REVIEW ARTICLE

The rises and falls of disconnection syndromes

Marco Catani and Dominic H. ffytche

Centre for Neuroimaging Sciences, Institute of Psychiatry, De Crespigny Park, London, UK

Correspondence to: Marco Catani, Centre for Neuroimaging Sciences, PO 89, Institute of Psychiatry,
De Crespigny Park, London, UK
E-mail: m.catani@iop.kcl.ac.uk

In a brain composed of localized but connected specialized areas, disconnection leads to dysfunction. This simple formulation underlay a range of 19th century neurological disorders, referred to collectively as disconnection syndromes. Although disconnectionism fell out of favour with the move against localized brain theories in the early 20th century, in 1965, an American neurologist brought disconnection to the fore once more in a paper entitled, 'Disconnexion syndromes in animals and man'. In what was to become the manifesto of behavioural neurology, Norman Geschwind outlined a pure disconnectionist framework which revolutionized both clinical neurology and the neurosciences in general. For him, disconnection syndromes were higher function deficits that resulted from white matter lesions or lesions of the association cortices, the latter acting as relay stations between primary motor, sensory and limbic areas. From a clinical perspective, the work reawakened interest in single case studies by providing a useful framework for correlating lesion locations with clinical deficits. In the neurosciences, it helped develop contemporary distributed network and connectionist theories of brain function. Geschwind's general disconnectionist paradigm ruled clinical neurology for 20 years but in the late 1980s, with the re-emergence of specialized functional roles for association cortex, the orbit of its remit began to diminish and it became incorporated into more general models of higher dysfunction. By the 1990s, textbooks of neurology were devoting only a few pages to classical disconnection theory. Today, new techniques to study connections in the living human brain allow us, for the first time, to test the classical formulation directly and broaden it beyond disconnections to include disorders of hyperconnectivity. In this review, on the 40th anniversary of Geschwind's publication, we describe the changing fortunes of disconnection theory and adapt the general framework that evolved from it to encompass the entire spectrum of higher function disorders in neurology and psychiatry.

Introduction

As originally outlined by Wernicke in his associationist theory, higher brain functions were the product of associative connections between cortical areas storing motor and sensory images. It followed that disorders of higher function resulted from a disconnecting breakdown of associative connections through white matter lesions (Wernicke, 1874). Today, this disconnection paradigm is still to be found within the neurology clinic and outside it within 'functional' disorders as diverse as schizophrenia (Bullmore *et al.*, 1997), autism (Frith, 2001) and dyslexia (Demonet *et al.*, 2004), where disconnecting 'lesions' remain inferred rather than demonstrable. However, it was not always so. For the first half of the 20th century, function in general was thought to relate to the brain as an equipotential whole, cortical connections, disconnections and the location of lesions becoming an irrelevance. One man is credited with the re-emergence of the disconnection paradigm, and 2005 is the 40th anniversary of the publication that founded the neo-associationist school. Norman Geschwind's 'Disconnexion syndromes in animals and man', published in *Brain* in two parts for editorial convenience although, in effect, a single monograph, outlined a general theory of higher brain function founded on what today might be called distributed brain networks. The importance of the paper is demonstrated by the exponential increase in citations from 1965 to 1985, at one time the paper being cited once every 5 days (Absher and Benson, 1993).

Behavioural neurology, cognitive neurology, neuropsychiatry and neuropsychology share at least one thing in common— they each owe much to Geschwind.

Geschwind's disconnection framework was both general and specific, giving it immediate clinical appeal. On the one hand, it helped classify higher dysfunction into a limited set of syndromes and on the other hand, it allowed a customized neuroanatomical account of a given patient's deficit pattern. For some higher dysfunctions our contemporary accounts remain largely as Geschwind left them, and for others, explanations have moved on with the recognition of specialized functional roles in association cortex. Yet, it is not the neurological details of Geschwind's model that have been his legacy—it has been the ambition of an overarching clinical theory, the return of clinicopathological correlations to neurology and the facilitation of a discourse between clinic and neuroscience laboratory.

Geschwind's theory, and that of Wernicke's school before him, was founded on the anatomy of connections, the knowledge of which was derived from human post mortem dissections and, for Geschwind, studies of the monkey brain. More recently, the advent of novel techniques for tracing connections non-invasively, such as diffusion tensor imaging (Le Bihan and Breton, 1985; Moseley *et al.*, 1990; Basser *et al.*, 1994) and tractography (Conturo *et al.*, 1999; Jones *et al.*, 1999; Mori *et al.*, 1999; Basser *et al.*, 2000; Poupon *et al.*, 2000) allow us to study connections in the living human brain, both in normal subjects and patients with neurological and psychiatric disorders. Other developments in electrophysiology and neuroimaging are focusing attention on connections by studying the implied connectivity of brain regions revealed by statistical correlation. For the first time we are in a position, not only to correlate disconnecting lesions with their clinical symptoms *in vivo*, thus testing the classical disconnectionist paradigm directly, but also to correlate clinical symptoms with increased connectivity between brain regions. In what follows we celebrate Geschwind's contribution with a review of disconnection theory and its syndromes before, during and after him, outlining the ebb and flow of their fortunes over the last two centuries. In the final section we update the framework that evolved from Geschwind, incorporating novel connectivity evidence in the spirit of the neurological revolution of 1965.

Disconnection syndromes before Geschwind—the classical associationist era

In the late 19th century a new paradigm emerged with which to understand normal brain function and its disorders. The paradigm was based on two central tenets: that of the localization of function in discrete cortical areas and that of connections between such cortical areas through white matter association pathways. Although the idea of localized functions in specific parts of the brain predates Franz Joseph Gall (1758–1828), it is to him that credit is due for recognizing

the specific functional importance of the cortex (Zola-Morgan, 1995). Often forgotten as a widely acclaimed neuroanatomist, Gall established the basic division between grey and white matter, recognizing that white matter was made up of ascending and descending conducting fibres originating from or projecting to the cortex. Gall developed a system of organology in which functional variations were correlated with the size of specific cortical regions (cortical organs) both across and within species. Of course, his use of external cranial features as an indirect measure of cortical organ size was flawed and the system fell into disrepute. In England Gall's ideas evolved into phrenology; in France, they had an important influence on the later clinicopathological correlation studies of Jean-Baptiste Bouillaud (1796–1881), Paul Broca (1824–80) and Jean Martin Charcot (1825–93).

The credit for the detailed anatomy of white matter pathways falls to Theodore Meynert (1833–92), the Professor of Psychiatry in Vienna, who, like Gall, was a neuroanatomist of international repute. He was the first to recognize the important functional role played by fibres connecting different parts of a single hemisphere, which he termed association fibres. He was also the first to classify white matter fibres into three groups. The first group consisted of projection fibres, the ascending or descending pathways arising and terminating in the cortex, the second of commissural fibres which connected cortex in both hemispheres and the third of association fibres which connected cortical regions within a hemisphere. Figure 1 shows tractography reconstructions of the major white matter tracts of the human brain as classified by Meynert (Catani *et al.*, 2002).

Although Meynert used his neuroanatomical findings to develop a theory of psychological function which had profound influence on the early development of psychiatry, including Freud's early work, it is Karl Wernicke (1848–1904) who is considered the father of disconnection theory. Wernicke conceived the brain as a mosaic-like arrangement of areas containing 'fundamental psychic elements' or 'memory images' related to motor acts and sensory experiences. These memory images areas were localized in primary sensory and motor areas according to the following principle:

> the acoustic images find their abode within the cortical terminals of the acoustic nerve; the visual images, within the cortical endings of the optic nerve; and the olfactory images in that of the olfactory nerve; and so on. Likewise the motor images or movement-representation could be located in the cortical sites of the motor nerve origins. (Wernicke, 1885)

Perhaps in an attempt to distance himself from phrenological theory, Wernicke was adamant that the higher functions were not localized in specific regions but were the result of associative connections between motor and sensory memory image areas. Thus, for Wernicke

> Any higher psychic process, exceeding these mere primary assumptions, could not, I reasoned, be
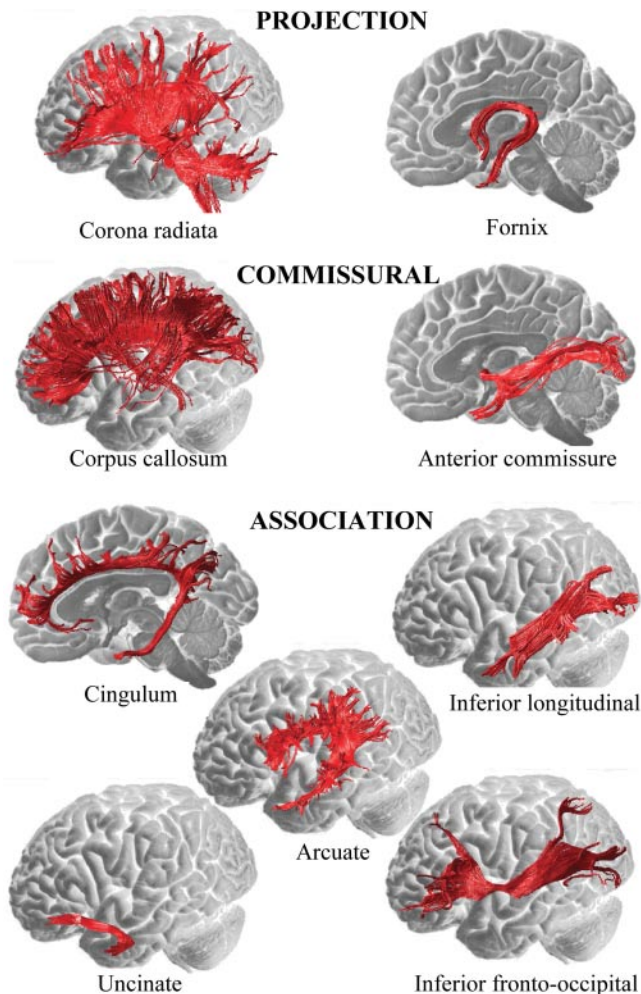
Fig. 1 Meynert's classification of white matter tracts visualized with diffusion tensor tractography and superimposed on medial and lateral views of the brain surface. Projection tracts connect cortical to subcortical structures. The corona radiata contains descending fibres projecting from the motor cortex to basal ganglia, midbrain motor nuclei (corticobulbar tract) and the spinal cord (pyramidal tract) and ascending fibres from the thalamus to the cortical mantle (thalamic projections). The fornix connects the medial temporal lobe to hypothalamic nuclei. Commissural tracts connect the two hemispheres. The corpus callosum is the largest white matter bundle and connects cortical regions within frontal, parietal, occipital and temporal lobes. The anterior commissure connects the left and right amygdalae and ventromedial temporo-occipital cortex. Association tracts run within each hemisphere connecting distal cortical areas. The cingulum connects medial frontal, parietal, occipital, temporal and cingulate cortices. The arcuate/superior longitudinal fasciculus connects perisylvian frontal, parietal and temporal cortices. The uncinate fasciculus connects orbitofrontal to anterior and medial temporal lobes. The inferior longitudinal fasciculus connects the occipital and temporal lobes. The inferior fronto-occipital fasciculus connects the orbital and lateral frontal cortices to occipital cortex (Catani *et al.*, 2002).

localised, but rested on the mutual interaction of these fundamental psychic elements mediated by means of their manifold connections via the association fibres (Wernicke, 1885).

