

## DORSAL COLUMN

### Grey Matter

# Fifty years of disconnection syndromes and the Geschwind legacy

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'I read a book one day and my whole life was changed. . . I sat at the table turning the pages, my mind barely aware that I was reading, and my whole life was changing as I read the new words on each page.' [From the opening paragraph of Orhan Pamuk's *Yeni Hayat* (New Life), English translation by Güneli Gün].

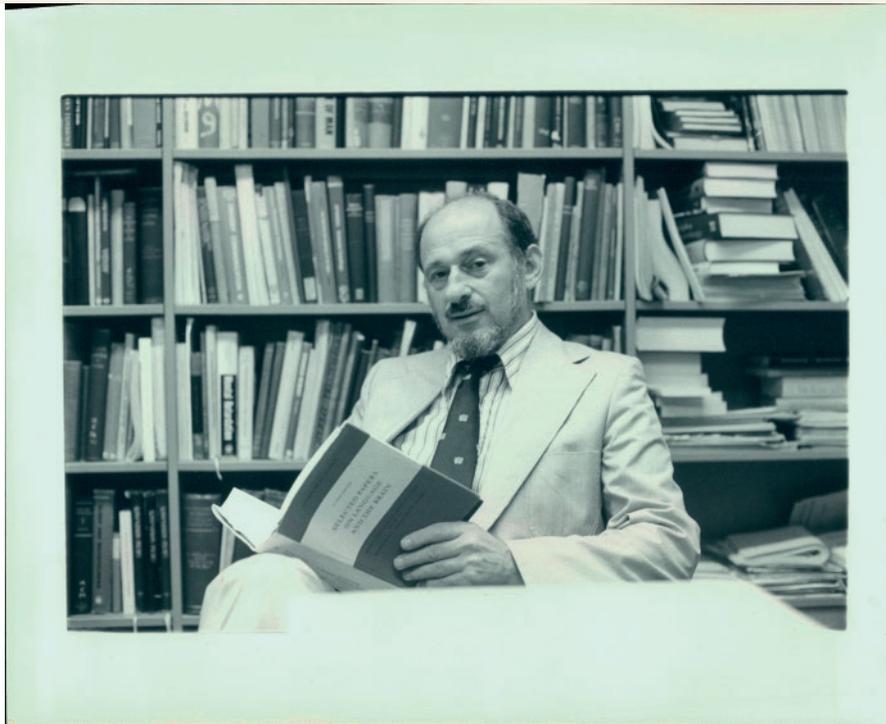
Had Pamuk's protagonist been a behavioural neurologist, he might have chosen similar words to describe his first encounter with Norman Geschwind's 1965 *Disconnection Syndromes in Animals and Man* (Geschwind, 1965a, b). His experience would not have been unique. For the past half century, this two-part monograph has remained the most influential work ever published in the discipline that came to be known as behavioural neurology (Fig. 1).

The monograph covered 116 pages of text, without a single table, figure or diagram. It offered an unprecedented synthesis of disparate neurological phenomena by translating them into the idiom of neuroanatomy at a particularly pivotal time in the history of neurological sciences. On the occasion of its 50th publication anniversary, the aim of this retrospective is to summarize for the general reader some of the main ideas in Geschwind's monograph, highlight those that inspired further discovery, mention the few that require revision or amplification, and interpret the legacy of this paper from the vantage point of contemporary neurology. A comprehensive coverage of *Disconnection Syndromes*, with a focus on broader themes related to the anatomy of cognition, appeared 10 years ago on the 40th publication anniversary of this work (Catani and ffytche, 2005).

## The historical context

The *Disconnection Syndromes* revived paradigmatic single case studies published by 19th century French and German neurologists, highlighted the functional rather than topographical subdivision of the cerebral cortex, espoused a hierarchical system of brain connectivity, and relied on animal models of human neuroanatomy. These four themes provided the matrix upon which the diverse phenomena of aphasia, apraxia, agnosia, confabulation, spatial neglect, and unity of cognition were conceptualized in terms of connections and disconnections.

