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## **Središnja medicinska knjižnica**

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**Invited review for the special issue of *Cognition, Brain and Behavior* journal „Brain asymmetry in development, psychopathology and evolution“ in the memory of Joseph E. Bogen (13 July 1926 – 22 April 2005)**

## **Brain asymmetries related to language with emphasis on entorhinal cortex and basal forebrain**

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Anatomical asymmetries of the human brain are important in at least four respects: 1) they can serve as potential indicators of the evolutionary foundations of language, 2) they can be used for comparative analysis of neural specializations for communication in primates, 3) they may provide underlying structural correlates for functional imaging (fMRI, PET) and genetic studies, and finally 4) they can be used for studying disorders which are suspected to result from either disturbed development of cerebral asymmetry or asymmetric damage to the brain. In the first part of this review, we give a general framework of this field through the brief descriptions of the milestone discoveries and major conceptual advances as they emerged throughout the last 150 years. In the second part, we provide a more detailed view on the functional relevance that asymmetries of the entorhinal cortex and basal forebrain may have on the language.

### **Language and development of the concept of lateralization of cerebral functions**

The specialization of the left hemisphere for language was one of the earliest observations of brain asymmetry. Already at the turn of the 18th century, a number of clinical reports confirmed the decussation of the motor pathways and suggested that left hemispheric damage, that caused right hemiplegia, was associated with loss of speech more frequently than right hemispheric damage, or left hemiplegia. The authors of these studies, however, did not pay enough attention to obvious laterality effects for speech itself (**Morgagni, 1769; Bouillaud, 1825; Andral, 1840**). This was probably because the numbers of analyzed patients were too small to direct attention to hemispheric differences and that different types of language disturbances were not distinguished. Terms such as „aphonia“ and „alalia“ were used interchangeably for designation not only of aphasias, but also mutism, articulation deficits and even stuttering. These physicians also knew that lesions and diseases of the cerebellum and brain stem could induce some of such disturbances. In addition, seemingly identical macroscopic appearance was a logical argument for both hemispheres to have identical functions and therefore represent „mirror images of each other“ (**Bell, 1811; Benton, 1976, 1977, 1984**).

In 1861, Broca described two men, 51- and 84-year old, who had none of the conventional motor deficits that may affect speech, yet they could neither speak or create complete sentences, nor express ideas in writing. One had suffered from epilepsy since his youth, could not speak since 1840 (when he was 30-year old) and had lost his ability to use his right arm 10 years later. Other patients called him „Tan“ because he could pronounce only this sound. The other was able to say only a few simple words, such as „yes“, „no“, „always“, „three“, showed good comprehension and used gestures in conversation. At autopsy, Broca found a lesion in the posterior third of the second and third frontal convolutions of the second case's left hemisphere. He concluded that this case was even clearer than the other one, and thought that he had confirmed his previous localization of a center for articulate language (**Broca, 1861a,b**). Broca described eight similar patients in the next four years, as well as one patient with destroyed inferior frontal gyrus in the *right* hemisphere, but with intact speech. Finally, in his celebrated paper of 1865, Broca reported that disturbances in speech functions occur only after lesions of the left hemisphere (**Broca, 1865**).