This is the doctrine of Wernicke's associationist school. Here higher functions arise through associative connections and disorders of higher function from their breakdown. Critically, there was no place for cortical specializations beyond those of primary sensory and motor functions in the classical associationist account. This theoretical framework helped explain distinctive patterns of language, praxis and vision deficits that, today, are referred to collectively as classical disconnection syndromes.
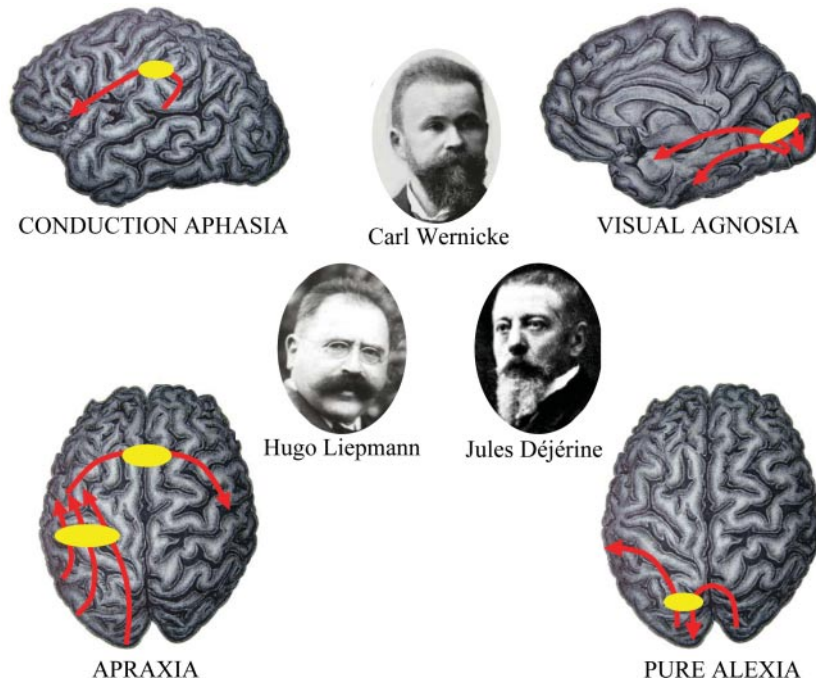
Conduction aphasia

Written at the age of 26 years, Wernicke's MD thesis 'The aphasic symptom-complex' contained a description of the disconnection syndrome that was to become the prototype for all others—conduction aphasia (Leitungsaphasie) (Wernicke, 1874).

Wernicke held that the motor component of language (the images of speech movements) was localized in a frontal region (Broca's area) and that the sensory component of language (auditory images of words) was localized in the posterior part of the superior temporal gyrus (later termed Wernicke's area). Lesions of the Broca and Wernicke centres led, respectively, to pure motor aphasia (impaired fluency but normal comprehension) and pure sensory aphasia (impaired comprehension but normal fluency). Wernicke hypothesized that lesions of the association tracts connecting them led to a conduction aphasia, a pure disconnection syndrome which, in its modern view, consists of a repetition deficit and paraphasic speech (the use of incorrect words or phonemes while speaking) with intact comprehension and fluency. Although not a part of Wernicke's original description, in his later work he argued that repetition deficits related to the failure of transfer of heard words from Wernicke's to Broca's area. Paraphasia was thought to relate to the loss of a higher internal monitoring function which relied on intact connections between Wernicke's and Broca's areas, the 'unconscious, repeated activation and simultaneous mental reverberation of the acoustic image which exercises a continuous monitoring of the motor images' (Wernicke, 1874). Figure 2 (top left) shows a schematic representation of Wernicke's proposed neuro-anatomical explanation for conduction aphasia. Although in his early work he proposed that frontal and temporal language centres were connected through the insula, he later argued that the important pathway was the arcuate fasciculus and that lesions to this pathway would result in conduction aphasia.

Agnosia

Wernicke's contribution to classical disconnection syndromes did not end with conduction aphasia, many key figures of the associationist school being linked to his psychiatric clinic in Breslau. Heinrich Lissauer (1861–91), an assistant in Wernicke's clinic, was one such figure. The year before he died (at the age of 30), he published a detailed case report of an 80-year-old salesman who, following a loss of consciousness

Fig. 2 The classical disconnection syndromes. The pathways implicated in each syndrome are shown in red with the causal lesion in yellow. Wernicke is linked to both conduction aphasia and associative agnosia, the lesion in the former disconnecting Broca's and Wernicke's areas, the lesion in the latter disrupting the outflow of the visual cortex to other brain areas. Liepmann is linked to apraxia where the left-hand motor area is disconnected from other brain regions. Déjérine is linked to pure alexia in which the visual verbal centre is disconnected from visual areas in both hemispheres. See text for further details.

(attributed by the patient to a head injury), lost the ability to recognize even commonplace objects presented visually, although a range of tests indicated that his visual perceptual abilities remained largely intact (Lissauer, 1890). The patient had been presented by Wernicke at a meeting in Breslau the previous year and was considered an example of visual agnosia (Seelenblindheit). The case was used to derive a theoretical classification of visual agnosias based on whether the lesion was primarily of the visual cortex itself (cortical) or of its associative fibre connections (transcortical), the two being manifest as apperceptive and associative subtypes of agnosia, a distinction still in use today. For Wernicke and Lissauer, a lesion which spared visual cortex but involved its white matter outputs would result in visual sensory images being disconnected from other brain areas (Fig. 2, top right). The consequence would be an associative visual agnosia where the ability to visually perceive an object was largely preserved but the visual percept would fail to elicit the wider associations required for recognition.

The apraxias

Hugo Liepmann (1863–1925) joined Wernicke's clinic as an assistant in 1895 and, when he left four years later, carried the Breslau associationist doctrine to Berlin. Here he developed an interest in the motor system which led him to propose a disconnectionist account of higher 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 councillor (Regierungsrat), admitted to the Berlin psychiatric service with a diagnosis of mixed aphasia and dementia (Liepmann, 1900). A striking feature of the patient was that although his spontaneous movements were normal (e.g. using a spoon while eating), 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 no evidence of paralysis, Liepmann hypothesized a disconnection of visual, auditory and somatosensory areas from motor areas. In his later work Liepmann developed a general theory of apraxia (Fig. 2, bottom left). He argued that the left hemisphere was dominant for complex movement control. A lesion localized to the left parietal lobe disconnected the left-hand area from visual, somatosensory and auditory input, leading to bilateral apraxia. In contrast, a lesion of the anterior portion of the corpus callosum disconnected the right hemisphere from the left leading to unilateral left-hand apraxia. Liepmann also argued for a third class of deficits (not shown in the figure) in which a lesion of the left motor area caused a bilateral apraxia, masked on the right by the paresis caused by the lesion (a sympathetic apraxia) (Goldenberg, 2003).

Pure alexia

Of the four classical disconnection syndromes, pure alexia (the inability to read with a preserved ability to write) is the only one not to be directly credited to Wernicke's school.

In Paris during the 1880s, the associationist theory of language was being taught by Charcot using a model consisting of a network of specialized areas (the 'bell' diagram; Brais, 1993), which included a visual centre for words. However, it was Jules Déjérine (1849–1917) who proposed the first disconnectionist account of pure alexia and identified the angular gyrus as the visual centre for words. His theory was based on the combined evidence of two case reports, the first published in 1891, the second in the following year. The first report described a 63-year-old sailor admitted to the Bicêtre hospital in the outskirts of Paris, where Déjérine was Head of Clinical Neurology, who lost the ability to both read and write following a left angular gyrus stroke (Déjérine, 1891).The second described a 68-year-old man with right hemianopia who lost the ability to read but whose writing was intact for 4 years until 6 days before his death (Déjérine, 1892). The patient had evidence of a mixture of lesions of different ages in the left hemisphere:

> recent lesions due to red softening in the inferior parietal lobe and the angular gyrus. Old lesions—atrophical yellow spots—localized in the lingual lobe, fusiform lobe the cuneus and the tip of the occipital lobe as well as a strongly marked atrophia of the optical radiations in the fold of the corpus callosum. (Déjérine, 1892)

Based on these findings, Déjérine proposed that a 'visual verbal centre', whose function was the storage of visual images of words, was located in the left angular gyrus. According to Déjérine, the alexia with agraphia of the first patient was related to a lesion of this area. In contrast, the pure alexia of the second was related to the longstanding left central white matter occipital lesion which both destroyed optic radiation inputs to left visual areas and disconnected left and right visual areas from the visual verbal centre. The patient's acute angular gyrus lesion damaged the visual verbal centre itself, adding agraphia to the clinical picture. Figure 2 (bottom right) illustrates Déjérine's model of pure alexia with a single lesion affecting connections of left and right visual cortices to the left angular gyrus and visual inputs to left hemispheric visual cortex (inputs not shown).

