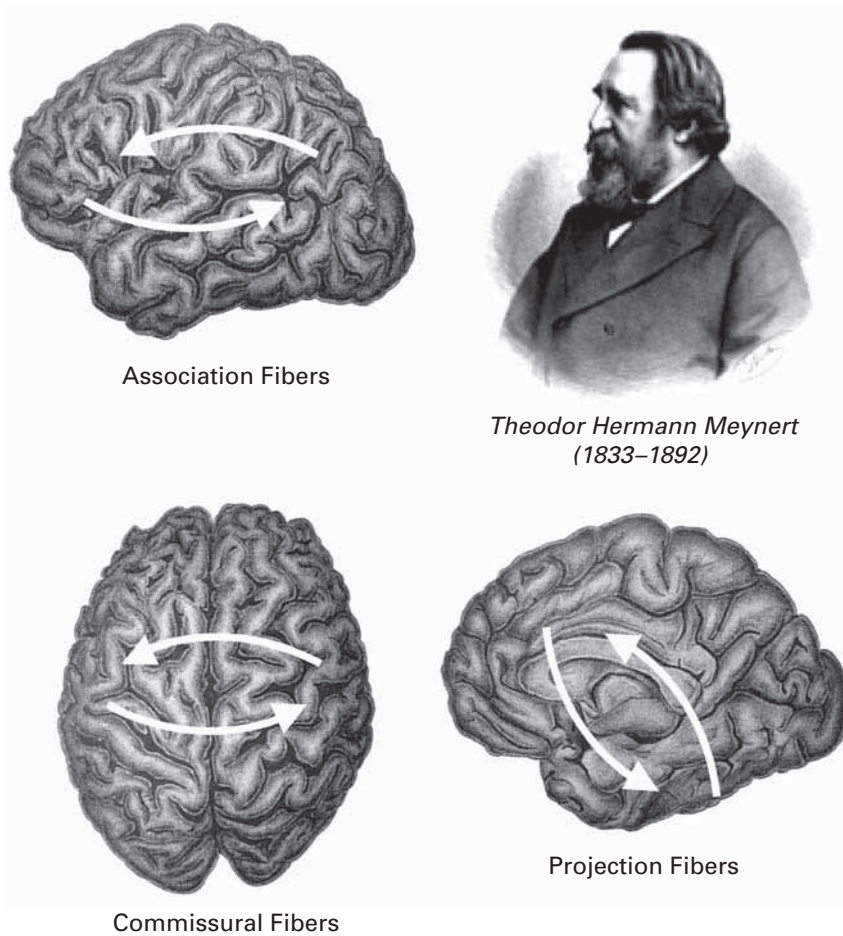
The idea of association has roots in Aristotle's writing and has been passed down the centuries from Epicurus through Hobbes to Hartley (Glassman & Buckingham, 2007). However, the credit for the formulation of an associationist theory grounded on anatomy falls to a psychiatrist known by his contemporaries as the great brain-anatomist, Theodor Meynert, Professor of Nervous Diseases and Director of the Psychiatric Clinic in Vienna. He took an original position with regard to the explanation of brain function and mental disorders (Catani & ffytche, 2005). He first rejected contemporary theories of predisposition, which became in psychiatry the theory of moral insanity:

As regards to the theory of predisposition, and more particularly the doctrine of hereditary, which has been carried to the extreme of assuming the existence of innate idea, and which in clinical medicine, has led to the erroneous theory of moral insanity, I have deemed it necessary to criticise, in its proper connections, Darwin's theory of the inheritance of acquired faculties, as has been done before me by other German authors, among them DuBois-Reymond and Weissman. It is taking altogether too simple a view of things, to regard morality as one of man's talents, and as a definite psychical property which is present in some persons and lacking in others. (Meynert, 1885, preface, viii)

Thus, "dissatisfied with the statistical method, which laid inordinate stress upon hereditary predisposition to disease," Meynert resolved for an anatomical approach to mental disorders:

In view of the necessity of starting from anatomical facts, I have endeavored, in every case, not only to give due weight to the structure of the brain as the fundamental basis for the various forms of disease, but have endeavored, with the same end in view, to insist upon and to explain every visible symptom exhibited by the patient. (Meynert, 1885, preface, vii)

Meynert's ambitious clinical research program aimed to establish the anatomical bases not only of mental disorders but also of specific symptoms; the success of its realization depending entirely on the deep anatomical knowledge of the human brain. In 1884 he published in German *Psychiatry—Clinical Treatise on Diseases of the Fore-Brain based upon a study of its structure, functions, and nutrition*, impelled by the conviction of a need for a "scientific" treatise on mental disease. The title is a direct attack on the "science of psychiatry [that] has been too largely subjective" and refers "to the fundamental studies [of structure] indispensable to an understanding of the clinical manifestations of mental disease" (Meynert, 1885, p. vi). The first volume of the *Treatise*, which Sachs translated and published in English the year after (Meynert, 1885), contains Meynert's description and classification of the main white matter tracts of the brain (see figure 7.2). Before him, other anatomists such as Vieussens, Vicq d'Azyr, Reil, Burdach, and Gall had described differences in origin, course, and termination of fibers, but Meynert was the first to put forward an orderly classification



**Figure 7.2**

Theodore Hermann Meynert and his classification of white matter in association, commissural, and projection fibers.

(Drawings of the brain are from Catani and ffytche, 2005, and were originally produced by Luca Santanicchia)

of white matter fibers into three groups. The first group consisted of *projection* fibers, the ascending or descending pathways arising and terminating in the cortex, the second of *commissural* fibers, which connect cortex in both hemispheres, and the third of *association* fibers, which connect cortical regions within a hemisphere. He further subdivided the association tracts (or “*fibrae propriae*”) into two groups, the *short U-shaped fibers* and the *long association bundles*, according to their cortical projections and the length of their subcortical course:

The U-shaped bundles of the cortex do not necessarily extend simply from one convolution to one next adjoining, but they may skip one, two, three, or an entire series of convolutions, and may thus join convolutions which are united among themselves to a convolution lying at some distance from these. The shortest *fibrae propriae* lie nearest to the cortex; the longest at the greatest depth, and are separated from the cortex by other intervening *fibrae propriae*, the length of which increases gradatim from the surface inward. (Meynert, 1885, p. 39)

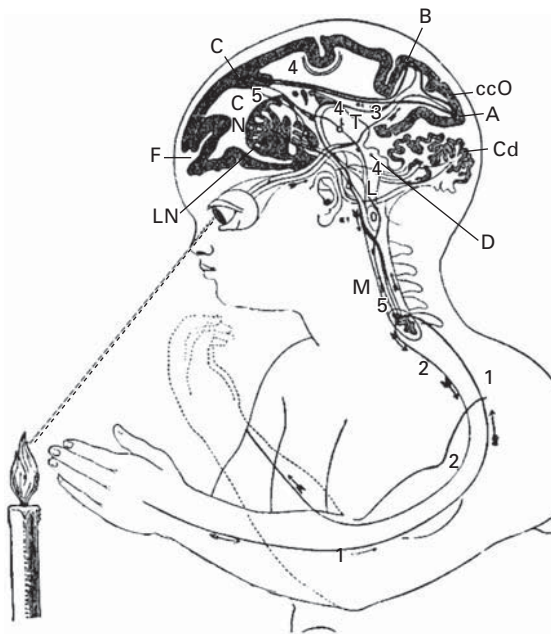
Once he had laid down the anatomical foundations of the model Meynert defined a specific role for each group of connections.