In fact, Dax first recognized a strong association among lesions of the left hemisphere, loss of speech, and paralysis of the right side of the body on a larger sample of human brains (more than 40 patients collected over a 20-year period). However, his report written in 1836 had not been read before the French Academy of Medicine until December 1864, and was only published in 1865 (**Dax, 1865**). The possibility that Broca may have seen or heard of the Dax's findings prior to his own written reports on cerebral dominance is still a matter of debate among historians of neuroscience. It is believed that Broca's brief and cautious reports from 1861 to 1863 (**Broca 1861a, 1861b, 1863**), which raised the possibility of left hemisphere specialization for language, were probably written before he knew of the Dax's report (**Finger, 1994**). However, since Broca's application for a membership in the Academy was published on the same page of the Academy's bulletin that announced the receipt of the Dax manuscript in 1863, this would suggest that Broca most probably had noted this before he described his famous eight aphasia cases, all with lesions on the left side (**Schiller, 1979**). Broca called the loss of articulate speech „aphemia“, while the term „aphasia“ (which is still in use today) had been introduced by Armand Trousseau in 1864 (**Geschwind, 1972; Finger, 1994**). To account for some instances of loss of speech after right hemisphere lesions, Broca postulated that speech in left-handed people is controlled by the same frontal region of the right hemisphere. Franz first challenged this view that language dominance and handedness are not perfectly correlated in 1914 when he discussed a case in which he found that a lefthanded person developed an aphasia after a lesion of the left frontal lobe (**Franz, 1914**). With time, it was recognized that approximately 97% of right-handers have their speech and language localized to the left hemisphere, while only 3% demonstrate a right hemisphere lateralization or bilateral language representation. A majority of left-handed people still has speech localized on the left side of the brain (70%) or exhibits more of a „mixed“ dominance. Thus, some right-handed patients have right-hemisphere dominance for language, while lefthanders may display a leftward dominance (**Desmond et al., 1995**).

In 1870, Fritsch and Hitzig showed that electrical stimulation of the precentral gyrus of the dog invariably produce movements in the contralateral limbs (**Fritsch and Hitzig, 1870**). These and several other findings led scientists of the late 19th century to realize that the left hemisphere controls both speech and the right hand movements, so the left hemisphere became to be regarded as „dominant“.

### **Further development of the concept of hemispheric dominance**

After Broca, probably Wernicke had been the most influential person for the new understanding of the functional organization of the brain. Based on 10 cases of which 4 were examined by autopsy, he described the new type of aphasia („sensory“ aphasia), characterized by a lesion in the dorsal part of the left upper temporal gyrus, without a paralysis of the opposite side of the body, but with seriously damaged ability to understand spoken and written language (**Wernicke, 1874**). After this discovery, in 1874, he established a new concept about different types of aphasia (that is still in use nowadays). Wernicke pointed out that Broca's speech area lies just in front of those cortical regions where organs of speech (face, tongue, lips, palate, and vocal cords) have their motor representation and therefore assumed that this region is „the supposed seat of movement images (rules) necessary for articulate speech“. In the aphasia that he described himself (now called Wernicke's aphasia), the damaged portion of the cerebral cortex (known as the Wernicke's area) lies immediately behind the primary auditory cortex. Wernicke proposed that this region is somehow involved in recognition of the patterns of the spoken language and concluded that a lesion of this center only would leave people fluent (since Broca's motor area is preserved), but unable to understand speech or use words properly. In his words, such a lesion would abolish sound images („*Klangbilder*“). Wernicke also suggested that the motor center for speech (Broca's area) and the sensory center for speech (Wernicke's area) are interconnected and defined „conduction aphasia“, a disorder characterized by misapplied words and an inability to read and possibly write, but in which there is a fairly good language comprehension and fluent output. The postulated large fiber bundle was described somewhat later and called the arcuate fascicle, which confirmed Wernicke's assumptions. Wernicke also defined „total aphasia“ as a lack of both expression and comprehension of speech (**Wernicke, 1881**).