The fall of the classical era

Although Déjérine's model of pure alexia was strongly influenced by the associationist school and its disconnection syndromes, in proposing a centre in the angular gyrus specialized for the visual representations of words, Déjérine broke Wernicke's cardinal rule on two counts. First, his model suggested that higher functions could be located in cortex rather than as the result of connections. Second, he gave his region specialized for higher visual function (in this case word images) a distinct anatomical locus outside visual cortex. For Wernicke, these developments constituted a retrograde step towards phrenology, a move away from the associationist doctrine of higher functions as the result of connections. In his view, visual areas only stored images of

single letters with alexia resulting from a disconnection between visual areas and more anterior temporal and frontal areas. Shortly before his death, Wernicke wrote an explicit critique of Déjérine's view (Bub *et al.*, 1993).

Despite Wernicke's opposition to higher functional centres, the allure of cortical specialization proved difficult to resist. Regions specialized for higher functions began to appear in many accounts of clinical deficits, the view being strengthened by developments in anatomy with Campbell's and Brodmann's division of the cortex into discrete cytoarchitectonic regions (see ffytche and Catani, 2005 for a review). By 1934, Kleist, ironically one of Wernicke's successors in Breslau, had published a detailed cortical map of higher functions which had become difficult to distinguish from phrenological maps of the previous century (Luria, 1980). This return to narrow localizationism was easy to criticize and the early 20th century saw the emergence of a holistic, anti-localizationist, anti-associationist approach to higher function that was to dominate until Geschwind. This movement was led amongst others, by Henry Head in England, who referred disparagingly to the classical school as diagram makers, Von Monakow in Switzerland, Kurt Goldstein in Germany and Karl Lashley in America (Geschwind, 1964). By 1965, localization theory, disconnection syndromes and any interest in clinicopathological correlations had been relegated to little more than footnotes in the history of neurology.

Geschwind's neo-associationism

It was the work of Myers and Sperry in the 1950s that began the shift away from pure holism which was to culminate in Geschwind's revived associationism. Their experiments on the consequences of callosal section, first in animals and then in patients with epilepsy revealed unequivocal evidence for hemispheric localization of brain functions. The work reawakened neurological interest in clinicopathological correlations in general and led Geschwind, then in his 30s and working in the aphasia research section of the Boston Veterans Administration Hospital, to 're-examine the older clinical literature and to re-assess our patients with disturbances of the higher functions' (Geschwind, 1965a). The outcome was his 1965 publication which was to become a manifesto for the neo-associationist school. In the following section we provide a brief summary of Geschwind's 1965 paper, a work which, in total, spanned 116 unillustrated pages of *Brain*, focusing on those areas in which he extended the classical associationist account.

The neuroanatomical and phylogenetic foundations of Geschwind's theory

Geschwind added two new components to the classical view: a forgotten principle—Flechsig's rule—and a comparative phylogenetic perspective to the development of associations. Paul Flechsig (1847–1929), Professor of Psychiatry in Leipzig, had performed detailed studies of cortical myelination at
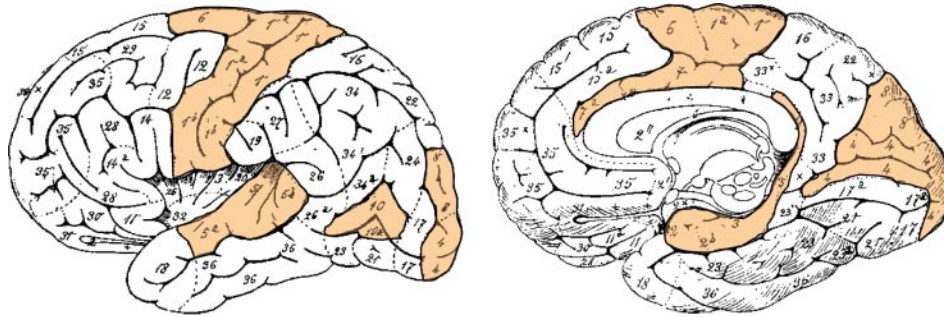
Fig. 3 Flechsig's myelogenetic map of human cortex. The numbering of each region refers to its chronological order of development. Those shown in colour are myelinated at birth and constitute his primordial zones (Flechsig, 1901).

different stages of human brain development (Fig. 3). One consequence of this work was the emergence of a general pattern of connections in which 'no long association system is known which connects two primordial zones that are to be regarded as sensory centres' (Flechsig, 1901). Flechsig's primordial zones were the cortical regions fully myelinated at birth and corresponding to primary sensory areas. For Flechsig, all connections between such areas were indirect as they passed through their respective surrounding mantles of association cortex. Although Flechsig's anatomical observations applied to sensory cortex only, Geschwind generalized the rule to include motor cortex and interhemispheric connections (Geschwind, 1965a, b). The rule formed the cornerstone of his theory, implying that association cortex acted, in effect, as an obligatory relay station between different brain regions and that a lesion to it would serve to disconnect them.

The second novel component of Geschwind's theory related to the phylogeny of Flechsig's rule and the light this shed on the evolution of higher functions. For Geschwind, the rule was one that had emerged in primate species:

> in the lower mammals connections between regions of the cortex may arise directly from the primary receptive or motor areas. As one moves up the phylogenetic scale, these connections come to be made between newly developed regions of cortex interspersed between the older zones. These regions are called association cortex . . . all intercortical long connections (whether in or between hemispheres) are made by way of these association areas and not between the primary motor or receptive areas. (Geschwind, 1965a)

The implication was that the evolution of association cortex underlay the evolution of higher function, the trend continuing with the evolution of non-human primates to man where the key anatomical development was the emergence of a higher-order association area in the human parietal lobe. This new area allowed a uniquely human pattern of connections between sense modalities that did not depend on the limbic system:

> While connections between primary receptive regions and limbic structures are powerful in subhuman forms, intermodal connections between vision, audition and

somesthesis are probably weak in these animals. . . . In man the situation changes with the development of the association areas of the human inferior parietal lobule, situated at the junction of the older association areas attached to the visual, somesthetic, and auditory regions. It is speculated that this new 'association area of association areas' now frees man from the dominant pattern of sensory-limbic associations and permits cross-modal associations involving non-limbic modalities. (Geschwind, 1965a)

Figure 4 summarizes Geschwind's evolutionary perspective. In the rabbit primary sensory cortices of different modalities are connected both directly and through the limbic system. In the monkey, with the evolution of Flechsig's rule, the limbic system continues to play an important role in connecting different sensory modalities; however, connections to the limbic cortex now arise from the mantle of association cortex surrounding primary sensory areas. In man, intermodality connections are freed from the limbic system through the development of the inferior parietal lobe (the angular and supramarginal gyri), an area connecting visual, auditory and somatosensory association areas. For Geschwind, the area and its multisensory connections played a particular role in language development:

> it is only in man that associations between two non-limbic stimuli are readily formed and it is this ability which underlies the learning of names of objects. . . . The angular gyrus is important in the process of associating a heard name to a seen or felt object, it is probably also important for associations in the reverse direction. A name passes through Wernicke's area, then via the angular gyrus arouses associations in the other parts of the brain. It is probably thus that Wernicke's area attains it essential importance in comprehension i.e. the arousal of association. (Geschwind, 1965a)

In a sense, by highlighting the importance of the angular gyrus in language, Geschwind was returning to Déjérine's model. However, the role of the angular gyrus was very different for Déjérine and Geschwind. Déjérine viewed the region as one storing visual memories of letters and words, whereas Geschwind viewed it as having a more general function in
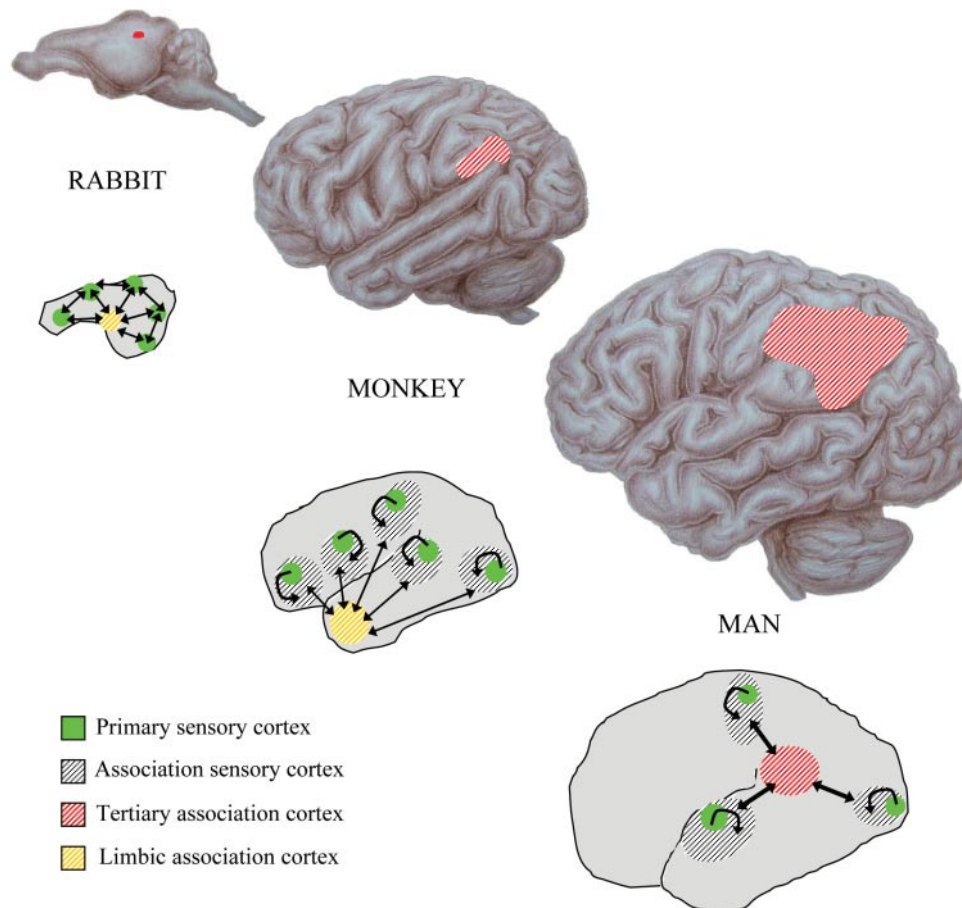
Fig. 4 Geschwind's view of the evolution of cross-modality associations. For simplicity only sensory cortex is illustrated. The top diagonal sequence shows the expansion of inferior parietal cortex from rabbit through monkey to man, considered by Geschwind as central for the development of language. The bottom diagonal sequence shows the differences in brain circuitry between the species. In the rabbit, Flechsig's rule does not apply and the primary cortices of different sensory modalities are connected directly to one another as well as through limbic cortex. In the monkey, primary cortices connect only to their association cortices with intermodality connections mediated by the limbic cortex. In man, the majority of intermodality connections are mediated by higher-order association cortex in the parietal lobe.

forming multimodality associations, a prerequisite function for language and semantics.