First Meynert extended Bell’s division of the sensory ascending (centrifugal) and motor descending (centripetal) tracts of the spinal cord to the brain, thus considering the projection fibers, the major communication system between specialized cortical regions and peripheral sensory organs and muscles. Then he added a layer of complexity to the model by introducing the association fiber system:

In examining the structure of the hemispheres, and remembering that different, distinctly limited and functionally separated portions of the cortex receive impressions from the various senses, we may naturally infer that the association-bundles, the *fibrae propriae* of the cortex, which form anatomical connections between the different cortical regions, effect the physiological associations of the images which are stored in these various parts. (Meynert, 1885, p. 153)

Thus, in this model, the cortex, through its projection and association connection system, becomes a place not only for sensation and motor response but also for higher cognitive functions and complex behaviors such as “logical functions” (e.g., *Schlussprozess*, induction), “recollection,” “learning,” and “initiation of conscious movement” (see figure 7.3). Meynert was an outstanding anatomist of international repute who attracted young doctors eager to learn anatomy from all over Europe and North America. Among them were Carl Wernicke, Sergei Korsakoff, Auguste-Henri Forel, Paul Flechsig, Bernard Sachs, and Sigmund Freud. Although Meynert used his neuroanatomical findings to develop a theory of psychological function, which had profound influence on the early development of psychiatry, it was one of his most talented students, Carl Wernicke, who brought the associationist model to the clinic by applying the disconnection paradigm to explain neurological and psychiatric disorders.





### Figure Legend

- A. Part of the visual cortex;
- B. Part of the cortical centre for cutaneous sensation;
- C. A centre in the cortex for sensations of innervation;
- Cd. Cerebellum;
- CN. Caudate nucleus;
- D. Mesencephalon;
- F. Frontal cortex;
- L. Pons Variolii;
- LN. Nucleus lenticularis;
- M. Medulla spinalis, terminating with a cross-section of the cervical spinal cord;
- ccO. Occipital cortex;
- T. Thalamus opticus

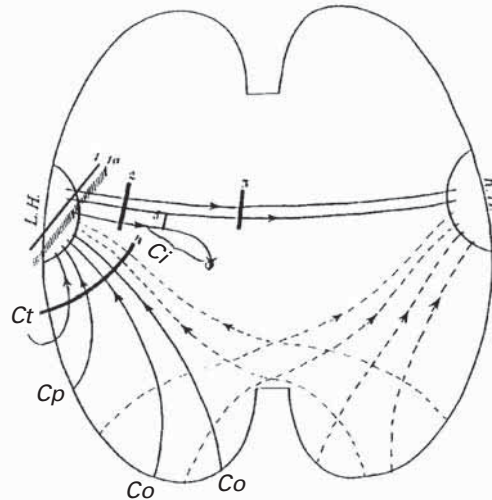
**Figure 7.3**

Diagram from Meynert's (1885) textbook used to explain the formation of conscious movements in a child's brain. Below is the Meynert's original explanation of the figure: "Let us suppose a flame to have injured the hand of a child, and that the latter withdrew the hand from the flame. This movement (the withdrawal of the hand) will be effected, without the intervention of the conscious impulses, by an impulse conveyed from the injured part by the centripetal tract 1, and transmitted through a spinal-cord centre along the path 2, which withdraws the hand from the flame. [...] The following records of this act will be transmitted to the cortex through the agency of the projection-systems: first, the visual image of the flame from the eye along the tract 3A; secondly, a painful sensation from the injured part along the tract 4B. Thirdly [...] the innervation-sensation C acts through the centrifugally-conducting tract 5 upon the central origin of those anterior roots which, through reflex excitation, protected the arm against the flame. Since the centre C is connected with the association bundle CB, CA, and the latter with one another by the bundle BA, the child need not actually burn its hand again before guarding against the flame; but the memory of the flame and of its effect (through association with the centre in which the painful sensation has been rooted), will suffice, through the one or the other of these associations, to initiate a movement which will put the arm beyond the reach of the flame."

### Disconnection Syndromes and Early Hodological Theories of Hemispheric Dominance

Carl Wernicke (1848–1904) was born in Tarnowitz, which was in those days a town in Prussian Upper Silesia but is now in Poland. He read medicine in Breslau (Wrocław) where he undertook most of his studies except for a six-month period in Vienna with Meynert (Keyser, 1994). Wernicke was greatly influenced by his teacher's associationist theory, and in his M.D. thesis "*Der aphasische Symptomencomplex*" he postulated that if higher cognitive functions arise through associative connections, disorders of higher function must derive from their breakdown. On the basis of this corollary he explained a disconnection syndrome that was to become the prototype for all others—conduction aphasia (*Leitungsaphasie*, Wernicke, 1874), that he later described as a language disorder characterized by normal comprehension and intact verbal fluency but impaired repetition due to a lesion of the fibers connecting Broca's and Wernicke's areas (Wernicke, 1908). In Breslau Wernicke established one of the most important associationist schools (Catani & ffytche, 2005). When the disconnection paradigm was applied not only to aphasia but also to other neurological (e.g., associative agnosia; Lissauer, 1890) and psychiatric (e.g., schizophrenia; Wernicke, 1906) disorders. However, it soon became evident that the disconnectionist paradigm per se was not sufficient to explain the association between certain manifestations and localization of lesion in one hemisphere (i.e., lateralization of symptoms). Surprisingly, Wernicke explained the lateralization of language disorders by postulating the existence of specialized language centers in the left hemisphere. Similarly, Jules Dejerine when describing a disconnection syndrome characterized by inability to read but preserved writing, namely pure alexia, localized the center specialized for reading in the left angular gyrus. It was one of Wernicke's students, Hugo Liepmann (see figure 7.4), who put forward an alternative explanation for the hemispheric dominance: the anatomical lateralization of connections.