Although Wernicke himself did not believe that writing disorders could be independent of spoken language, this model was confirmed and expanded by Déjérine, who was the first to describe the „alexia with agraphia“ syndrome (the loss of ability to read and write) in a case study in 1891 (**Déjérine, 1891**). This patient, however, could speak and was able to understand every word he had heard. The postmortem examination showed a lesion of the left angular gyrus. Because this lesion disrupted connections between visual and auditory areas, although the patient could see letters and written words, they were without meaning to him. To understand a word, what is seen needs first to be „converted“ into an auditory form; similarly, to write a word, first its auditory form needs to be transformed into a visual one. Upon careful analysis of another patient who could speak, write and understand speech, but could not read written words, Déjérine was also the first to note the importance of information transfer from one hemisphere to the other (**Geschwind, 1970**). Namely, the autopsy of the brain of this patient showed, together with the damage of the left visual cortex, also a lesion of the posterior part of the splenium. Déjérine proposed that due to the damage of the corpus callosum, visual information could not be transferred from the calcarine region in the healthy right hemisphere to speech areas of the left angular gyrus (**Déjérine 1892**). Although this syndrome of „pure word blindness (alexia)“ (without agraphia) was actually the first direct evidence that a lesion of corpus callosum can disrupt the transfer of information from one hemisphere to the other, at that time, Déjérine did not consider pathology of the callosum to be so critical. Nevertheless, Brissaud and Redlich (Brissaud, 1900; Redlich, 1895) soon pointed out the role of posterior callosal lesions in preventing visual images in the healthy, right hemisphere from crossing to the left hemisphere. Several of Wernicke's students, notably Liepmann, Goldstein and Bonhöffer (Geschwind, 1972), later described many different callosal syndromes that confirmed the crucial role of the corpus callosum for information transfer between hemispheres. For example, in 1906 Liepmann suggested that a disruption in the callosal pathways between the motor- and language-organizing areas on the left side and the motor areas for the left hand on the right side of the brain could cause

ideomotor apraxia for the left side of the body (but not the right side). This could prevent the left hemisphere, which is involved in planning skilled movements, from communicating the necessary information to the right hemisphere, which controls the left hand (**Liepman, 1906**). In 1937 Trescher and Ford described the first case of disturbed information transfer from one hemisphere to another due to a surgical intervention for the removal of a tumor of the third ventricle) (**Trescher and Ford, 1937**). This finding, as well as several later ones, such as pure word deafness syndrome, conduction aphasia syndrome, syndrome of isolation of speech area, easily fitted into the Wernicke's theory. At first, before the late 1920s and 1930s, the concept of dominant hemisphere was noted only in relation to language functions.

### **Critics of the classical concept: cortical functions in split-brain subjects**

The described „classical“ concept of the dominant hemisphere represented the dominant view well into the 1950s (**Geschwind, 1974**). However, description of new syndromes, such as spatial apraxia led slowly to widening of the concept. It was considered that the left hemisphere is dominant („major hemisphere“) in all cognitive functions, while the right („minor hemisphere“) begun to be considered as a „sub-dominant“ (**Beaumont, 1974; Hécaen and Marcie, 1974; Goldstein, 1974; Levy, 1974**).

It was Erikson in 1940 that first showed in experimental animals that the corpus callosum is the main pathway for spreading of epileptic seizures from one hemisphere to the other (**Sperry, 1964; Sechzer et al., 1977**). Encouraged by this finding, Van Wagenen and Herren surgically split hemispheres by cutting a part of or the entire corpus callosum in 24 epileptic patients (**Van Wagenen and Herren, 1940**). The subsequent reports by Akelaitis on these patients indicates that a number of them were improved (**Akelaitis, 1940, 1943; Zangwill, 1974; Finger, 1994**). The psychologist K.U. Smith, carefully examined most of these patients, but found no consistent deficits resulting from the procedure. Because of these findings, the functional importance of the corpus callosum remained mysterious at that time (**Sperry, 1964**): it seems that Anglo-Saxon authors forgot the importance of the corpus callosum or did not know of the works of central-European neurologists who knew this already at the turn of the 19th century (see above) (**Geschwind, 1972**).