Geschwind's disconnection syndromes

For Wernicke and his school, disconnection and its syndromes had implied a white matter lesion to the association tracts connecting two areas. For Geschwind, basing his argument on Flechsig's rule, disconnection syndromes went beyond this to imply a lesion of association cortex itself, particularly that in the parietal lobe. In Geschwind's 1965 model, even a pure lesion of association cortex could cause a disconnection syndrome, little distinction being made between such lesions and those restricted to white matter tracts.

> lesions of association cortex, if extensive enough, act to disconnect primary receptive or motor areas from other regions of the cortex in the same or in the opposite

hemisphere. . . . Thus a 'disconnexion lesion' will be a large lesion either of association cortex or of the white matter leading from this association cortex. (Geschwind, 1965*a*)

Based on this broader view, Geschwind reappraised disorders of higher functions, couching many of them in terms of disconnection. Figure 5 summarizes the underlying anatomical principles for the most important disconnection syndromes as set out in 1965, loosely classified by the type of connections involved.

Disconnections between sensory areas and limbic cortex

For Geschwind, limbic structures were important for learning and emotional response. The disconnection of a specific sense modality from limbic structures would result in the failure of a stimulus presented in that modality to evoke memories or affective responses (Fig. 5, dotted lines).
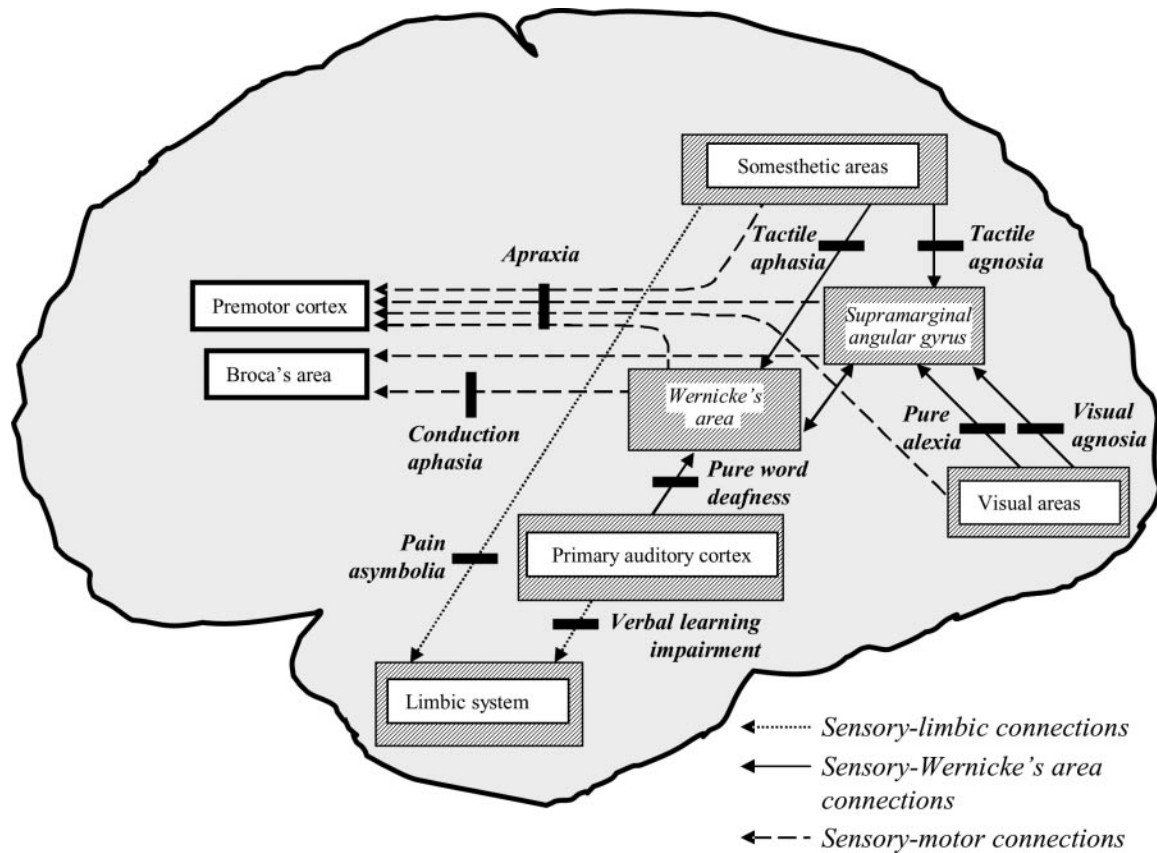
Fig. 5 Geschwind's disconnection syndromes. The pathways implicated in the principle syndromes described by Geschwind, classified into three types: sensory–limbic disconnection syndromes (dotted lines), sensory–motor disconnection syndromes (dashed lines); sensory–Wernicke's area disconnection syndromes (solid lines). See text for further details.

Lesions causing such syndromes were located in limbic association cortex (e.g. temporal pole, parahippocampal gyrus and insula) and less commonly, sensory association cortex or the white matter tracts connecting the two. In man, such sensory–limbic disconnection occurred in the somatosensory and auditory but not visual systems. Disconnection of somatosensory cortex from the limbic lobe resulted in pain asymbolia (no response to pain in the presence of normal tactile discriminatory function). Disconnection of auditory cortex from the limbic lobe resulted in a range of symptoms (verbal learning impairment, euphoria and symptom denial) commonly found in patients with Wernicke's aphasia. In the visual system, the development of an indirect connecting pathway between visual and limbic structures through the inferior parietal lobe meant that symptoms commonly seen in non-human primates with visual–limbic disconnections did not occur in man (Geschwind, 1965*a*).

Disconnections between sensory areas and Wernicke's area

Disconnection of Wernicke's area from specific sensory areas would lead to modality-specific language deficits, caused either by a lesion of direct connections between Wernicke's and sensory areas or by a lesion of indirect connections through the angular gyrus (Fig. 5, solid lines). Geschwind distinguished four such syndromes. The first consisted of tactile aphasia (the inability to name a held object in the presence of preserved speech and naming in other sense modalities), today referred to as tactile anomia. The second consisted of pure word deafness, a syndrome originally described by Liepmann, an inability to understand spoken words in the presence of preserved hearing (Liepmann, 1898). The third consisted of pure alexia for which Geschwind used Déjérine's explanatory model. The fourth consisted of modality-specific agnosias (inabilities to recognize objects in the presence of intact elementary sensation). Geschwind focused on visual agnosia, his account differing from the classical Lissauer–Wernicke model in its emphasis on language. For Geschwind, both perception and language were intact in visual agnosia, the deficit arising from a failure of their communication. He argued that visual agnosia was a highly isolated disturbance of naming, the result of a disconnection of visual areas from the inferior parietal lobe, and hence indirectly to Wernicke's area, with the consequent inability of a sensory percept to arouse language associations.

Disconnections between sensory areas and motor cortex

In the left hemisphere, disconnections of the hand motor cortex from posterior sensory areas or Broca's area from Wernicke's area resulted in apraxia and conduction aphasia respectively (Fig. 5, dashed line). Geschwind's account of apraxia adhered faithfully to Liepmann's classical explanation. His account of conduction aphasia added to Wernicke's model in that he suspected the preserved ability of patients with conduction aphasia to produce semantically related words when asked to repeat was related to indirect connections through the angular gyrus (a semantic detour) (Geschwind, 1965*b*).

Disconnection between the hemispheres

For convenience, Fig. 5 has illustrated Geschwind's disconnection syndromes from the perspective of the left hemisphere; however, his 1965 paper emphasized the importance of interhemispheric disconnection, although it did not constitute a separate 'callosal' disconnection syndrome. The role of callosal disconnection in his model was the same as that put forward by Déjérine and Liepmann in their respective models of pure alexia and apraxia.

Disconnection syndromes after Geschwind

In a sense, Geschwind became for the 20th century what Wernicke was for the 19th century, a generation of neurologists influenced by his approach, among them Marsel Mesulam, Antonio Damasio, Frank Benson and Albert Galaburda, all of whom passed through Geschwind's neurology department in Boston (Damasio and Galaburda 1985; Mesulam, 1985*b*). (Geschwind and Wernicke also share in common the fact that their family origins were <150 miles apart in what is now southern Poland and that both died prematurely in their 50s.) He was not simply Wernicke's, Liepmann's and Déjérine's translator across centuries and languages, his own contribution being to enrich the classical associationist view with the idea of association cortex as an obligatory relay, the theory of hierarchies of associations within the inferior parietal lobe and the importance of this region in the phylogeny and ontogeny of language. However, Geschwind's 1965 framework held most, if not all, disorders of higher function to be related to disconnection and although the theory did not fall after its publication, with time it became integrated into a more general model in which the specializations of association cortex were given equal footing with corticocortical connections (see below). This evolution to a more general account took two separate but closely related paths, both delineated in Geschwind's 1965 *Brain* paper. One path used as its starting point brain lesion location, capitalizing on the emerging imaging techniques of computerized tomography, PET and SPET scanning. This was the path taken by Damasio, leading to important insights into the neural mechanisms of perception (Damasio, 1985), language (Damasio and Damasio, 1983; Damasio and Geschwind, 1984) and emotion (Damasio, 1999, Damasio *et al.*, 2000). The second path used as its starting point the connections of brain regions, capitalizing on emerging techniques for tracing neural connections, primate neurophysiology and computational theory. This was the path taken by Mesulam, leading to important insights into the dynamic brain networks underlying memory, attention and language (Mesulam, 1990*b*), the neural mechanisms of perception (Mesulam, 1998), neglect (Mesulam, 1981), aphasia (Mesulam, 2001) and cholinergic pathways (Mesulam, 1990*a*; Selden *et al.*, 1998). Although Geschwind never returned to the grand perspective of his 1965 theory, over the next 20 years he continued to work on clinicopathological correlations from both of these perspectives with members of his school, extending the remit of his 1965 model beyond classical neurology into neurodevelopmental disorders, such as dyslexia. Together with his 1965 paper, this corpus of work founded behavioural neurology, strongly influenced the development of related disciplines, such as neuropsychiatry and neuropsychology and prepared the ground for neural network and connectionist theories in the cognitive sciences.