Hugo Liepmann joined Wernicke's clinic as an assistant in 1895 and carried the Breslau associationist doctrine to Berlin when he left four years later (Goldenberg, 2003). Here he developed an interest in the motor system, which led him to propose a disconnectionist account of goal-directed movement disorders—the apraxias. Liepmann's theory of apraxia, first published in 1900, was based on his case study of a 48-year-old imperial counselor (*Regierungsrat*) who was admitted to the Berlin psychiatric service with a diagnosis of mixed aphasia and dementia (Liepmann, 1900). Although his spontaneous movements were normal (e.g., using a spoon while eating), a striking feature of the patient was that when asked to perform or copy gestures with his hand (e.g., point to your nose) or manipulate imaginary objects (e.g., show how you use a harmonica), he did so in an absurd fashion. Since the patient was able to understand the command, had no visual impairment, and had no evidence of paralysis, Liepmann formulated a network model for praxis (see figure 7.4) and



*Ct, temporal cortex, Co, Occipital cortex; Cp, parietal cortex; Ci*

**Figure 7.4**

Hugo Liepmann and his diagrammatic explanation of the network underlying praxis and apraxia syndrome (from Liepmann, 1925). The model implies a general left-hemisphere (L. H.) dominance for movement control based on the asymmetrical distribution of association and commissural sensory-motor connections. The left motor region receives connections mainly from the temporal (Ct), parietal (Cp), and occipital (Co) cortex of the left hemisphere whereas the corresponding connections from the right hemisphere (R. H.) have only “subordinate significance” (dashed lines). Bars indicate possible lesion sites causing apraxia along the network. C.i., capsula interna.

hypothesized a disconnection of visual, auditory, and somatosensory areas from motor areas to explain the symptoms displayed by the counselor:

I do not think there is a praxis center, or even that it is located [...] in the supramarginal gyrus. I never postulated that the apraxia of the counselor is only due to a lesion in the supramarginal gyrus or that this is true for all cases of apraxia. In my case report I have postulated an interruption of the sensory-motor region of the right extremities from the most important cortical regions of both hemispheres, and thought that in this case the evidence is the disruption of the white matter of the supramarginal gyrus and the callosal connections from the other side. And I was right as the autopsy confirmed. (Liepmann, 1908, p. 77)

Liepmann generalized his conclusions to all cases of apraxia for which he postulated a disconnection mechanism at different segments and nodes of the network and speculated on the leftward asymmetry of the praxis networks to explain the higher frequency of left hemisphere lesions in these patients:

Eupraxis movement results from the collaboration of many brain regions with the hand area. Lesions to the cortical regions and especially their connections with the hand centre at different points can impair praxis. [...] Especially the left hemisphere hand centre including its connections to the rest of the brain in particular in the same hemisphere is irreplaceable, therefore, lesions to the left hemisphere are disastrous for praxis of all extremities. (Liepmann, 1908, p. 77)

Unlike his predecessors, Liepmann took an original position to explain the neurobiological underpinnings of left-hemisphere dominance for praxis. His model does not imply the existence of a left-dominant cortical area for complex movement control. Instead, left dominance for praxis is considered the result of an asymmetrical distribution of the sensory-motor pathways: "The contralateral connections are of subordinate importance as compared to the link of the left hand area with the rest of the brain."

Liepmann added that *his diagram is not only relevant to apraxia*, as if it could also explain other lateralized syndromes. Liepmann's explanation was highly speculative in the absence of experimental evidence to support his claims (for a review, see Goldenberg, 2003, 2009). If the associationist school and the disconnectionist paradigm were to replace cortical localizationism in the neurology clinics, anatomical support was urgently needed. In the next sections we review the methodological advancements that took place in the twentieth century and the main findings derived from applying them to the study of the asymmetry of white matter pathways.

### From Postmortem to Neuroimaging Studies of White Matter Lateralization

The techniques developed by early neuroanatomists for gross dissections of white matter tracts led to important anatomical insights but were inadequate for quantitative studies of tract lateralization. A methodological revolution in this field occurred at the turn of the nineteenth century with the development of new techniques of microscopy, specimen preparation, and staining. The introduction, for example, of staining for fiber degeneration, such as the method of Weigert-Pal or Marchi (Bolton, 1898), and the study of serial sections of the specimens allowed the visualization of tracts in the brain of patients with corticosubcortical lesions (mainly vascular) or in experimentally lesioned animal brains (Ranson et al., 1941). However, these methods as applied to the study of lateralization presented several limitations, including the rarity of lesions occurring in symmetrical regions of the human brain and the difficulty of reconstructing volumes of intercortical pathways from a series of slices along the course of the tracts.

Others tried to ameliorate previous techniques for gross blunt dissections using ingenious methods for preparing the specimens. Examples of this approach are Rosett's (1933) method based on the "microexplosions" of the brain in a gas-compressed tank, or Klingler's (1935) preparation based on the freezing of the brains for several weeks. Following these preparations, the bundles of the large tracts are

mechanically separated and can be manually isolated with great ease. However, blunt dissections require neuroanatomical knowledge, experience, and patience to obtain reliable results, and other methods for studying the cortical cytoarchitecture advanced at a fast pace (Brodmann, 1909). Thus, contrary to what one would have expected from the enthusiasm generated by the associationist ideas, in the first half of the twentieth century the scientific interest for anatomy shifted from connections to cortical cartography. As we will see in the next section, the only exception to this general trend was the study of the corticospinal tract (CST).

In the 1960s an enormous increase in knowledge about connectivity arose from the use of cellular transport mechanisms to detect connections between nerve cells (Lanciego & Wouterlood, 2000). Most of the axonal tracing methods are based on active transport mechanisms in the living cell. The tracer is injected into a special brain region and is transported via the axons into connected brain areas (Barbas & Mesulam, 1981; Petrides & Pandya, 1988). Although this method is not applicable to the study of human brain connections, the interest generated by monkey tracing studies revitalized the hodological theme. With the development of brain imaging many clinicians began to expand once again the clinicopathological correlation beyond cortical areas and alternative hypothesis emerged for classical cortical syndromes. Naser et al., for example, reported severe nonfluent aphasia in patients with lesions to the subcallosal tract of the left hemisphere, while Leibovitch et al. (1998) described unilateral neglect with lesions of the deep white matter tracts of the temporo-parietal junction (i.e., inferior and superior longitudinal fasciculus). At the same time, the convergence of neuropsychological studies in split-brain patients and the return to the clinicoanatomical correlation reawakened interest in the neuroanatomical correlates of functional lateralization (Geschwind & Levitsky, 1968). Nevertheless, despite networks and connections being a cardinal feature of most of the neurological models proposed at that time, the lack of adequate methodology did not allow for study of lateralization of white matter tracts beyond the CST. It is only in the last decade that MRI has been used in large cohorts to study asymmetry of white matter—in particular, to characterize changes during brain development. Below, the studies on the lateralization of white matter tracts derived from postmortem and structural neuroimaging are reviewed in detail. The advantages and limitations of these studies will be discussed before moving to the final section on diffusion tensor imaging (DTI).