It was not until Sperry and Myers did a series of experiments on split-brain cats that the role of the corpus callosum became clearer (**Sperry, 1964**). After they surgically divided the corpus callosum and optic chiasm, they had two separate, independent systems. These classical experiments of Myers and Sperry on cats and monkeys with surgically separated hemispheres showed that the two hemispheres were not able to communicate with each other and that each learned the required visuomotor task in about the same amount of time (**Myers and Sperry, 1953; Myers, 1955, 1956, 1957; Myers and Sperry, 1958; Sperry, 1967**). They concluded that unilateral visuomotor learning leads to the formation of a single, unihemispheric engram in the absence, whether functional or anatomical, of the corpus callosum, i.e. it is only the corpus callosum that enables hemispheres interhemispheric transfer of visuomotor skills.

These experiments opened the way to analyses of callosal function in man. Vogel, Fischer and Bogen, performed commissurotomy on a 49-year old man who suffered from intractable epilepsy due to wounds inflicted during the World War II (**Bogen et al., 1965**). The patient showed no radical changes in personality, mood, or intelligence. However, under controlled testing conditions, it was revealed that his left hemisphere was more verbal than his right, as well as more analytic and more rational, while the right came out being more holistic, emotional and impulsive. The cerebral functions of this and other similar patients were tested in a series of psychological tests (**Gazzaniga, Bogen and Sperry, 1965; Gazzaniga and**

**Sperry, 1967; Gazzaniga, 1972**). In short, it was shown that the right hemisphere is not, as previously thought, deaf and blind to words. It is to some extent, but capable of understanding some words, and read and comprehend meaning of words that were displayed in the left part of the visual field (that is, projected to the right hemisphere). In addition, it was shown that, upon the cutting the corpus callosum, each hemisphere used its own perceptions, mental images, associations and ideas, and had its own processes for learning and memory, unrelated to conscious experience in the opposite hemisphere (**Sperry, 1981**). However, although in laboratory conditions, the separated hemispheres functioned as two distinct minds („twinbrain“), these patients continued to exhibit a unified mind in everyday life (**Bogen, 1969, 1979**). After these findings, many researchers again turned to analyze structural backgrounds of these (functional) asymmetries.

### **Morphological asymmetries of the brain related to language**

The asymmetrical trajectory of the Sylvian (lateral) fissure was one of the first anatomical asymmetries to be described. At the end of the 19th century, Eberstaller and Cunningham were the first to describe differences in length and course of the lateral cerebral fissure of Sylvius. At its posterior limit, the right Sylvian fissure curves upwards more anteriorly than the left (so that the left is 12% longer than the right) (**Eberstaller, 1884, 1890; Shellshear, 1937; Rubens, 1977**), while the left has a gentler slope (with respect to the horizontal line) (**Cunningham, 1892; Geschwind and Levitsky, 1968; Rubens, 1977**). Due to such an arrangement of the lateral fissure, the surface area of the left parietal operculum is larger than right, particularly in the region of the angular gyrus (**von Economo and Horn, 1930; Pfeiffer, 1936; Connolly, 1950; Hochberg and LeMay, 1975**). This was later confirmed by the analysis of carotid arteriograms and coronal sections of the brain through the caudal part of the Sylvian fissures (**LeMay and Culebras, 1972**). The analysis of fossil endocasts suggested that this difference was already present in Neanderthals (**LeMay and Culebras, 1972; LeMay, 1982**), as a part of a geometric distortion of the hemispheres also known as „Yakovlevian twisting effect“ or „anticlockwise torque“ (structures surrounding the right Sylvian fissure are „torqued forward“ relative to their counterparts on the left) (**LeMay, 1976**).