By the time *Disconnection Syndromes* was published in 1965, accounts of complex cognitive disorders based on interruptions of cortical connections had been part of the neurological thinking for over a century. As contributors to this field, Wernicke, Lichtheim, Liepmann, Déjerine, Charcot and many others had described influential case studies and conceptual models published predominantly in the French and German literature. Following the two World Wars, however, continental European neurology experienced a temporary lull. At the same time, English emerged as the dominant language of medical science, leading to a gradual neglect of works that had been published in other languages. A major contribution of *Disconnection Syndromes* was to reverse this trend through extensive quotations and annotated synopses of connectivistic accounts by French and German masters. These accounts, many of which remain unsurpassed in clarity, provided the canonical authority for many of the interpretations offered in the *Disconnection Syndromes*.



**Figure 1** Norman Geschwind. (With kind permission of Claudia Geschwind).

The connectivistic approach of pre-war German and French neurological literature was based on conceptual connections, connections that ought to exist if a given phenomenon was to occur, rather than real connections demonstrated through anatomical experimentation (Fig. 2). This is not surprising as knowledge of human brain connectivity was (and still is) rudimentary at best. Geschwind set himself the task of translating these conceptual connections into anatomically identified synaptic relays, heavily borrowing from results obtained in the animal laboratory.

A first order of business was to choose a reference map that could be used to explore principles of cortical localization and connectivity. Geschwind was fortunate to have Paul Yakovlev's guidance for this task. Architectonic approaches, including those of Exner, Brodmann and von Economo, had offered maps that ranged in complexity from 50 to 500 subdivisions, delineated by subtle regional variations in the columnar and laminar arrangement of neurons and fibre bundles (Exner, 1881; Brodmann, 1909; von Economo and Koskinas, 1925). An alternative approach, one followed by Broca, Yakovlev, Campbell, Filimonoff and others, avoided detailed (and occasionally arbitrary) subdivisions in favour of much broader classifications based on functional attributes, usually linked to some common phylogenetic or ontogenetic feature (Broca, 1878; Campbell, 1905; Filimonoff, 1947; Yakovlev, 1959). Geschwind chose to base the anatomical foundations of *Disconnexion Syndromes* on this second approach, as

exemplified by the work of Paul Flechsig (1896), an anatomist who had also influenced Yakovlev's explorations of cortical myelogenesis (Yakovlev and Lecours, 1967). The choice turned out to be providential as Flechsig's myelogenetic laws, disarmingly simple as they may initially appear, provided the backbone not only for *Disconnexion Syndromes* but also for subsequent reformulations of behavioural neuroanatomy and its connectivistic foundations (Fig. 3).