The contemporary neuroanatomical basis of higher brain functions

Geschwind's 1965 anatomical framework for higher function and its disorders, although correct in many respects, also had weaknesses which he himself and members of his school amended in later years as new evidence became available.

Although admitting it a simplification, Geschwind held in 1965 that association cortex was a little more than a homogeneous relay station between primary sensory and motor areas with no specialized roles of its own. That this homogeneous view might be wrong became increasingly apparent in the 1960s and 1970s with anatomical and neurophysiological work in the monkey and clinical evidence in man and by 1985, both Mesulam and Damasio had incorporated specific functional roles for association cortex into their neuroanatomical accounts of higher function (Damasio, 1985; Mesulam, 1985*a*). The functional subdivision of association cortex was later confirmed in man using functional imaging techniques (Zeki *et al.*, 1991). Such cortical specialization is more complex than envisaged by classical localizationist theory. What were once considered localized centres (e.g. Broca's and Wernicke's areas) are today held to be extended territories composed of many specialized cortical subregions serving different but related functions (see for example Cannestra *et al.*, 2000; Boatman, 2004; Damasio *et al.*, 2004; Hickok and Poeppel, 2004 for evidence in the language domain). A further weakness of Geschwind's 1965 position was the predominantly feed forward, serial nature of his account. Information passed from posterior sensory cortices, through hierarchies of association cortices to limbic and anterior frontal cortices in a serial fashion with little attention

being paid to the functional implications of feed-back and parallel pathways. The contributions to higher function made by these anatomical features were later emphasized by Damasio in his retroactivation model (Damasio, 1989; Damasio and Damasio, 1994) and Mesulam in his large-scale network model (Mesulam, 1990*b*). The presence in man of parallel, bidirectional and distributed processing for higher functions has recently been confirmed (for example, in the domain of language see Matsumoto *et al.*, 2004; Bitan *et al.*, 2005; Catani *et al.*, 2005). The contemporary framework for clinicopathological correlations that evolved from Geschwind's 1965 model thus consists of a network of multiple specialized cortical areas, grouped into territories and connected through parallel, bidirectional pathways. In this model, two key elements underlie higher function deficits: (i) the loss of specialized cortical function and (ii) damage to connecting pathways. Of these, in man, the former is better understood than the latter as brain lesion studies and functional imaging have helped advance our understanding of cortical specialization and its related deficits. In contrast, our anatomical knowledge of connecting pathways has, until recently, relied on primate tracing studies (Mesulam, 2005). An important consequence of this limitation is that it has allowed for hypothetical *post hoc* disconnection explanations of higher function deficits. For a given lesion, the absence of a predicted deficit (or for a given deficit, the absence of a predicted lesion) is amenable to explanation by any number of alternative pathways making it difficult to test or falsify the disconnectionist account.

The advent of new techniques is beginning to redress the imbalance between our knowledge of the cortex and that of its connections. Tractography, although lacking the anatomical precision of post mortem tracing, is helping advance our understanding of human white matter anatomy and may have an important contribution to make in testing the disconnection paradigm. Other techniques exploring mathematical 'connections' between areas in electrophysiological and neuroimaging data provide complementary evidence on the functional roles of such connections. Together these techniques allow us to broaden the remit of the contemporary clinicopathological correlation framework beyond disorders of disconnection and cortical deficit to include disorders of hyperconnection and cortical hyperfunction. In the final part of this review we accommodate the evidence of these emerging techniques within the existing framework, illustrating how we envisage the updated framework can be used clinically with specific tractography-derived examples.

A hodotopic framework for clinicopathological correlations

The general framework we propose is summarized in Fig. 6A. In the figure, territories are simplified as being composed of two specialized areas or subregions. It is important to realize that functionally specialized cortical subregions, and the territories they form, need not respect cytoarchitectonic
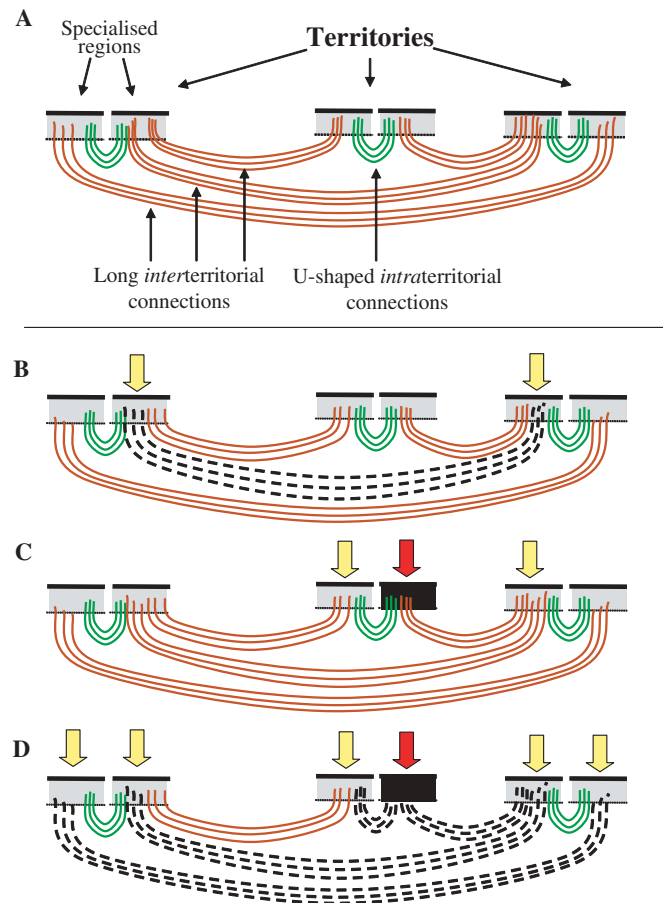
Fig. 6 A hodotopic framework for clinicopathological correlations. (**A**) The contemporary view of the cortex and its connections. Different regions of specialized cortex (grey rectangles) are connected by U-shaped fibres (green) to form extended territories, themselves connected by long, interterritorial fibres (red). (**B**) The consequence of white matter pathology. The dashed pathway is either hyper- or hypofunctional. Yellow arrows indicate dysfunctional cortical regions, in this case through a hodological mechanism. (**C**) The consequence of cortical pathology. The black region of cortex is hyper- or hypofunctional. The red arrow indicates cortex dysfunctional through a topological mechanism. For some tasks distant cortical regions may be dysfunctional through a secondary hodological mechanism (yellow arrows). (**D**) The consequence of combined white matter and cortical pathology. The black area of cortex and dashed pathways are hyper- or hypofunctional. Yellow arrows indicate widespread cortical regions affected by a hodological mechanism while the red arrow indicates a region of topological dysfunction. See text for further details.

boundaries (several specialized visual areas are located within Brodmann area 18; for example Zeki, 1978). It is at present unclear whether different specialized areas are always anatomically distinct (e.g. the occipital lobe areas V1, V2, V3) or overlap (e.g. the rostrocaudal segregation of Broca's territory). Nor is it clear how many territories there are with respect to broadly defined functions, such as language, praxis and vision. The predominant intraterritorial connections are likely to be U-shaped association fibres, although neighbouring cortical regions within a territory may be linked at

their border by intracortical fibres (not shown in the figure). Tractography evidence suggests that territories are connected by multiple parallel long association fibre pathways (Catani *et al.*, 2005). Although the anatomical details of these interterritorial connections are yet to be worked out, existing data suggest that they connect specific specialized subregions in different territories in parallel.

What are the functional consequences of pathology in this updated model? Here we introduce a new terminology to allow us to extend the model beyond classical neurological disorders of white matter disconnections and cortical deficits to include those involving white matter hyperconnectivity and cortical hyperfunction. According to the new terminology, a topological mechanism (from the Greek *topos* = place) refers generally to a dysfunction of the cortex irrespective of whether the dysfunction is one of deficit, hyperfunction or a combination of the two. Topologically-related dysfunctions range from deficits related to the loss of a specialized cortical region, e.g. prosopagnosia from lesions of face-specialized cortex in the fusiform gyrus (Sergent *et al.*, 1992), to specific positive symptoms, such as face hallucinations related to the hyperexcitability and spontaneous activation of face-specialized cortex (ffytche *et al.*, 1998). A hodological mechanism (from the Greek *hodos* = road or path) refers generally to dysfunction related to connecting pathways, irrespective of whether the dysfunction is one of disconnection, hyperconnection or a combination of the two. Hodologically-related dysfunctions range from classical disconnection syndromes such as the conduction aphasia of pure subcortical lesions (Naeser *et al.*, 1982) to the combination of frontofrontal hyperconnectivity with frontal disconnection from other brain regions in autism (Courchesne and Pierce, 2005).