### **Corticospinal Tract and Other Projection Pathways**

The CST is the main descending projection system between the motor cortex and the spinal cord and thereby subserves motor control functions for the muscles of the arms, legs, and trunk. It originates mainly from the precentral frontal region, passing through the internal capsule and brainstem to terminate in the spinal cord. Just before entering into the spinal cord, the CST crosses from one side to the other. The crossing of the CST

was first described by Domenico Mistichelli (1709) and François Pourfour du Petit (1710); but, it is only when Paul Emile Flechsig applied his myelogenetic method to sections of newborn brains that experimental evidence for CST asymmetry emerged. Flechsig found that in the majority of specimens (75%) most of the CST fibers cross from one side to the other, but the crossing pattern differs between the two sides in 40% of the brains (Flechsig, 1876). Among these asymmetrical cases, the uncrossed component was more often larger on the right side of the spinal cord than on the left. Yakovlev and Rakic (1966) used Flechsig's method in a larger sample, and they not only reiterated his findings but found that the decussating bundle of the left CST was larger and crossed the midline at a most dorsal level in 87% of cases. Considering that the fibers crossing at the most rostral level are likely to originate from the hand region of the precentral gyrus, these observations were thought to be of relevance to handedness. Kertesz and Geschwind (1971) studied the variation on the crossing pattern with respect to manual preference in adults. They confirmed the finding of Yakovlev and Rakic (73% of cases with left-to-right rostral crossing), but they found no correlation with handedness. Similarly Nathan and colleagues (Nathan et al., 1990) described a greater number of pyramidal fibers in the right side of the spinal cord in 75% of cases. Because of the higher incidence of right-handedness in the population, reaching approximately 90%, Nathan et al. (1990) rejected the hypothesis that CST asymmetry may be a structural correlate for the lateralization of handedness. A recent work studied hemispheric differences in the volume of the CST, which was found to be greater on the left as compared to the right in 70% of subjects (Rademacher et al., 2001).

Voxel-based morphometry (VBM) studies of MRI structural images (e.g., T1 weighted) show larger white matter volumes in the left internal capsule without a clear association with handedness (Good et al., 2001; Hervé et al., 2006). Application of MRI to large cohorts of children and adolescents shows a greater age-related increase in white matter density of the left internal capsule compared to the right throughout childhood and adolescence (Paus et al., 1999). A well-known problem with the VBM approach is the difficulty in attributing hemispheric differences to specific white matter tracts. For example, the differences in the internal capsule mentioned above are not necessarily located in the cortical spinal tract but could involve other fibers of the projection system.

The projection system also includes ascending pathways of which the *thalamic radiations* represent the largest portion. Most of the post-mortem and neuroimaging studies reported no difference between left and right thalamus with respect to volume and neuronal density. Eidelberg and Galaburda (1982) showed a slight rightward asymmetry of the medial geniculate nucleus and a leftward asymmetry of the lateralis posterior nucleus, which projects to the inferior parietal lobule. The latter findings have been suggested to have some association with development of left dominance for language. However, to date there are no studies that have addressed the lateraliza-

tion of the thalamic projections. Bürgel and colleagues (2006) recently showed asymmetries in the position and size of the human *optic radiation* using post-mortem dissections. In their sample of 10 subjects, nine showed a leftward asymmetry in the volume of the lateral geniculate and optic radiations.

### Association Tracts

The *uncinate fasciculus* is the main association tract between the anterior temporal lobe and the inferior orbitofrontal cortex and is considered part of the extended limbic system. Pathology involving the uncinate fibers and its cortical projections has been associated with several symptoms including memory impairment, language deficits, and neuropsychiatric syndromes (Mega et al., 1997). The asymmetry of the volume and density of fibers of the uncinate fasciculus has been revealed in only one study using microscopy on human brains. The uncinate fasciculus was asymmetrical in 80% of subjects, containing on average 30% more fibers on the right than the left hemisphere (Highley et al., 2002). VBM studies of the white matter region containing uncinate fibers (i.e., anterior floor of the external capsule) are contrasting with both leftward (Hervé et al., 2006) and rightward (Good et al., 2001) asymmetry reported.

The *arcuate fasciculus* is a large association tract connecting perisylvian areas of the frontal, parietal, and temporal lobes. The arcuate fasciculus is involved in higher cognitive functions showing various degrees of functional lateralization such as language, visuospatial processing, and social behavior. MRI has been used for VBM studies of the arcuate fasciculus. In general, the white matter regions containing fibers of the arcuate fasciculus are larger on the left compared to right (Good et al., 2001; Hervé et al., 2006). However, there is also some evidence for regional differences in the asymmetry within different segments of the arcuate fasciculus, with most ventral regions being larger on the left and dorsal regions being larger on the right (Good et al., 2001). Furthermore, an increase in white matter density in the left arcuate fasciculus during childhood and adolescence has been reported (Paus et al., 1999). In a recent study, Blanton et al. (2004) documented significant gender differences in the white matter of the left inferior frontal gyrus, a region containing anterior projections of the arcuate fasciculus: boys but not girls showed a linear age-related increase in the white matter volume in this region. It remains to be determined whether such differences are to be attributed to only the arcuate fasciculus or other tracts connecting perisylvian regions. This is an issue that has been partially resolved with diffusion-tensor imaging (DTI) tractography.

### DTI Contribution to Pathways Lateralization

In 1985, a modification of conventional MRI sequences permitted quantification of the diffusion characteristics of water molecules in vivo (Le Bihan & Breton, 1985).

Given that within cerebral white matter, water molecules diffuse more freely along myelinated tracts than across them -a property termed anisotropy of diffusion- (Moseley et al., 1990), it is possible to obtain *in vivo* estimates of white matter fiber orientation by measuring the principal direction of diffusivity of water (Basser et al., 1994). This has led to the development of diffusion tensor tractography (Basser et al., 2000; Conturo et al., 1999; Jones et al., 1999; Mori et al., 1999; Poupon et al., 2000), in which white matter tracts are reconstructed in three dimensions by sequentially piecing together discrete and shortly spaced estimates of fiber orientation to form continuous trajectories. Although these tracts are “virtual,” the connections being defined mathematically and not necessarily implying a true axonal pathway, the technique has been used with some success in the living human brain to study the major projection, association, and commissural tracts (Basser et al., 2000; Catani et al., 2002; Lawes et al., 2008; Mori et al., 1999). Diffusion tensor tractography offers the advantage of being completely noninvasive, as previously established methods for tracing fiber pathways, such as those used in axonal tracer studies, are restricted for use in nonhuman primates only. Furthermore, the MRI method used to provide data for the tractography process can be readily obtained on standard MRI systems with acquisition times typically ranging from 5 to 20 minutes (depending on image data quality required). Furthermore tractography offers the possibility of extracting quantitative diffusion indices along the dissected tract, thus obtaining tract-specific measurements indicative of the microstructural organization, composition, and integrity of the fibers of interest. The most used indices are fractional anisotropy (FA; an indirect measure of fiber organization and composition) and mean diffusivity (an indirect measure of tissue density; Jones, 2008). The number of streamlines is also commonly used as a surrogate measure of tract volume (Catani et al., 2007). These indices have been used in recent years to study the lateralization pattern of the macro- and micro-architecture of the projection and association pathways. Below, we review the DTI studies that have reported data on lateralization.