Bilateral intracranial arteriograms proved useful in assessing cerebral dominance. Bilateral intracranial arteriograms of 123 right-handed patients and 38 left-handed patients showed that the angulation of the branches of the right and left middle cerebral arteries as they leave the Sylvian fissure are quite different (Hochberg and LeMay, 1975, LeMay, 1976). The height of the end-point („posterior tip“) of the Sylvian fissure has been shown to correlate negatively with the volume of the posterior part of the superior temporal lobe (known as planum temporale) and was higher on the left side in about 67% of right-handers, but in only 21% of non-right-handers. In a sample of 100 human brains, Geschwind and Lewitsky (**Geschwind and Levitsky, 1968**) have shown that planum temporale is larger on the left side in approximately 65% of human brains, the same in 24%, and larger on the right side in 11%. This asymmetry was visible grossly because the left planum temporale is, on average, one third larger from the right. This finding was confirmed later by several authors: the size of the planum temporale was shown to be larger on the left side in 69-90% of reported cases, averaging of 78% of the subjects in 22 studies (for a review, see **Shapleske et al., 1999**). The anatomic pattern and left hemisphere size predominance of the planum temporale are also present in chimpanzees (*Pan troglodytes*). The left planum temporale was found to be significantly larger in 94% (17 of 18) of chimpanzee brains examined (**Gannon et al., 1998**). Therefore, anatomic hemispheric asymmetry of this cortical region is clearly not unique to

humans: the evolutionary origin of human language may have been founded on this basal anatomic substrate, which was already lateralized to the left hemisphere in the common ancestor of chimpanzees and humans 8 million years ago (**Gannon et al., 1998**). Moreover, the results of the recent study of Gannon and colleagues indicate a rightward asymmetry of the parietal plane in chimpanzee and orangutan brains, that is comparable to the one observed in humans and independent of the temporal brain asymmetry (**Gannon et al., 2005**).

The planum temporale also shows a marked leftward volume asymmetry that is related to the degree of right-handedness: an analysis of 121 MRI scans of right-handers and 33 MRI scans of lefthanders found that right-handers have greater planum temporale asymmetry (-0.30 vs. -0.16) (**Steinmetz, 1996**). Actually, the left planum temporale, which is an extension of Wernicke's posterior receptive language area responsible for phonological encoding during speech perception, is up to ten times larger than its right-hemisphere counterpart and therefore probably represent the most prominent human brain asymmetry (**Steinmetz, 1996**).

This asymmetry is recognizable already in fetus between the 29th (**Wada et al., 1975**) and the 31st (**Chi et al., 1977**) week of gestation, and can be easily seen in newborns (**Witelson and Pallie, 1973**). During the 29th week of gestation, the asymmetry of the frontal operculum is also readily observable (**Wada et al., 1975**).

Although to a lesser extent than the temporal planum, larger volume than their homologues in the right hemispheres (that is probably related to language functions) has been also documented for Heschl's gyrus (primary auditory area) (**Rademacher et al., 1993**), Broca's speech area (**Falzi et al., 1982, Amunts et al., 1999**), cytoarchitectonic area Tpt (**Galaburda et al., 1978**), entorhinal cortex (**Šimić et al., 2005**), and many other cortical regions (for a review, see **Toga and Thompson, 2003**). Interestingly, some subcortical structures such as the lateral posterior nucleus of the thalamus (**Eidelberg and Galaburda, 1982**) and the subputaminal nucleus (Ayala) of the basal forebrain (**Šimić et al., 1999**) have been documented for leftward asymmetry as well.

### **Asymmetry of the entorhinal cortex and its possible functional importance**

The entorhinal cortex spreads over the gyrus ambiens and a considerable part of the parahippocampal gyrus (**Brodmann, 1909; Braak, 1972**). On the surface of these gyri, small elevations are present with shallow grooves in between. Retzius was the first to observe these elevations, and to describe them, coining the term „verrucae gyri hippocampi“ (**Retzius, 1896**). Ramón y Cajal (1901-1902) and von Economo and Koskinas (**von Economo and Koskinas, 1925; von Economo, 1927**) showed that verrucae are formed from groups („glomeruli“) of layer II neurons which cause an elevation on the cortical surface. Verrucae are human specific feature and allow delineation of the entorhinal region macroscopically even with the unaided eye (**Klinger, 1948; Braak, 1980; Braak and Braak, 1992; Insausti et al., 1995; Solodkin and Van Hoesen, 1996**).