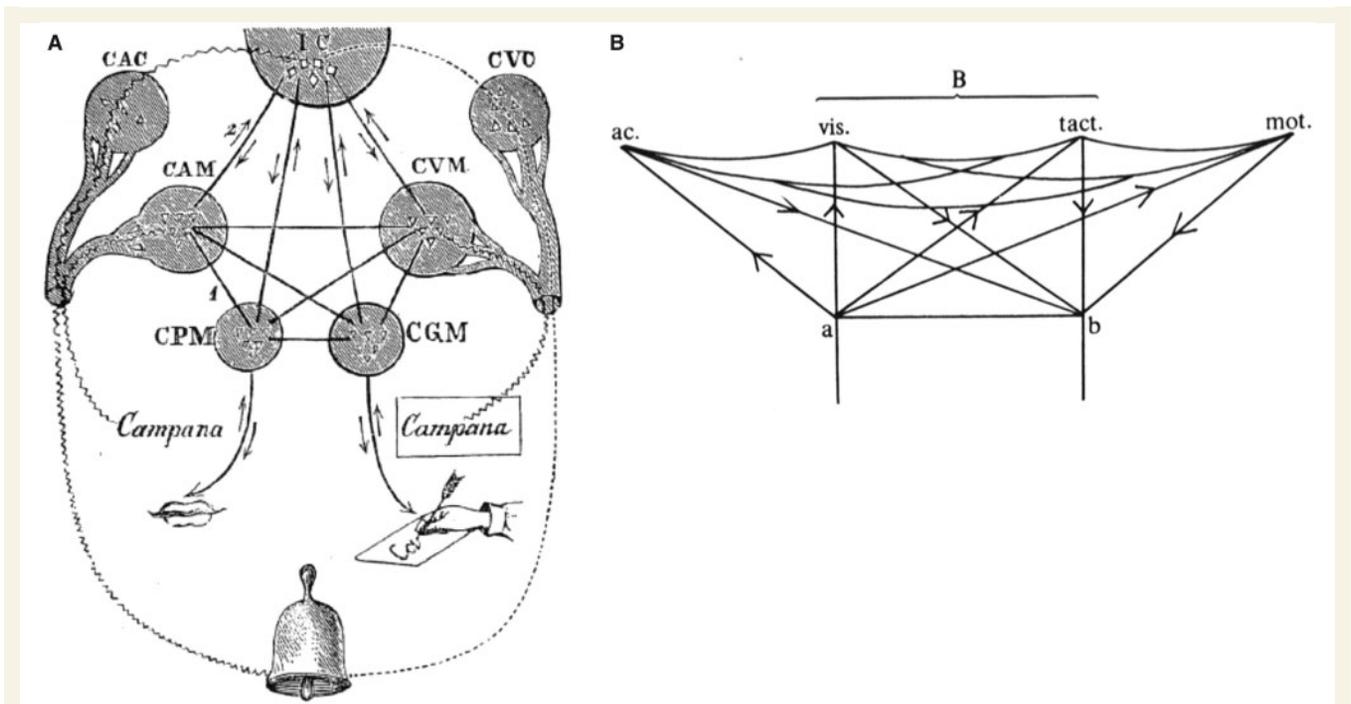
## Flechsig's hierarchical laws

Flechsig was not prone to self-doubt. In response to alternative explanations of his myelogenetic law, he wrote

'It has been said... that the order of succession in which the nerve-fibers receive medullary substance is in relation to the diameter of the fibers (Vogt), or that this order of succession is in relation to the position of the blood-vessels (von Monakow). These opinions, however, ... are found to be ill-supported and totally useless from a scientific point of view.' (Flechsig, 1901).

He also seems to have been hard to please. The assistant he assigned to this project, a retired Army captain named Blanca, is said to have died from overwork (von Bonin, 1950).

Flechsig based his system of cortical parcellation on the spatio-temporal appearance of subcortical myelination in



**Figure 2 Conceptual connectivity.** The two diagrams depict ‘connections’ that should exist if the desired behaviour is to occur. They illustrate cognitive models rather than verified pathways in the brain. **(A)** Diagram by Charcot (1884), first published in an Italian version. It outlines the communication channels that mediate the ability to name a bell (*campana*) and write its name. CAC = general auditory centre; CAM = auditory word centre; CGM = word writing centre; CPM = word articulation centre; CVC = general visual centre; CVM = visual word centre; IC = ideation centre. (Reproduced from Miliotti, 1885). **(B)** Wernicke’s version of Charcot’s diagram (Wernicke, 1893; Eggert, 1977). a = auditory word centre; b = motor speech centre (presumably equivalent to a word articulation centre); B = conceptualization (of the bell); ac = acoustic imagery; vis. = visual imagery; tact. = tactual imagery. Geschwind did not offer diagrams of his own in *Disconnexion Syndromes*, perhaps to avoid being included among Henry Head’s ‘diagram makers’ (Head, 1926). (Reproduced with permission from Eggert GH. Early sources in aphasia and related disorders. De Gruyter Mouton 1977. p. 180, Figure 1).

the course of ontogeny (Flechsig, 1896). Areas with the earliest myelination, encompassing primary sensory-motor and limbic cortices, were designated ‘primordial’. The next phase of myelination occurred in ‘intermediate’ (parasensory) areas that surrounded the primordial zones. The areas that were the latest to myelinate, located in prefrontal, posterior parietal and lateral temporal cortex, were designated ‘terminal’ and were singled out as the components that most clearly distinguished human from anthropoid brains.

The power of Flechsig’s system lies in its implication for laws of cortical connectivity (i.e. associations).

‘The areas (of the cortex)...differ in a most extraordinary manner with respect to the long association systems. The terminal zones are the richest in them; they are the endings of the long association systems. On the other hand, no long association system is known which connects two primordial zones that are to be regarded as sensory centers...If a visual and auditory impression meet one another anywhere in the cortex of the cerebrum, this can only happen through the instrumentality of the intermediate and terminal zones.’ (Flechsig, 1901).