### **Projection Tracts**

DTI has been applied to study the *in vivo* asymmetry of the CST at different levels (e.g., corona radiata, internal capsule) using VBM, region-of-interest (ROI), and tract-specific approaches (see table 7.2; Catani, 2006).

Büchel et al. (2004) used VBM on DTI data sets to show, in a right-handed group of healthy adults, higher FA values in a region of the left hemisphere corresponding to the white matter of the precentral gyrus. The reverse pattern was found in a group of left-handers. Using a similar approach, Park et al. (2004) found higher FA in the right internal capsule (anterior limb) compared to the left, while Ardekani and colleagues (Ardekani et al., 2007) found reduced FA in the right internal capsule (posterior limb) compared to the left.



**Table 7.2**

Methods for the analysis of diffusion tensor imaging data (from Catani, 2006)

Data-led analysis	Hypothesis-led analysis
<p><i>Whole-brain voxel-based morphometry (VBM) analysis:</i></p> <p>This is an operator-independent approach that allows the analysis of the entire brain volumes without an a priori hypothesis regarding the anatomical location of between-groups differences. This can be very useful as exploratory analysis, especially where white matter changes are diffuse. Adapting the voxel-based morphometry approach, developed for functional and structural imaging data [14], to DT-MRI data, however, is not necessarily straightforward. Coregistration of low-resolution, high-contrast fractional anisotropy maps may generate significant misregistration and partial volume artifacts in regions of high and low anisotropy (e.g., around the ventricles). Also the accurate localization of differences is difficult as data are often heavily smoothed as part of the preprocessing. This results in low-resolution parametric maps from which to infer group differences. Anatomical identification of regions exhibiting significant group differences can be difficult, as clusters of voxels will not typically lie neatly within a single tract.</p>	<p><i>Region-of-interest (ROI) approach:</i></p> <p>The ROI approach allows the identification of between-groups differences in a specific brain region. Specification of the anatomical location of the putative differences is therefore a prerequisite. Hence, the ROI approach is often used to test findings derived from previous studies (e.g., voxel-based morphometry). The major problem with the ROI approach is the inability to attribute changes to a specific tract within regions containing two or more white matter bundles. Also, the manual definition of a ROI for the entire length of a tract is rarely achieved. Further, the conventional ROI approach may lack sufficient statistical power because of the high degree of intra- and intersubject variation of the fractional anisotropy values, even within a highly homogeneous tract.</p> <p><i>Tract-specific measurements:</i></p> <p>This approach allows the testing of between-groups differences within a specific tract of interest. It overcomes some of the limitations of the voxel-based morphometry and ROI analysis (e.g., better anatomical localization of the single tracts, analysis throughout almost the entire length of the bundle). However, it suffers from a number of problems including a priori knowledge of the anatomy (operator-dependent placement of regions from which tracking starts) and difficulties in resolving the crossing or meeting of different fibers. Hence reconstructions of the virtual tracts may be artifactual due to the presence of false negatives (partial reconstruction of the bundles) and false positives (visualization of nonexistent tracts).</p>

The same authors used a ROI approach to show higher FA in the anterior limb of the right internal capsule compared to the left but lower FA in the posterior limb of the right internal capsule compared to the left. Toosy et al. (2003) found higher FA on the right posterior internal capsule compared to the left with a similar ROI approach, while Westerhausen and colleagues (Westerhausen et al., 2007) obtained the opposite results, with higher FA on the left posterior internal capsule compared to the right. The latter authors were unable to show an interaction between asymmetry and handedness. Thus, overall VBM and ROI studies of FA maps show contrasting results for the asymmetry of the CST.

To partially overcome some of the limitations of the VBM and ROI approaches, some groups have used tract-specific measurements (i.e., sampling the diffusion parameters along the virtually dissected tract of interest). Reich et al. (2006) found no differences in volume and FA between the left and right CST in adults. Euvathingal and colleagues (Euvathingal et al., 2007) showed higher FA on the left CST compared to the right in 70% of a group of healthy children and adolescents. Differences between studies may be related to sample size, age range, DTI acquisition parameters, and selection of the ROI for tractography. Our investigation on a group of 40 right-handed adults (20 males and 20 females) with homogeneous age range (18–22 years; see figure 7.5/plate 3) shows that overall the CST volume has a moderate, but statistically significant, leftward asymmetry,  $T(39) = 5.3$  ( $p < .001$ ). This pattern of asymmetry is present in 70% (28/40) of the subjects, while 12.5% (5/40) have an opposite pattern. The remaining 17.5% (7/40) of the subjects show a bilateral and almost symmetrical distribution. There were no differences in FA and no differences between males and females for both volumes and FA. These results are very similar to the findings derived from previous postmortem dissections (Nathan et al., 1990; Rademacher et al., 2001). By extending the analysis to other fibers of the projection system, we were able to show that although some degree of lateralization is present in other tracts, the CST shows the most significant asymmetry (see figure 7.5/plate 3).

### Association Tracts

DTI has been applied to study the in vivo asymmetry of the larger association tracts. Büchel et al. (2004) used VBM and found higher left FA in a region corresponding to the arcuate fasciculus. Opposite results were reported by Park et al. (2004) with higher FA in the right arcuate fasciculus compared to the left. They also found lower FA on the left hemisphere for the uncinate and inferior and superior longitudinal fasciculus but reduced FA in the right cingulum compared to the right.

A ROI approach has been adopted for a number of regions containing the major association tracts. Higher FA was found in the left superior longitudinal fasciculus compared to the right (Makris et al., 2005), uncinate (Kubicki et al., 2002; Rodrigo et al., 2007), and cingulum (Gong et al., 2005; Huster et al., 2007).