Figure 6B–D illustrates the different patterns of cortical dysfunction that occur as the result of pathologies within this hodotopic framework. The first pattern relates to a pathology of white matter pathways, such as might be caused by localized vascular, neoplastic or demyelinating lesions leading to disconnection or to hyperconnectivity, e.g. through a failure to prune connections (Fig. 6B). Distant cortical regions connected by the affected pathway are dysfunctional as the consequence of pure hodological effects (the yellow arrows in the figure). For some tasks this dysfunction may simply reflect the failure or excess of transfer of outputs from one area to another; however, for tasks requiring the simultaneous cooperation of cortical regions (e.g. synchronous bimanual coordination) one can consider the function itself to be distributed (a functional loop), the lesion disrupting or enhancing the function as a whole. Whether for a serial or distributed task, the dysfunction of connected regions may only be apparent for those tasks requiring both connected areas, the function of each area individually being normal when they form a part of a different task network (a dynamic diaschisis; Price *et al.*, 2001). Cortical pathology causes a different pattern dysfunction (Fig. 6C). Here cortical lesions or hyperactivity lead to dysfunction through a topological mechanism (red arrow). The dysfunction may go beyond the affected cortical site to include cortical regions connected to it. These effects arise through a hodological mechanism but differ from those described above in that the white matter is not directly affected. One may wish to refer to these remote effects as secondary hodological (yellow arrows). As for pure hodologically based dysfunction, these remote effects will demonstrate a dynamic diaschisis, only being apparent for tasks normally requiring both regions. Both neuroimaging (Kempler *et al.*, 1988; Price *et al.*, 2001) and clinical (De Renzi and Vignolo, 1962) studies of the language network have found evidence for these remote functional effects. Focal pure cortical lesions are rare and include superficial vascular or neoplastic lesions which spare long associative fibres (whether or not such lesions encroach superficial white matter makes little difference to the ensuing pattern of deficit). An equivalent pattern of deficits will also arise in a range of localized neurodegenerative disorders, such as posterior cortical atrophy, primary progressive aphasia and frontotemporal dementia. Pure topological hyperactivity occurs in conditions such as sensory deafferentation (Burke, 2002) and focal seizures. The third type of dysfunction involves both hodological and topological mechanisms (Fig. 6D). In relation to deficits, this is the pattern most likely to be encountered clinically and would typically be caused by a stroke, tumour or brain injury. Here the lesion involves both cortical and subcortical structures with superficial and deep white matter affected. In this case, combined topological (red arrow) and hodological effects (yellow arrows) produce widespread cortical dysfunction. Auditory hallucinations in schizophrenia provide an example of combined hodological and topological hyperfunction, with increased activation of Broca's, Wernicke's and Geschwind's territory (Lennox *et al.*, 2000; Shergill *et al.*, 2000) and indirect, diffusion tensor tractography evidence of increased anatomical connectivity between these regions (Hubl *et al.*, 2004).

We acknowledge that the hodotopic framework is an oversimplification and merely follows the now 40-year tradition of incorporating new anatomical and functional details into Geschwind's scheme as they become available. However, we hope it adds clinically useful features to existing models, in particular, extending them beyond classical neurological deficits and disconnections to encompass a broader range of disorders. Of course, its main clinical usefulness will come not from the generalizations outlined above, but from its application to specific functional domains. In some domains, our understanding of cortical and white matter anatomy is already sufficient to provide a sketch of the type of account we envisage. The following three examples help illustrate the contribution we hope the hodotopic framework will eventually make to the classification and assessment of patients with disorders of higher function.

Language network disorders
Figure 7 shows our recent tractography reconstruction of the parallel perisylvian language network. One pathway connects
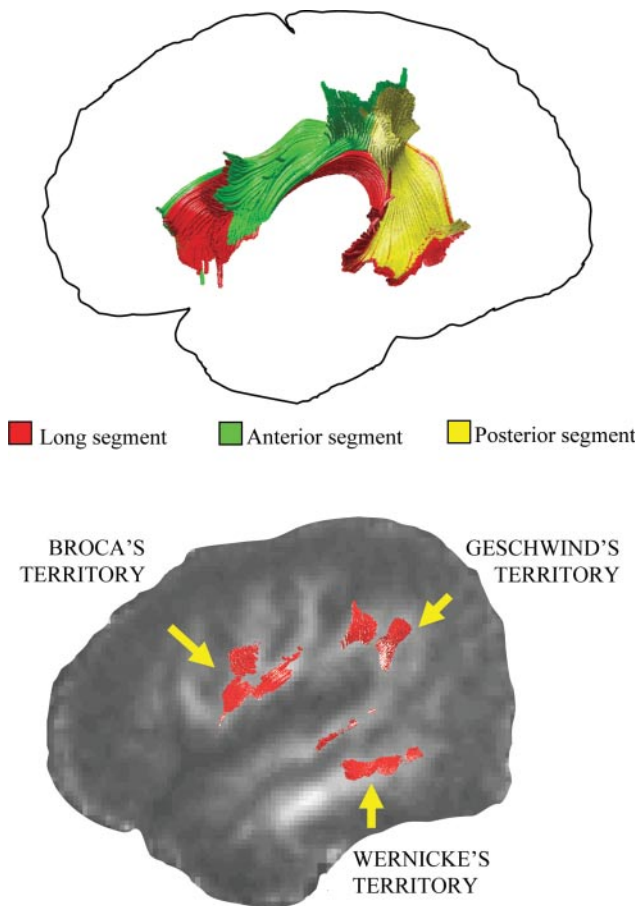
Fig. 7 The parallel perisylvian language network. Top panel: a 3D reconstruction of the direct and indirect perisylvian pathways in the left hemisphere (lateral view) derived from an average brain. The long segment fibres (red) connect Broca's and Wernicke's territories. The anterior segment fibres (green) connect Broca's and Geschwind's territories. The posterior segment fibres (yellow) connect Wernicke's and Geschwind's territories. Bottom panel: a parasagittal section through the diffusion tensor anisotropy volume with fibre tracts coregistered. The terminal portions of all three segments are displayed in red. Adapted from Catani *et al.* (2005).

Broca's and Wernicke's territory directly (the long segment) and corresponds to the classical arcuate fasciculus (shown in red). An additional parallel indirect pathway between Broca's and Wernicke's territory passes through the inferior parietal lobe, a region we named after Geschwind (Catani *et al.*, 2005). This indirect connection consists of a posterior segment connecting temporal and parietal cortex (shown in yellow) and an anterior segment connecting parietal and frontal cortex (shown in green). The cortical terminations of these pathways are shown superimposed on a parasagittal anisotropy image, the three projection zones corresponding to Broca's territory (inferior part of the precentral gyrus and posterior part of the middle and inferior frontal gyri), Geschwind's territory (angular and supramarginal gyri) and Wernicke's territory (posterior part of the superior and middle temporal gyri). Although evidence is not yet available, it is likely that each

of these connecting pathways plays a different functional role, the direct pathway being involved in phonologically based language functions such as repetition, the indirect pathway being involved in semantically based language functions, such as auditory comprehension (posterior segment) and vocalization of semantic content (anterior segment) (Catani *et al.*, 2005). From the perspective of our hodotopic model, lesions affecting different territories, white matter segments or their combination would be expected to cause different types of language deficit as illustrated by the following scenarios in relation to a lesion in the inferior parietal lobe. Two scenarios result from a pure hodological mechanism: (i) If the lesion is purely subcortical, affecting the long segment only, we would expect to find a classical conduction aphasia with a repetition deficit in the presence of normal auditory comprehension and verbal fluency. (ii) If the subcortical lesion affects both direct and indirect pathways we would expect to find a global aphasia despite intact cortex (Naeser *et al.*, 2005). In contrast, a cortical lesion encroaching on Geschwind's territory would be expected to produce a pattern of deficit which varied depending on which cortical subregions are affected: (i) If involving only the anterior portions of Geschwind's territory (the cortical endstation of the anterior segment), the syndrome will be one of non-fluent aphasia with spared repetition and comprehension (see Basso *et al.*, 1985 for an example of this deficit pattern with a retrorolandic lesion). (ii) If involving all of Geschwind's territory (the cortical endstation of both anterior and posterior segments), the deficit will be one of a mixed transcortical aphasia with normal repetition but both reduced verbal fluency and comprehension. (iii) The same lesion extending into the deep white matter would present with a global aphasia with impaired repetition, fluency and comprehension. Hyperfunction involving different territories, segments and their combination would also be expected to cause a heterogeneity of positive symptoms with, for example, hyperfunction in the indirect pathway causing semantically based symptoms and hyperfunction in the direct pathway causing disorders of excessive repetition (e.g. the echolalia of autism). Although only a few studies have been performed to test this prediction, there is already evidence of specific indirect pathway hyperfunction in schizophrenic patients with auditory hallucinations (Lennox *et al.*, 2000; Hubl *et al.*, 2004).

Praxis network disorders

Figure 8 illustrates the frontoparietal network thought to underlie praxis. The contemporary view of praxis derived from work in the monkey is of multiple functions related to different body parts (e.g. the trunk, face or limb) and motor acts (e.g. reaching/grasping, motor sequencing and posture in relation to the limb) (Rizzolatti *et al.*, 1998). Each of these praxic functions has distinct cortical loci and connecting circuitry. At least three sets of fibre connections equivalent to those underlying praxis in the monkey can be identified in the human brain. The dorsolateral frontoparietal
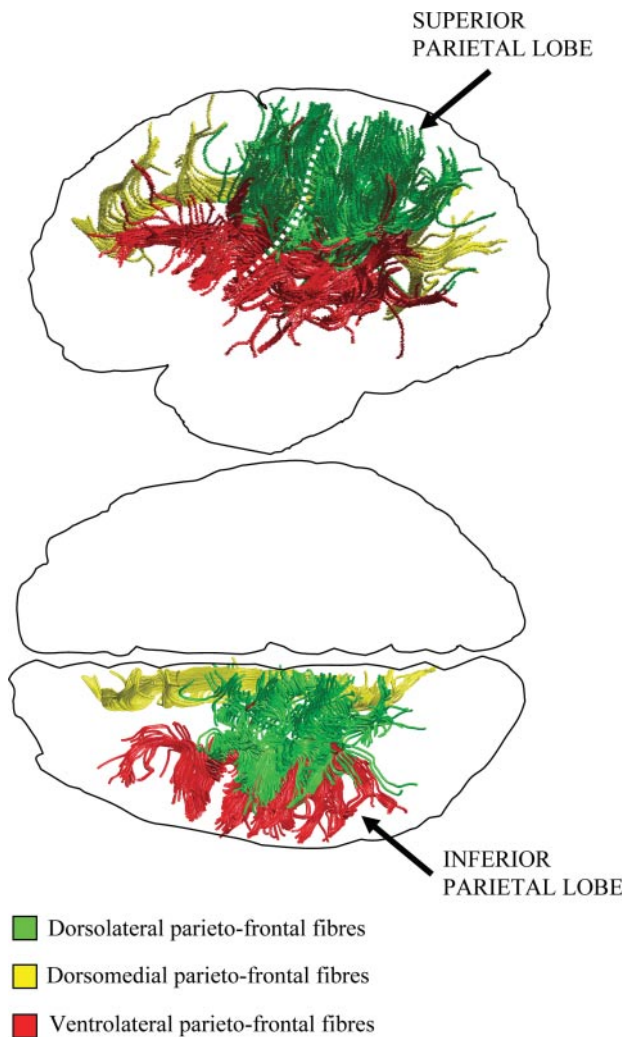
Fig. 8 Praxic frontoparietal circuitry. A 3D reconstruction of the fibre connections between parietal and frontal lobes in the left hemisphere derived from a single brain and shown from the left (top panel) and top of the brain (bottom panel). The pathways have been defined using a two-region of interest approach (Catani *et al.*, 2002). One pair of regions was used to identify dorsolateral fibres connecting the superior parietal lobe and dorsal motor and premotor cortex (green fibres). Another pair of regions was used to identify ventrolateral fibres connecting the inferior parietal lobe and ventrolateral motor and premotor cortex. The third pair of regions was used to identify dorsomedial fibres connecting the medial parietal lobe with the medial frontal lobe. The dotted white line is the central sulcus.