The Flechsig hierarchy seemed to confine the connectivity of primordial (primary sensory, primary motor, limbic)

areas to immediately surrounding intermediate (parasensory, paramotor, paralimbic) areas, each presumably devoted to the domain of its primordial core. In turn, intermediate rather than primordial areas communicated with terminal zones located in prefrontal, inferior parietal and lateral temporal areas. The terminal zones emerged as the principal sites where associations of associations could be formed, especially for the integration of visual, auditory and tactile impressions.

Geschwind reasoned that the lesser development of terminal areas in anthropoids explained their poor performance on tasks that require cross-modal associations in the visual, auditory and tactile modalities. In monkeys, these three sensory channels establish cross-modal associations predominantly with limbic sensations (pain, olfactory, gustatory, visceral) rather than with each other, creating a setting where interactions with ambient events are dominated by their immediate contingencies for reward and punishment. In humans, the inferior parietal lobule, a terminal zone sitting at the confluence of visual, auditory and tactile parasensory areas becomes a principal site of cross-modal associations. According to Geschwind, it is the prominence of this area that enabled the emergence of language, a faculty that depends on extensive auditory-visual



cross-modal associations. Through this anatomical property, the ‘parietal association area frees man to some extent from the limbic system’ (Geschwind, 1965).

Even the asymmetric hemispheric dominance for language was attributed to the greater cross-modal association capacity of the left inferior parietal lobule. Geschwind subsequently pursued this hypothesis through an investigation of autopsied brains and found that the planum temporale, a part of the temporal lobe adjacent to the inferior parietal lobule, tended to be larger in the left hemisphere (Geschwind and Levitsky, 1968). The more speculative aspect of his hypothesis, namely that the left parietal lobe is computationally superior for cross-modal associations, has been challenging to address and has thus far received only partial support in functional activation studies (Hasegawa *et al.*, 2004). In keeping with Geschwind’s emphasis on parietal cortex as the anatomical substrate of uniquely human cognitive faculties, the designation ‘Geschwind territory’ has been proposed for the left inferior parietal lobule (Catani *et al.*, 2005).

## Varieties of disconnexion

In the summary to Part I, Geschwind defines a disconnexion lesion as ‘a large lesion either of association cortex or of the white matter leading from this association cortex’. If taken literally, this definition is so broad as to encompass nearly all cortical syndromes with a few trivial exceptions such as those that cause hemianopia or hemiparesis. But Geschwind had something far more specific in mind. Perhaps his monograph should have had a more pedantic title such as ‘Selective Dissociation Syndromes’. Indeed, the one common denominator for all the phenomena he covers is the selective interruption of information flow along a mono- or multisynaptic route (callosal, motor, visual, auditory, tactile, limbic) in a setting where the points of origin and termination display a relative preservation of other connections and functions. Using this phenomenon of selective dissociation as its core construct, *Disconnexion Syndromes* offered an anatomically-anchored and unified explanation of phenomena that until then appeared to have little in common and outlined principles of connectivity that guided an entire generation of experimental neuroanatomy.

In monkeys, where sensory-limbic interactions dominate the landscape of cortico-cortical connectivity, the Klüver-Bucy syndrome was offered by Geschwind as a prime example of an anthropoid disconnexion syndrome (Klüver and Bucy, 1938; Downer, 1962). In this syndrome, ablations in the anterior temporal lobe, where both visual and limbic association areas are located, interfere with visual-limbic associations so that visual stimuli fail to guide appetitive, defensive or amorous behaviours. As the damage encompasses association rather than primary sensory cortex, basic visual functions remain preserved. Furthermore, the limbic system remains responsive to other types of sensory input, such as

those in the tactile modality. In the Klüver-Bucy syndrome it can be said that the limbic system, but not the animal as a whole, has become blind.