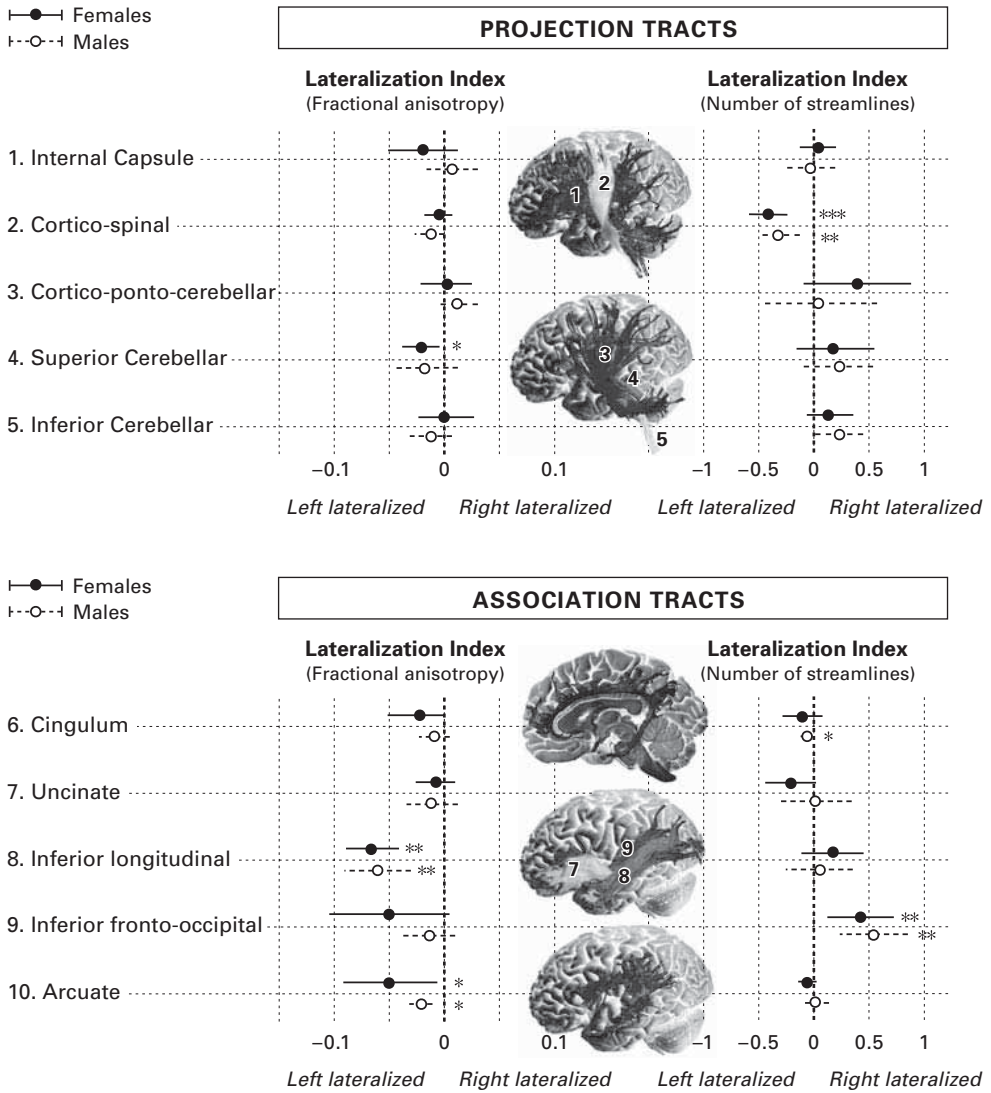


Figure 7.5 (plate 3)

Asymmetry of the projection and association tracts. The images are based on tractography indices derived from the analysis of 40 healthy subjects. \* $p < .05$ ; \*\* $p < .01$ ; \*\*\* $p < .001$ . Intervals are 95% confidence intervals.

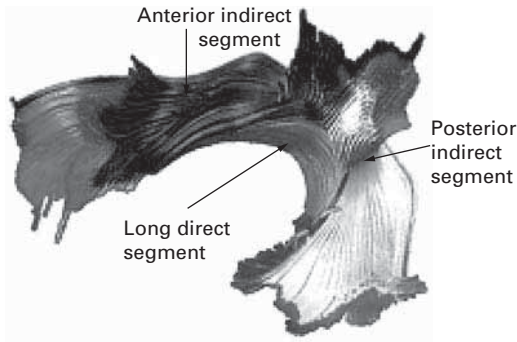
Eluvathingal et al. (2007) used tract-specific measurements and found higher FA in the left uncinate compared to the right in a group of children and adolescents. Wakana et al. (2007) dissected the major association tracts in 10 healthy subjects and found greater volume for the left superior longitudinal fasciculus, inferior longitudinal fasciculus, and cingulum. Ashtari et al. (2007) found higher FA in the left inferior longitudinal fasciculus. Our own data confirm a leftward FA asymmetry for the inferior longitudinal fasciculus,  $T(39) = 6.2$  ( $p < .001$ ), and the arcuate fasciculus,  $T(39) = 3$  ( $p < .01$ ). We also found a rightward asymmetry only for the number of streamlines of inferior fronto-occipital fasciculus (see figure 7.5/plate 3).

### **Asymmetry of Perisylvian Pathways and Behavioral Correlates**

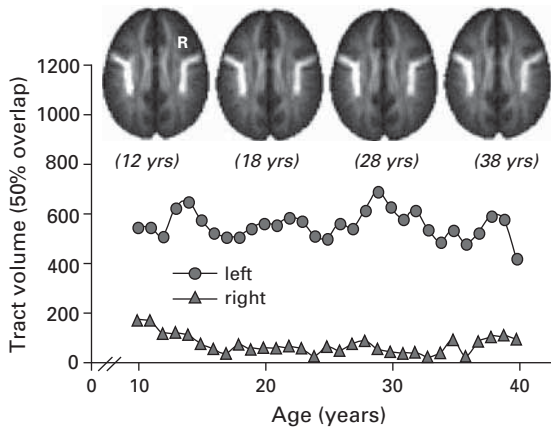
The first tractography studies applied to the perisylvian pathways showed that the anatomy of the arcuate fasciculus is more complex than previously thought (see figure 7.6/plate 4 and figure 2, Catani, Jones, & ffytche, 2005; Parker et al., 2005). In addition to the long direct segment connecting Wernicke's area with Broca's territory (i.e., the arcuate fasciculus *sensu strictu*), there is an indirect pathway consisting of two segments, an anterior segment linking Broca's territory with the inferior parietal lobule (Geschwind's territory), and a posterior segment linking the inferior parietal lobule with Wernicke's territory (Catani et al., 2005). This arrangement not only supports the more flexible architecture of parallel processing (Mesulam, 1990) but also is in keeping with some of the classical neurological models of aphasia, contemporary models of verbal working memory (Baddeley, 2003), and recent functional neuroimaging findings (Jung-Beeman, 2005; Sakai, 2005; Stephan et al., 2003). Additional support for the existence of the three perisylvian segments of the "arcuate fasciculus" comes from other DTI studies (Eluvathingal et al., 2007; Lawes et al., 2008), human intra-operative electrocorticography (Matsumoto et al., 2004), functional connectivity (Schmithorst & Holland, 2007), post-mortem dissections (Lawes et al., 2008), and experiments in homologous parts of the monkey brain (Deacon, 1992).