set connects the dorsal motor and premotor cortex to the superior parietal lobe (green fibres); the ventrolateral frontoparietal set connects the ventrolateral motor and premotor cortex to the inferior parietal lobe (red fibres) and the medial frontoparietal set connects the medial frontal lobe to the medial parietal lobe (precuneus) (yellow fibres). From the perspective of our hodotopic model, a lesion involving the cortical territories and white matter connections involved in praxis will have different effects depending on its cortical location and subcortical extension. If the lesion is restricted

to superior parietal cortex, its consequence will depend on which praxic subfunctions within the territory are affected. If the lesion extends into white matter, additional abnormalities would be expected (see Leiguarda and Marsden, 2000 for a review of clinicopathological correlations in apraxia). The hyperfunctional and hyperconnectivity disorders of this network are at present unclear.

Visual network disorders

Although Geschwind's 1965 model held all agnosias as disconnections between visual and language areas, today visual agnosia is often considered a family of disorders, each related to a specific deficit of visual form perception (e.g. faces or objects). This cortical deficit account is partly a translation to the domain of visual form perception of the model used to explain deficits of other visual attributes, such as colour (achromatopsia) or motion (akinetopsia) (Damasio, 1985; Zeki, 1990, 1991) and has been applied to prosopagnosia and alexia (Sergent *et al.*, 1992; Leff *et al.*, 2001). Whether both accounts of the associative agnosias (cortical deficit or disconnection) are correct remains to be established; what is certain is that the white matter connections of visual areas are complex and the contribution they make to visual perception and its deficits is not fully understood. Tractography has recently helped delineate occipitotemporal connections in the human brain (Catani *et al.*, 2003), shown in Fig. 9. As in the monkey (Tusa and Ungerleider, 1985), visually specialized cortical areas in the human brain are connected by chains of U-shaped fibres, a subset of which forms the occipitotemporal projection system. Here we have illustrated a chain on the lateral surface (red fibres) but equivalent chains are found on the ventral surface. Recent tractography evidence confirms the existence in man of a parallel, direct occipitotemporal pathway (the inferior longitudinal fasciculus, green fibres) connecting prestriate cortex to medial temporal structures (the hippocampus, parahippocampal gyrus and amygdala) (Catani *et al.*, 2003). Although the different functions of these two sets of connections is unclear, it seems likely that they differ, one possibility being that the indirect system relates to visual perceptual qualities and the direct with emotional qualities and visual memory. From the perspective of our hodotopic model, a ventral or lateral temporal cortical lesion would lead to specific deficits related to the cortical specializations lost, an extension into medial white matter would lead, in addition, to visual hypoemotionality (a deficit of visually evoked emotions with preserved emotional responses to non-visual stimuli; see Bauer, 1982 for an example) or visual amnesia (a deficit of registering novel visual experiences in short term memory with the preserved ability to register non-visual images; see Ross, 1980 for an example). Hyperfunction of specialized visual cortical areas is associated with hallucinations of specific visual attributes (ffytche *et al.*, 1998; ffytche and Howard, 1999). The consequences of hyperconnectivity within the indirect or direct occipitotemporal pathways are unclear but may
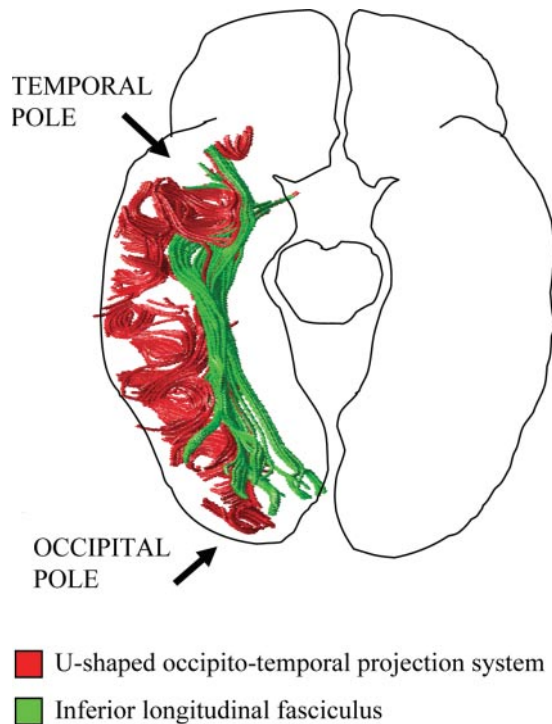
Fig. 9 Occipitotemporal pathways. A 3D reconstruction of fibre connections between right hemispheric occipital and temporal lobes derived from a single brain and viewed from below. Two sets of fibres are shown. One consists of a chain of U-shaped fibre connections (red) which contribute to the indirect occipitotemporal projection system. The other consists of direct occipitotemporal connections forming the inferior longitudinal fasciculus (green). Adapted from Catani *et al.* (2003).

underlie symptoms, such as synaesthesia between visual attributes (e.g. grapheme-colour synaesthesia) and excessive emotional responses to visual stimuli (e.g. in phobic disorders).

Conclusion

The disconnection paradigm has lost none of the clinical appeal it had when first formulated in the classical era or during its neo-associationist revival in 1965. However, a pure disconnectionist account is in itself not sufficient to explain the entire spectrum of higher function disorders as it ignores both the role of specialized cortex and the clinical consequences of hyerconnectivity. Geschwind's original model, notably through the contributions of Mesulam and Damasio, evolved over the last 40 years to include both connections between brain regions and the specializations of association cortices. Here we have further expanded the model to encompass hyperconnectivity and cortical hyper-activity disorders. Although many of these hyperfunctional disorders have yet to be demonstrated, today we are in a unique position to examine connections non-invasively in man through combinations of functional and anatomical imaging techniques (Mesulam 2005; ffytche and Catani 2005) and to correlate their pathology to specific clinical

symptoms. These new techniques reinvigorate the journey along Geschwind's 40-year-old path, signposting future directions for biological psychiatry and cognitive neurology.

References

Absher JR, Benson DF. Disconnection syndromes: an overview of Geschwind's contributions. Neurology 1993; 43: 862–7.

Basser PJ, Mattiello J, LeBihan D. MR diffusion tensor spectroscopy and imaging. Biophys J 1994; 66: 259–67.

Basser PJ, Pajevic S, Pierpaoli C, Duda J, Aldroubi A. In vivo fiber tractography using DT-MRI data. Magn Reson Med 2000; 44: 625–32.

Basso A, Lecours AR, Moraschini S, Vanier M. Anatomoclinical correlations of the aphasias as defined through computerized tomography: exceptions. Brain Lang 1985; 26: 201–29.

Bauer RM. Visual hypoemotionality as a symptom of visual-limbic disconnection in man. Arch Neurol 1982; 39: 702–8.

Bitan T, Booth JR, Choy J, Burman DD, Gitelman DR, Mesulam MM. Shifts of effective connectivity within a language network during rhyming and spelling. J Neurosci 2005; 25: 5397–403.

Boatman D. Cortical bases of speech perception: evidence from functional lesion studies. Cognition 2004; 92: 47–65.

Brais B. Jean Martin Charcot and aphasia: treading the line between experimental physiology and pathological anatomy. Brain Lang 1993; 45: 511–30.

Bub DN, Arguin M, Lecours AR. Jules Déjérine and his interpretation of pure alexia. Brain Lang 1993; 45: 531–59.

Bullmore ET, Frangou S, Murray RM. The dysplastic net hypothesis: an integration of developmental and dysconnectivity theories of schizophrenia. Schizophr Res 1997; 28: 143–56.

Burke W. The neural basis of Charles Bonnet hallucinations: a hypothesis. J Neurol Neurosurg Psychiatry 2002; 73: 535–41.

Cannestra AF, Bookheimer SY, Pouratian N, O'Farrell A, Sicotte N, Martin NA, et al. Temporal and topographical characterization of language cortices using intraoperative optical intrinsic signals. Neuroimage 2000; 12: 41–54.

Catani M, Howard RJ, Pajevic S, Jones DK. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. Neuroimage 2002; 17: 77–94.

Catani M, Jones DK, Donato R, ffytche DH. Occipito-temporal connections in the human brain. Brain 2003; 126: 2093–107.

Catani M, Jones DK, ffytche DH. Perisylvian language networks of the human brain. Ann Neurol 2005; 57: 8–16.

Conturo TE, Lori NF, Cull TS, Akbudak E, Snyder AZ, Shimony JS, et al. Tracking neuronal fiber pathways in the living human brain. Proc Natl Acad Sci USA 1999; 96: 10422–7.

Courchesne E, Pierce K. Why the frontal cortex in autism might be talking only to itself: local over-connectivity but long-distance disconnection. Curr Opin Neurobiol 2005; 15: 225–30.