Geschwind does not mention human cases of the Klüver-Bucy syndrome although subsequent publications have identified such patients (Lilly *et al.*, 1983). The short list of human limbic syndromes addressed by Geschwind includes memory impairments, pain asymbolia, and anosognosia. Scoville and Milner (1957) had already shown that hippocampal removals cause multimodal learning deficits, presumably through the process of sensory-limbic disconnexion. Geschwind speculated that more specific interruptions of hippocampal afferents could yield modality-selective impairments of learning and memory, a prediction that was later confirmed anatomically in monkeys and clinically in neurological patients (Jones and Powell, 1970; Ross, 1980). He also pointed out that anosognosia is more common with Wernicke’s than Broca’s aphasia because the lesion in the former syndrome is more likely to undercut pathways running between language areas and limbic cortex of the temporal lobe. Another limbic syndrome, pain asymbolia, arises in patients who have no difficulty distinguishing dull from sharp or responding appropriately to other limbic stimulation while remaining emotionally indifferent to pain. In pure forms of pain asymbolia, the limbic system, but not the whole person, becomes hypalgesic. Geschwind identified the insula as the site where lesions causing pain asymbolia might interrupt tactile-limbic interactions, a prediction that was subsequently corroborated in the animal laboratory (Mishkin, 1979; Mesulam and Mufson, 1985).

Non-limbic syndromes dominate the landscape of human cortical disconnexions covered by Geschwind’s monograph. Among these, pure alexia without agraphia is arguably the most iconic (Déjerine, 1892; Geschwind and Fusillo, 1966). Geschwind frequently addressed this topic in lectures delivered with particular flair and gusto. In the idealized version of pure alexia, a strategic combination of lesions in the left primary visual area and the splenium of the corpus callosum, selectively isolate the left hemisphere from visual input. Words read through the intact left visual field can access right hemisphere visual cortices but not the left angular gyrus because of the splenial lesion and therefore cannot activate visual-lexical associations necessary for comprehension. Other functions of the left visual field (e.g. face and object recognition) and of the language areas (e.g. speech, auditory comprehension, writing) remain relatively preserved. In such patients, the language system, but not the whole brain, is blind but not deaf. Access to the visual memories of words stored in the angular gyrus remains intact as shown by accurate writing and spelling of words that cannot be read. Naming of an object seen through the left visual field may remain intact because the incoming visual information evokes non-visual associations of that object in more anterior areas of the right hemisphere. These associations can then be transferred across the intact anterior parts of the corpus callosum to

language areas of the left hemisphere. Colours, on the other hand, can be recognized (as shown by the ability to match chips to objects with characteristic colours) but cannot be named because they evoke no intrinsic non-visual associations and therefore have no access to the anterior corpus callosum.

Pure word deafness constitutes an auditory analogue of pure alexia. In this syndrome, damage to auditory association areas or their efferent pathways selectively isolates Wernicke's area from auditory input. The patient can hear and interpret environmental sounds (through primary auditory cortex), read (through the angular gyrus) and speak (through Wernicke's and Broca's areas) but fails to understand or repeat spoken language. In this syndrome, the language area has become deaf but not blind. A related disconnection syndrome, conduction aphasia, arises when Wernicke's area cannot communicate with Broca's area so that fluency and comprehension are preserved but not speech repetition.

Ideomotor apraxia is presented as an example of selective verbal-motor disconnection whereby parts of the pyramidal motor system lose the ability to execute verbal instructions in a patient who preserves other language functions (as shown by the ability to understand the meaning of the verbal instruction) and motor abilities (as shown by accurate handling of the object). A core assumption, based on the Flechsig rule, is that posterior sensory and language areas of the left hemisphere communicate with primary motor cortex indirectly through the left premotor association cortex, a region which is also the source of transcallosal projections to the premotor association cortex of the right hemisphere. Cortical or white matter lesions that disconnect language from premotor areas of the left hemisphere can therefore lead to bilateral ideomotor apraxia. When the lesion is predominantly in the anterior corpus callosum, as in the case of a patient reported by Geschwind and Kaplan (1962), the apraxia encompasses only the left hand. As part of a broader callosal syndrome, this patient also displayed a cross-hemispheric tactile-verbal disconnection. When blindfolded, he could neither utter nor recognize the name of an object placed in the left hand. His left hand could nonetheless accurately demonstrate the use of the object. In this patient, the object recognition ability of the left hand had become impaired in the verbal but not motor domain.