Tractography is also revealing unexpected findings about the projection of the arcuate fasciculus, whose cortical terminations extend beyond the classical limits of Wernicke's and Broca's areas to include part of the posterior middle temporal gyrus and regions of the posterior middle frontal gyrus and inferior precentral gyrus, respectively (Catani et al., 2005). More anterior and ventral portions of Broca's territory seem to be connected to posterior temporal and occipital regions through the uncinate and the inferior fronto-occipital fasciculus of the ventral pathway system (Anwander et al., 2007; Barrick et al., 2007). Finally tractography applied to language pathways highlights the importance of the inferior parietal cortex as a separate primary language area with dense connections to classical language areas through the indirect pathway. Geschwind's territory corresponds to Brodmann's areas 39 and 40, and although its importance as a linguistic region has been recognized for some time, the exact role of

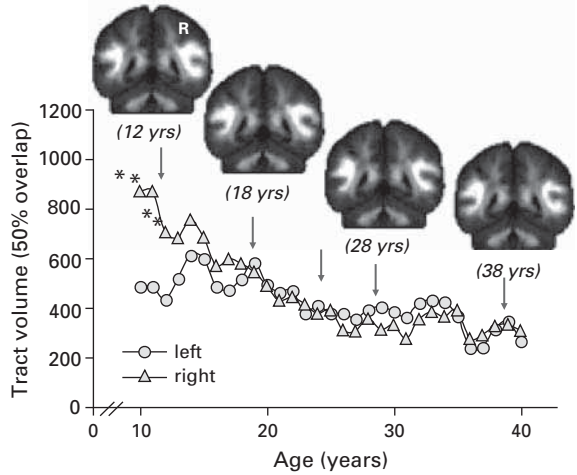
**A Virtual in vivo dissection of the arcuate**



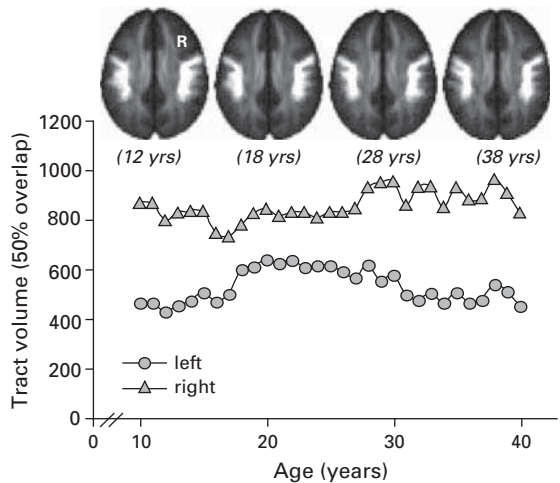
**B Long direct segment**



**C Posterior indirect segment**



**D Anterior indirect segment**



**Figure 7.6 (plate 4)**

(A) Tractography reconstruction of the direct (long segment) and indirect pathway (anterior and posterior segment) of the arcuate fasciculus. (B–D) The lateralization of the three segments of the perisylvian network from childhood to adulthood. The lateralization remains stable for the long and anterior segment, while the posterior segment becomes progressively symmetrical.

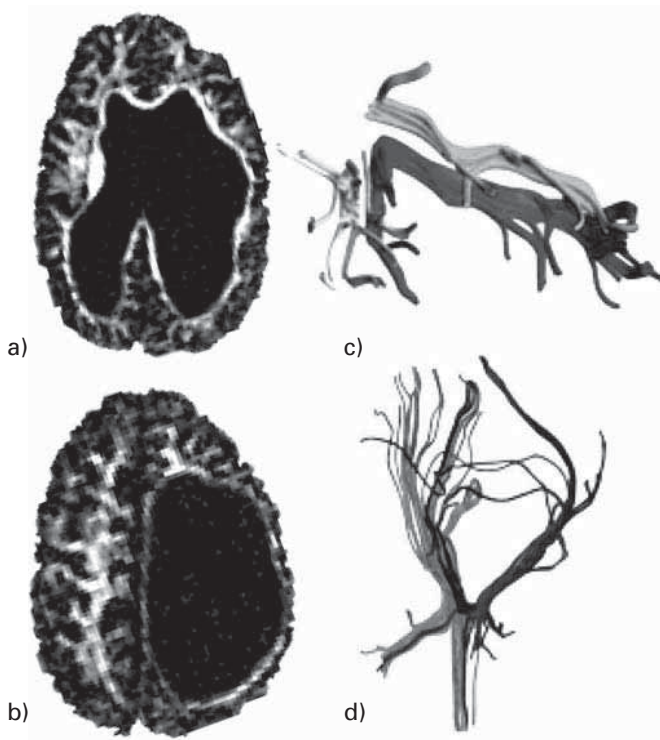
\*Indicates statistical significant difference.

(Panel A reprinted from Catani et al., 2005.)

this area is still largely unknown (Catani et al., 2005). Recent functional imaging studies have shown that Geschwind's territory is part of an extended network activated during comprehension of global coherence of narratives (Martin-Loeches et al., 2008), processing concrete concepts (Sabsevitz et al., 2005), episodic memory retrieval of words (Vilberg & Rugg, 2008), and verbal working memory (Jacquemot & Scott, 2006). Also thanks to its anatomical position, Geschwind's territory is a convergence and integration zone for sensory and motor information and their temporal dynamics, and is therefore well suited to play a key role in self-awareness of speech and actions in general (Jardri et al., 2007). Furthermore cortical thickness of Geschwind's territory has been demonstrated to correlate in bilinguals with proficiency and age at acquisition of the second language (Mechelli et al., 2004).