Damasio AR. Disorders of complex visual processing agnosias, achromatopsia, Balint's syndrome, and related difficulties of orientation and

construction. In: Mesulam MM, editor. Principles of behavioural neurology. Vol. 1. Philadelphia: Davis; 1985. p. 259–88.

Damasio AR. Time-locked multiregional retroactivation: a systems-level proposal for the neural substrates of recall and recognition. Cognition 1989; 33: 25–62.

Damasio AR. The feeling of what happens: body and emotion in the making of consciousness. New York: Harcourt Brace; 1999.

Damasio AR, Damasio H. The anatomic basis of pure alexia. Neurology 1983; 33: 1573–83.

Damasio AR, Geschwind N. The neural basis of language. Annu Rev Neurosci 1984; 7: 127–47.

Damasio AR, Galaburda A. Norman Geschwind. Arch Neurol 1985; 42: 500–4.

Damasio AR, Damasio H. Cortical systems for retrieval of concrete knowledge: the convergence zone framework. In: Koch C, editor. Large-scale neuronal theories of the brain. Cambridge MA: MIT Press; 1994. p. 61–74.

Damasio AR, Grabowski TJ, Bechara A, Damasio H, Ponto LLB, Parvizi J, et al. Subcortical and cortical brain activity during the feeling of self-generated emotions. Nat Neurosci 2000; 3: 1049–56.

Damasio H, Tranel D, Grabowski T, Adolphs R, Damasio A. Neural systems behind word and concept retrieval. Cognition 2004; 92: 179–229.

De Renzi E, Vignolo LA. The token test: a sensitive test to detect receptive disturbances in aphasics. Brain 1962; 85: 665–78.

Déjérine J. Sur un cas de cécité verbale avec agraphie suivi d'autopsie. Mém Soc Biol 1891; 3: 197–201.

Déjérine J. Contibution a l'étude anatomo-pathologique et clinique des differentes variétés de cécité-verbale. Mém Soc Biol 1892; 4: 61–90.

Demonet JF, Taylor MJ, Chaix Y. Developmental dyslexia. Lancet 2004; 363: 1451–60.

ffytche DH, Howard RJ, Brammer MJ, David A, Woodruff P, Williams S. The anatomy of conscious vision: an fMRI study of visual hallucinations. Nat Neurosci 1998; 1: 738–42.

ffytche DH, Howard RJ. The perceptual consequences of visual loss: positive pathologies of vision. Brain 1999; 122: 1247–60.

ffytche DH, Catani M. Beyond localisation: from hodology to function. Philos Trans R Soc Lond B Biol Sci 2005; 360: 767–79.

Flechsig P. Developmental (myelogenetic) localisation of the cerebral cortex in the human subject. Lancet 1901; 2: 1027–9.

Frith U. Mind blindness and the brain in autism. Neuron 2001; 32: 969–79.

Geschwind N. The paradoxical position of Kurt Goldstein in the history of aphasia. Cortex 1964; 214–224. Reprinted in: Devinsky O, Schacter SC, editors. Norman Geschwind: selected publications on language, behavior and epilepsy. Boston: Butterworth–Heinemann; 1997. p. 53–61.

Geschwind N. Disconnexion syndromes in animals and man. I. Brain 1965a; 88: 237–94.

Geschwind N. Disconnexion syndromes in animals and man. II. Brain 1965b; 88: 585–644.

Goldenberg G. Apraxia and beyond: life and work of Hugo Liepmann. Cortex 2003; 39: 509–24.

Hickok G, Poeppel D. Dorsal and ventral streams: a framework for understanding aspects of the functional anatomy of language. Cognition 2004; 92: 67–99.

Hubl D, Koenig T, Strik W, Federspiel A, Kreis R, Boesch C, et al. Pathways that make voices: white matter changes in auditory hallucinations. Arch Gen Psychiatry 2004; 61: 658–68.

Jones DK, Simmons A, Williams SC, Horsfield MA. Non-invasive assessment of axonal fiber connectivity in the human brain via diffusion tensor MRI. Magn Reson Med 1999; 42: 37–41.

Kempler D, Metter EJ, Jackson CA, Hanson WR, Riege WH, Mazziotta JC, et al. Disconnection and cerebral metabolism. The case of conduction aphasia. Arch Neurol 1988; 45: 275–9.

Le Bihan D, Breton E. Imagerie de diffusion in-vivo par résonance magnétique nucléaire. C R Acad Sci 1985; 301: 1109–12.

Leff AP, Crewes H, Plant GT, Scott SK, Kennard C, Wise RJS. The functional anatomy of single-word reading in patients with hemianopic and pure alexia. Brain 2001; 124: 510–21.

Leiguarda RC, Marsden CD. Limb apraxias: higher-order disorders of sensorimotor integration. Brain 2000; 123: 860–79.

Lennox BR, Park SBG, Medley I, Morris PG, Jones PB. The functional anatomy of auditory hallucinations in schizophrenia. Psychiatry Res 2000; 100: 13–20.

Liepmann H. Ein Fall von reiner Sprachtaubheit. Breslau: Schletter; 1898.

Liepmann H. Das Krankheitsbild der Apraxie (motorische Asymbolie) auf Grund eines Falles von einseitiger Apraxie. Monatssch Psychia Neurol 1900; 8: 15–44, 102–32, 182–97.

Lissauer H. Ein Fall von Seelenblindheit nebst einem Beitrage zur Theorie derselben. Arch Psychiat Nervenkr 1890; 21: 222–70.

Luria AR. Higher cortical functions in man. New York: Basic Books Inc.; 1980.

Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibasaki H, et al. Functional connectivity in the human language system: a cortico-cortical evoked potential study. Brain 2004; 127: 2316–30.

Mesulam MM. A cortical network for directed attention and unilateral neglect. Ann Neurol 1981; 10: 309–25.

Mesulam MM. Patterns in behavioral neuroanatomy: association areas, the limbic system and hemispheric specialisation. In: Mesulam M, editor. Principles of behavioral neurology. Philadelphia: F.A. Davis Co.; 1985a: 1–70.

Mesulam MM. Norman Geschwind, 1926-1984. Ann Neurol 1985b; 18: 98–100.

Mesulam MM. Human brain cholinergic pathways. Prog Brain Res 1990a; 84: 231–41.

Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. Ann Neurol 1990b; 28: 597–613.

Mesulam MM. From sensation to cognition. Brain 1998; 121: 1013–52.

Mesulam MM. Primary progressive aphasia. Ann Neurol 2001; 49: 425–32.

Mesulam MM. Imaging connectivity in the human cerebral cortex: the next frontier? Ann Neurol 2005; 57: 5–7.

Mori S, Crain BJ, Chacko VP, van Zijl PC. Three-dimensional tracking of axonal projections in the brain by magnetic resonance imaging. Ann Neurol 1999; 45: 265–9.

Moseley ME, Cohen Y, Kucharczyk J, Mintorovitch J, Asgari HS, Wendland MF, et al. Diffusion-weighted MR imaging of anisotropic water diffusion in cat central nervous system. Radiology 1990; 176: 439–45.

Naeser MA, Alexander MP, Helm-Estabrooks N, Levine HL, Laughlin SA, Geschwind N. Aphasia with predominantly subcortical lesion sites: description of three capsular/putaminal aphasia syndromes. Arch Neurol 1982; 39: 2–14.

Naeser MA, Martin PI, Nicholas M, Baker EH, Seekins H, Helm-Estabrooks N, et al. Improved naming after TMS treatments in a chronic, global aphasia patient—case report. Neurocase 2005; 11: 182–93.

Poupon C, Clark CA, Frouin V, Regis J, Bloch I, Le Bihan D, et al. Regularization of diffusion-based direction maps for the tracking of brain white matter fascicles. Neuroimage 2000; 12: 184–95.

Price CJ, Warburton EA, Moore CJ, Frackowiak RS, Friston KJ. Dynamic diaschisis: anatomically remote and context-sensitive human brain lesions. J Cogn Neurosci 2001; 13: 419–29.

Rizzolatti G, Luppino G, Matelli M. The organization of the cortical motor system: new concepts. Electroencephalogr Clin Neurophysiol 1998; 106: 283–96.

Ross ED. Sensory-specific and fractional disorders of recent memory in man. I. Isolated loss of visual recent memory. Arch Neurol 1980; 37: 193–200.

Selden NR, Gitelman DR, Salamon-Murayama N, Parrish TB, Mesulam MM. Trajectories of cholinergic pathways within the cerebral hemispheres of the human brain. Brain 1998; 121: 2249–57.

Sergent J, Ohta S, Macdonald B. Functional neuroanatomy of face and object processing. Brain 1992; 115: 15–36.

Shergill SS, Brammer MJ, Williams SCR, Murray RM, McGuire PK. Mapping auditory hallucinations in schizophrenia using functional magnetic resonance imaging. Arch Gen Psychiatry 2000; 57: 1033–38.

Tusa RJ, Ungerleider LG. The inferior longitudinal fasciculus: a reexamination in humans and monkeys. Ann Neurol 1985; 18: 583–91.

Wernicke K. The aphasia symptom-complex. 1874. Breslau, Cohn and Weigert. Translated in: Eling P, editor. Reader in the history of aphasia. Vol. 4. Amsterdam: John Benjamins; 1994. p. 69–89.

Wernicke K. Some new studies on aphasia. Fortschr Med 1885; 824–30. Translated in: Eling P, editor. Reader in the history of aphasia. Vol. 4. Amsterdam: John Benjamins; 1994. p. 90–98.

Zeki S. A century of cerebral achromatopsia. Brain 1990; 113: 1721–77.

Zeki S. Cerebral akinetopsia (visual motion blindness)—a review. Brain 1991; 114: 811–24.

Zeki S, Watson JDG, Lueck CJ, Friston KJ, Kennard C, Frackowiak RSJ. A direct demonstration of functional specialization in human visual cortex. J Neurosci 1991; 11: 641–9.

Zeki SM. Uniformity and diversity of structure and function in rhesus monkey prestriate visual cortex. J Physiol 1978; 277: 273–90.

Zola-Morgan S. Localization of brain function: the legacy of Franz Joseph Gall (1758–1828). Annu Rev Neurosci 1995; 18: 359–83.