In each of these syndromes, diagnosis depends not only on detecting the functions that are disrupted but also those that are relatively spared. The process requires assessment strategies to be individualized for that particular set of circumstances and results to be interpreted flexibly making allowances for the disengagement of the 'knowing' part of the brain from the 'responding' part. The deductive logic of the clinical examination, the hunt for dissociations, and the whodunit approach to the identity of the damaged pathway lie at the core of the process-oriented disconnection perspective jointly promoted by Geschwind and his colleague Edith Kaplan (Weintraub, 2011).

## The logocentric bias

Although *Disconnection Syndromes* is justifiably valued for the broad canvas it covers, it can also be criticized for its narrow logocentric bias. For example, all of the non-limbic syndromes listed above are conceptualized as selective disconnections (of vision, hearing, touch or motor systems) from the language area of the left hemisphere. It is as if consequential disruptions of higher cortical functions can only occur if they interrupt some aspect of verbal faculties. This perspective is occasionally carried too far. For one, the assertion is made that most classical agnosias may reflect disconnections of sensory impressions from language rather than impairments of general recognition. One example comes from a patient who had received a diagnosis of visual agnosia because of a failure to describe familiar routes. In this case, Geschwind argues that a visual-verbal disconnection may have been the more accurate diagnosis since the patient accurately navigated the route that could not be described verbally. It is interesting that the monograph devotes much more space to circumstances where agnosias are misdiagnosed and so little to the pathophysiology of legitimate agnosias. Perhaps Geschwind was trying to highlight the ambiguity in the terminology of agnosias. However, the coverage of *Disconnection Syndromes* would have been more comprehensive if recognition impairments that cannot be attributed to verbal disconnection, such as prosopagnosia, were discussed more thoroughly as examples of modality-selective non-verbal recognition impairments where ventral visual association cortex is selectively and partially disconnected from other information processing streams (Damasio *et al.*, 1982).

Even more puzzling is Geschwind's approach to what he identifies as the 'problem' of the right hemisphere. Instead of giving serious consideration to the specialized role of the right hemisphere in spatial attention, he suggests that the greater frequency of contralesional neglect after right hemisphere damage may reflect the synaptic 'disadvantage' of the right hemisphere, which is at least one neuron further away from the left hemisphere language area. Right-sided lesions may therefore cause a greater degradation of information reaching the language centres, which may explain at least some of the phenomenology of neglect syndromes. Even the Welch and Stuteville (1958) experiment, where unilateral lesions in the frontal eye fields caused multimodal contralesional inattention, is (mis)interpreted by Geschwind as an apraxia caused by sensory-motor disconnection rather than a neglect syndrome caused by damage to a non-verbal spatial attention system (Heilman and Valenstein, 1979; Mesulam, 1981).

*Disconnection Syndromes* tended to equate intellect with language. In keeping with this emphasis, Geschwind singled out the terminal zone of the parietal lobe for special commendation but ignored Flechsig's other equally developed terminal zones in prefrontal and inferior temporal cortex. The relative neglect of these additional terminal zones, each

as extensive as posterior parietal cortex and each capable of triggering its own type of disconnection, contributes to the logocentric bias that permeates the monograph. Later in his career, Geschwind did turn his attention to more complex non-verbal sensory-limbic disconnection syndromes in humans, especially those that arise in conjunction with temporal lobe epilepsy (Benson, 1991).

## The neuroanatomical revolution

The Flechsig doctrine was based on regional variations of myelin staining, not verified connections. *Disconnexion Syndromes* could not have been published at a more propitious time for verifying the synaptic basis of this doctrine. At around the time that *Disconnexion Syndromes* appeared, the work of Hubel and Wiesel (1965) was revealing a striking physiological (and presumably synaptic) hierarchy among the simple, complex and hypercomplex neurons of primary and parasensory visual cortex, setting the stage for explorations of analogous hierarchies at the larger scale of cortico-cortical connectivity. Neuroanatomical experiments that could address such questions became possible with the advent of sensitive methods for tracing Wallerian degeneration in animals with targeted cortical lesions. By 1969 and 1970 two key publications offered powerful verification of the Flechsig hierarchy in the rhesus monkey brain (Pandya and Kuypers, 1969; Jones and Powell, 1970). It is interesting that one of these two papers quotes Geschwind but neither mentions Flechsig.