Based on dissociated verbal and nonverbal retrieval and learning in a subject with circumscribed anterior temporal damage, a functional asymmetry of the entorhinal cortex with the left side being more involved in verbal and the right in non-verbal processing has been proposed (**Tranel, 1991**). More recent findings obtained using voxel-based mapping of the correlations between cognitive scores and resting state brain glucose utilization measured by PET in early Alzheimer's disease further support this observation (**Eustache et al., 2001**). By using MRI volumetry, decreased memory performance in Alzheimer's disease has also been shown to correlate with an increased rate of entorhinal atrophy, with the left side being more affected (**Du et al., 2003**).

A recent cast analysis of the number and area of entorhinal verrucae in brains from 60



neurologically normal patients found that both number and area of verrucae are higher in the left than in the right hemisphere, indicating an anatomical asymmetry (Šimić et al., 2005). The dominance of the left hemisphere in the number and size of entorhinal verrucae is best illustrated by the fact that only two out of sixty brains had comparable total area of verrucae in both hemispheres (all other were larger on the left). This finding is potentially making the entorhinal region one of the most consistently lateralized part of the brain. An illustration of the asymmetry of the entorhinal cortex is given in Figure 1. Layer II entorhinal neurons receive major inputs from the ipsilateral auditory association areas, such as Brodmann area 22 (in the superior temporal gyrus) that projects mostly to the medial part of the entorhinal cortex, and Brodmann area 52 (parainsular cortex) that projects mostly to the lateral division of the entorhinal cortex (Amaral et al., 1983; Insausti et al., 1987). Since areas 22 and 52, together with Broca's motor-speech area (Brodmann areas 44 and 45) (Uylings et al., 1999), consistently show anatomical and functional asymmetry from early infancy (Karbe et al., 1995; Galuske et al., 2000; Amunts et al., 2003), it is reasonable to speculate that the larger size of the entorhinal cortex on the left side may play a role in memory processing of language in the left hemisphere. Because the entorhinal cortex serves as a gateway between the neocortex and the hippocampus, thus playing a key role in the processes of memory and learning (Zola-Morgan et al., 1989; Fernández et al., 1999), this may also explain the specialization of the left hippocampus (or left medial temporal lobe in general) compared with the right in its increased capacity for verbal episodic memory (Milner, 1970; Damasio and Geschwind, 1984; Kelley et al., 1998).

### **Asymmetry of the basal forebrain and its possible functional importance**

The most important feature of the basal forebrain is the presence of a complex chain of the magnocellular nuclei, which represent an extension of the brainstem reticular core (Brockhaus, 1942). The largest cytoarchitectural entity is the basal nucleus. The well-known eponym „nucleus basalis of Meynert“ was given by Kölliker (Kölliker, 1896), although Meynert's work does not exactly show this cell group (Meynert, 1872). It was Brockhaus who first realized that the magnocellular neurons in the Meynert's nucleus are only one component of the whole complex of basal forebrain magnocellular groups (Brockhaus, 1942). The prominence of the basal nucleus is explained by the extraordinary expansion of the cortical mantle, which represents its main innervation target (Gorry, 1963; Divac, 1975). Different divisions of the basal nucleus have physiologically and morphologically heterogeneous neurons with discrete projection patterns. One cell group, which is topographically, cytochemically and cytoarchitecturally intimately related to the basal nucleus, was named and described as the nucleus subputaminalis in 1915 by Ayala (Ayala 1915, 1924). Still, with the exception of five studies (Hedreen et al., 1984; Kostović, 1986; Kračun and Rösner, 1986; Halliday et al., 1993; Ulfing, 1989), the subputaminal nucleus has been neglected in both classical (Brockhaus, 1942; Kölliker, 1896) and recent studies. A detailed analysis of subputaminal nucleus in 36 neurologically normal subjects revealed several surprising and potentially important findings (Šimić et al., 1999)(Fig. 1). The human subputaminal nucleus was found to be best developed at the anterointermediate basal forebrain level, which is much smaller or missing in monkeys (Jones et al., 1976; Hedreen et al., 1984). Moreover, at the most rostral level a previously non-described component of the lateral (periputaminal) subdivision of the subputaminal nucleus was found (Šimić et al., 1999). This part of the subputaminal nucleus has not been described in non-human primates (Gorry 1963, Divac 1975). The obviously larger size of subputaminal nucleus on the left side at the most rostral and anterointermediate levels (Šimić et al, 1999, Halliday et al., 1993), the