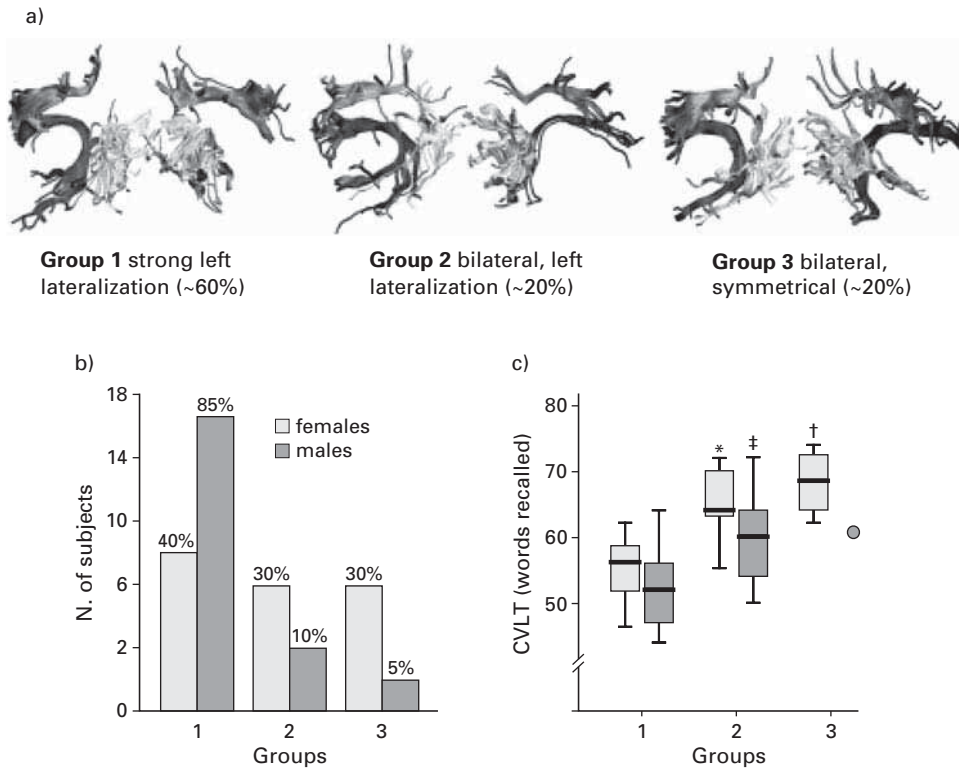
Tractography analysis reveals that the three segments of the arcuate differ in terms of lateralization. The long segment is larger in the left compared to the right, while the anterior segment is larger on the right compared to the left. Both segments remain lateralized throughout adolescence and early adulthood. The posterior segment shows a greater volume in the right compared to the left before adolescence, but throughout adolescence, its volume reduces more on the right than the left, thus causing a shift in the pattern of lateralization that becomes symmetrical (see figure 7.6/plate 4; Pugliese et al., 2008). These modifications in volume are likely to reflect biological changes in white matter accompanying cortical pruning occurring during adolescence. These preliminary data are of special relevance to the issue of plasticity after brain injury. Several functional studies have demonstrated the importance of the contralateral language networks for recovery in conditions including white matter vascular pathology, epilepsy, and brain injury. The application of DTI in these disorders could reveal important information on the mechanisms underlying these white matter reorganization after brain injury. Figure 7.7 (plate 5) shows the DTI images of an 18-year-old male born preterm at 26 weeks with very low weight (<1 kg). The images show severe ventricular dilation and almost complete absence of the corpus callosum. Tractography dissections reveal an extreme right lateralization of all three segments of the perisylvian pathways (complete absence of the left arcuate) and rightward asymmetry of the CST. The above patterns of lateralization are rarely observed in the male population and may have a compensatory significance considering the normal verbal IQ of the subject and his left-handedness.

After adolescence, the degree of lateralization of the long segment is quite heterogeneous. Figure 7.8 (plate 6) shows the pattern of lateralization of the long segment in the adult population. An extreme degree of leftward lateralization is observed in approximately 60% of the normal population (Catani et al., 2007). The remaining 40% of the population show either a mild leftward lateralization (~20%) or a bilateral, symmetrical pattern (~20%). Similar results are reported for left-handed subjects



**Figure 7.7 (plate 5)**

Diffusion-tensor imaging of an 18-year-old male born very preterm at 26 weeks of gestation. (a, b) The axial fractional anisotropy images show marked dilatation of the lateral ventricles, particularly in the left hemisphere. (c) Tractography reconstruction of the perisylvian language pathways was only possible for the right hemisphere. (d) The asymmetry of the corticospinal tract is also evident with a rightward lateralization, which is usually observed in less than 15% of the male population (red streamlines indicate the left CST). Considering the normal IQ of this subject and the left-handedness, a compensatory reorganization of the lateralization of language and motor tracts may have followed the white matter damage at birth.



**Figure 7.8 (plate 6)**

(a) Distribution of the lateralization pattern of the direct long segment (red) and (b) gender differences. (c) Performances on the California Verbal Learning Test (CVLT) according to the lateralization pattern and gender \* $p < .05$  vs. group 1; † $p < .01$  vs. group 1; ‡ $p < .05$  vs. group 1).

(Hagmann et al., 2006; Vernooij et al., 2007). Of particular interest is the report of a gender dimorphism with respect to the lateralization of the long segment, with females more likely to have a bilateral pattern compared to males (Catani et al., 2007; Hagmann et al., 2006).

An important question is the extent to which structural differences between the two hemispheres correlate with functional lateralization and whether the anatomical lateralization of language pathways reflect differences in language performance. Preliminary studies combining DTI tractography and fMRI show no correlation between the lateralization of the arcuate volume and the degree of functional lateralization as determined by fMRI during tasks of verbal fluency, verb generation, and reading comprehension (Powell et al., 2006; Vernooij et al., 2007). The lateralization of the frac-



tional anisotropy values of the arcuate fasciculus seems to correlate better with the functional lateralization as demonstrated in healthy individuals (Powell et al., 2006) and in patients with temporal lobe epilepsy (Rodrigo et al., 2008).

There are also preliminary findings showing that the extreme left lateralization of the direct long segment is associated with worse performance on a complex verbal memory task that relies on semantic clustering for retrieval (i.e., the California Verbal Learning Test; CVLT). The correlation remained significant after splitting the group according to gender, suggesting that the main determinant of CVLT performance is the anatomy (symmetry) of the language pathways, not the gender. Overall, these findings support the notion that lateralization of language to the left hemisphere is an important aspect of human brain organization, but paradoxically a bilateral representation might ultimately be advantageous for certain cognitive functions (Catani et al., 2007).

Other components of the perisylvian networks seem to have a more bilateral distribution or rightward lateralization. Interhemispheric differences have been found in the fractional anisotropy of the anterior indirect segment with higher values in the right side (Catani et al., 2007; Eluvathingal et al., 2007). Another tract connecting the superior temporal lobe to the superior parietal lobe shows a similar rightward lateralization (Barrick et al., 2007). This may be related to the specialization of the right parietal and frontal cortex for visuospatial processing (Doricchi et al., 2008; Thiebaut de Schotten et al., 2005; Thiebaut de Schotten et al., 2008).

## Conclusions

Although the hodological approach to cognition has a long history, the study of tract lateralization is surprisingly still at its infancy. If the lack of methods suitable for anatomical studies of connections in the living human brain can in part justify this gap in knowledge, the complete absence of data on the monkey brain, for which powerful axonal tracing techniques are indeed available, is unforgivable. For decades, anatomical drawings of tracts have been passed on to the anatomical textbook of the next generation, and often the presence of those tracts in both sides of the brain taken for granted. The recent flourishing of techniques based on diffusion imaging suggests that this leap of faith may not necessarily be true for tracts underlying unique human abilities. Clearly, we need a research program that sets off from the footsteps of the “great neuroanatomists” of the nineteenth century, leading us to address those questions that for too long have remained unanswered.

With unprecedented access to the connectivity of living human brain we can compare asymmetry of connections across species, formulate novel neuropsychological models based on anatomical findings on laterality, and take into account interindividual variability within the spared hemisphere to predict recovery in patients with

brain disorders. At the same time, we are well aware that, at present, the hodological approach is more aspirational than proven and stands or falls on the methodological developments and empirical contributions to come.

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