The rhesus monkey experiments showed that each major primary sensory area (visual, somatosensory, auditory) projects to its own parasensory cortex, that parasensory areas project to secondary association areas also devoted to that modality, and that the secondary association cortices send partially overlapping projections to interconnected convergence zones in prefrontal, temporoparietal and paralimbic cortices. In keeping with Geschwind's review of the literature, limbic areas were shown to receive association input in all major modalities and motor cortex was shown to be dependent on premotor association cortex for input coming from other parts of the cortex. These studies also added a new feature to the Flechsig hierarchy, namely that parasensory areas in the three major sensory modalities have no substantial interconnections among each other, presumably to protect their modality-specificity. Intermodal integration therefore occurs at a relatively more advanced synaptic stage, through projections of secondary sensory association areas to frontal and temporoparietal convergence zones. In contrast to Geschwind's assertion that non-limbic cross-modal associations were prominent only in humans, these studies revealed extensive multi-modal convergence zones in the monkey, but obviously not at a level that can sustain language.

Following the publication of his monograph, and upon assuming the chairmanship of the Neurology Department at Boston City Hospital in 1969, Geschwind recruited Deepak Pandya and Gary Van Hoesen to establish a primate laboratory. Pandya investigated neocortical sensory convergence areas, callosal connections and motor cortex; Van Hoesen investigated projections from neocortical association areas into the hippocampus and amygdala (Fig. 4). Over years, and especially with the advent of more powerful methods based on the axonal transport of tracers, Pandya, Van Hoesen and their colleagues discovered many details of connectivity that largely support the formulations of both Geschwind and Flechsig and that continue to guide our current concepts of higher cortical function (Pandya and Kuypers, 1969; Van Hoesen *et al.*, 1972, 1979; Herzog and Van Hoesen, 1976; Rosene and Van Hoesen, 1977; Pandya and Yeterian, 1985).

Geschwind was a serious student of neuroanatomy. His personal copy of Crosby's *Correlative Anatomy of the Nervous System* (Crosby *et al.*, 1962) had many passages he had underlined, usually with additional comments and questions in the margins. Although the neuroanatomical laboratories at Boston City Hospital were only a short flight of stairs away, however, he rarely visited them. He was much more comfortable with verbal descriptions of pathways than with the visual analysis of the underlying evidence.

## The granularity of knowledge

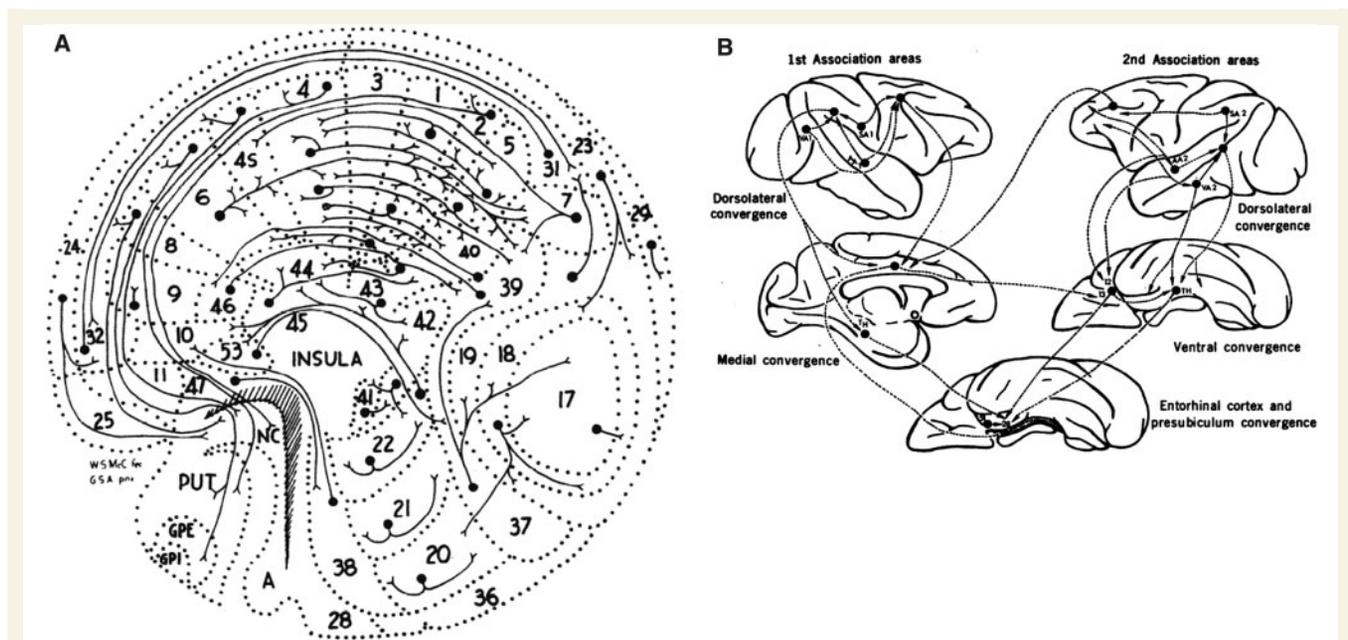
In part II, Geschwind wrote:

'I believe in fact that there is no single faculty of "recognition" but that the term covers the totality of all the associations aroused by any object. Phrased in another way, we "manifest recognition" by responding appropriately; to the extent that any appropriate response occurs, we have shown "recognition". But this view abolishes the notion of a unitary step of "recognition"; instead, there are multiple parallel processes of appropriate response to a stimulus.'

In short, *Disconnexion Syndromes* leaves no room for a Cartesian pineal gland, where all attributes of an object congregate within a unified semantic hub. Knowledge, even of a single object, is granular and distributed. Recognition impairments are almost always partial, reflecting selective dissociations of the constituent components. It is this formulation that has sharply distinguished the disconnection approach from phrenological and holistic accounts of behavioural anatomy.

## The Geschwind legacy

*Disconnexion Syndromes* was written at a time when the division of labour in the cerebral cortex seemed relatively straightforward. In Geschwind's words, Wernicke's area functions 'as the "storehouse" of auditory associations'



**Figure 4 The systematization of cortical connectivity.** (A) Connections of the monkey cerebral cortex as revealed by strychnine neuronography (McCulloch, 1944). Numbers correspond to those of the Brodmann map in *Cercopithecus* (Brodmann, 1909). The information is remarkably rich for its time. However, it represents a compendium of pathways without segregation into functional information processing systems. (Reproduced with permission from McCulloch, 1944). (B) Afferent connections into entorhinal and adjacent limbic cortices. Large numbers of pathways are depicted. However, instead of being enumerated as a list, they are grouped systematically according to information processing hierarchies of the type proposed by Flechsig (Van Hoesen *et al.*, 1972). The authors of this work, Van Hoesen, Pandya and Butters, thanked Geschwind for having inspired this study. AAI, SAI, VAI = parasensory (1st) association areas in the auditory, somatosensory and visual modalities; AA2, SA2, VA2 = secondary association areas in the auditory, somatosensory and visual modalities; TH = parahippocampal gyrus in the von Bonin and Bailey nomenclature (von Bonin and Bailey, 1947); numbers refer to the Brodmann (*Cercopithecus*) and Walker (*Macaca*) maps (Brodmann, 1909; Walker, 1940). (Reproduced with permission from Van Hoesen *et al.*, 1972).

while the angular gyrus functions ‘as a visual memory centre for words’ and ‘turns written language into spoken language and vice versa.’. Cortical pathways, moreover, behaved as conduits that are either wide open or totally closed. Over time, these notions have undergone considerable modification to incorporate large-scale distributed networks, top-down modulation of sensory hierarchies and inferential predictive encoding (Damasio, 1989; Mesulam, 1990, 1998, 2008; Friston, 2005).

Nonetheless, and at the risk of hyperbole, it could be said that Geschwind gave to neurology what Mendeleev gave to chemistry. Existing building blocks were reordered in a way that brought new light to past discoveries and offered a blueprint for assimilating future developments. It is no surprise, therefore, that *Disconnexion Syndromes* remains as consequential today as it was 50 years ago. Its details are constantly being updated but its principles, articulated with the characteristic verve and scientific optimism of its author, are likely to enjoy considerable longevity.

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