ascension of subputaminal cholinergic fibers through the external capsule (**Kostović, 1986**) towards the inferior frontal gyrus (**Šimić et al., 1999**), its most progressive phylogenetic cytochemical properties (in comparison to other cholinergic cell groups) (**Šimić et al., 1999**) and the most protracted development among all the magnocellular aggregations within the basal forebrain (**Kračun and Rösner, 1986**) strongly suggest that the subputaminal nucleus is human specific and connected with the cortical speech area (**Šimić et al., 1999, Boban et al., 2006**).

These findings opened many questions about the possible role of subputaminal nucleus in various neurodegenerative, neurological and psychiatric disorders, particularly Alzheimer's disease, primary progressive aphasia and schizophrenia. A significant subgroup of Alzheimer's disease patients present with characteristics of primary progressive aphasia during the early course of the disease (**Goldblum et al., 1994**). Moreover, it would be of particular importance to investigate possible pathological changes of subputaminal nucleus in the primary progressive aphasia (**Heath et al., 1983; Mesulam, 1982**) since causes and mechanisms underlying the anatomical selectivity of this neurologically distinct disorder have not been elucidated (**Espert et al., 1996; Kertesz and Munoz, 1997**). Since the cholinergic system is the most important for the generation and modulation of the P300 amplitude and latency, the negativity of the P300 potential in the affected (left) hemisphere in four patients with primary progressive aphasia (**Onofrij et al., 1995**) strongly suggest that pathological changes in the subputaminal nucleus may represent the missing link to explain this enigmatic disease (**Šimić et al., 1999**). Finally, the subputaminal subdivision of the basal nucleus may be also important in respect to disturbed speech functions in schizophrenia (**Heimer, 2000**).

## **Summary and conclusions**

Physicians and neurologists of the 19th century, particularly Broca, Wernicke and Déjérine, have first shown lateralization of functions, particularly those related to language, in the human brain. However, they did not know much about cognitive abilities of the right hemisphere. Further discoveries around the mid 20th century have revealed that the right hemisphere is indeed much involved in different cognitive domains, and in some respects more so the left. The key experiments were those done in experimental animals and humans with surgically divided hemispheres by Myers, Sperry and Bogen. These studies showed that each hemisphere has its own „intellectual“ and „emotional“ life, while the „unity“ or „wholeness“ of the human experience and behavior is achieved by communication between hemispheres through the corpus callosum. Morphological, neurohistological and neurochemical studies were the first to show multiple asymmetries in the shape and structure of the brain. Most of these asymmetries are related to language functions. It is now clear that the greatest asymmetries of the brain structure are localized to the perisylvian language areas. Recent neuroanatomical studies have, among other regions, revealed asymmetries in the entorhinal cortex and subputaminal nucleus, possibly also in relation to language. These findings have implications for both normal and altered brain function. The degree to which functional asymmetries parallel those observed anatomically still have to be fully described. It is believed that the integration of data from all of the available approaches (such as genetic databases, studies of molecular mechanisms and functional brain imaging) will eventually provide a clearer understanding of the mechanisms of brain lateralization.

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**Figure 1.** An illustration of the asymmetry of the entorhinal cortex. Picture is a reconstruction of entorhinal cortex islands from tangential sections. Male subject, 32 years of age, scale bar = 1 mm. L = left, R = right.

