



ELSEVIER
MASSON

available at www.sciencedirect.com



journal homepage: www.elsevier.com/locate/cortex



Special issue: Original article

The arcuate fasciculus and the disconnection theme in language and aphasia: History and current state

Marco Catani^{a,*} and Marsel Mesulam^b

^aNatbrainlab, Section of Brain Maturation, King's College London, Institute of Psychiatry, London, UK

^bCognitive Neurology and Alzheimer's Disease Center, Northwestern University, Chicago, IL, USA

ARTICLE INFO

Article history:

Received 27 March 2008

Reviewed 11 April 2008

Revised 14 April 2008

Accepted 15 April 2008

Keywords:

Arcuate fasciculus

Aphasia

Diffusion tensor imaging (DTI)

Language

Tractography

ABSTRACT

Few themes have been more central to neurological models of aphasia than the disconnection paradigm and the role of the arcuate fasciculus. Introduced by luminaries of 19th Century neurology and resurrected by the charismatic work of Norman Geschwind, the disconnection theme has triggered spectacular advances of modern understanding of language and aphasia. But the disconnection paradigm had alternate fortunes, ranging from irrational exuberance to benign neglect, and its followers have not always shared the same view on its functional consequences and anatomical correlates. Our goal in this paper is, first, to survey the 19th Century roots of the connectionist approach to aphasia and, second, to describe emerging imaging technologies based on diffusion tensor imaging (DTI) that promise to consolidate and expand the disconnection approach to language and its disorders.

© 2008 Elsevier Masson Srl. All rights reserved.

1. Introduction

Language is an exceedingly complex faculty that allows us to encode, elaborate and communicate thoughts and experiences through the mediation of arbitrary symbols known as words. The coherent function of the language network and its interactions with other neurocognitive networks depend on an orderly set of interconnections. Much of current understanding of language-related pathways is based on the pioneering work of 19th Century neuroanatomists, such as Reil, Burdach, Meynert, Wernicke, Dejerine. In the 1960s, in a series of influential papers, Geschwind crystallized those early anatomical findings adding new insights into brain connectivity as derived from anatomical, physiological and

neuronographic studies both in animals and humans (Geschwind, 1965, 1970; Geschwind and Levitsky, 1968).

The neuroanatomy of the human brain that Geschwind relied on was based principally on hand dissection of fixed specimens and the tracing of degeneration in sections stained for myelin. Recent developments in magnetic resonance imaging have introduced new methods, based on diffusion tensor imaging (DTI) tractography (see also Jones, 2008, this issue; Catani and Thiebaut de Schotten, 2008, this issue) that can reconstruct white matter pathways in the living human brain. The resultant influx of information on human connective anatomy is likely to modernize the disconnection approach to behavioural neurology and to reinvigorate models of cognition based on distributed large-scale networks (Catani

* Corresponding author. Natbrainlab, Section of Brain Maturation PO50, Institute of Psychiatry, De Crespigny Park, SE5 8AF London, UK.
E-mail address: m.catani@iop.kcl.ac.uk (M. Catani).

0010-9452/\$ – see front matter © 2008 Elsevier Masson Srl. All rights reserved.

doi:10.1016/j.cortex.2008.04.002

and Mesulam, 2008, this issue). An overview of these trends, and of their historical contexts, with a special focus on the arcuate fasciculus and language, constitutes the subject matter of this paper.

2. Disconnection accounts of language disorders

The term disconnection is generally used to indicate classical syndromes where lesions to white matter connections lead to dysfunction of higher cognitive abilities (Catani and ffytche, 2005; Mesulam, 2005). The term became popular in the second half of the 19th Century following Wernicke's (1874) description of the disconnection syndrome that was to become the prototype for all others – conduction aphasia. Wernicke, like his predecessor Theodore Meynert, conceived the brain as a mosaic of areas containing 'memory images' related to motor acts (localized in primary motor areas) and sensory experiences (localized in primary visual, somesthetic, auditory, olfactory and gustatory areas). He also assumed that higher cognitive functions, in contrast to movements and perceptions, are not localized in specific regions but emerge from associative connections linking areas where images of motor and sensory memories reside. On the basis of this 'general principle', Wernicke (1874) elaborated the first network model of language (Fig. 1): '*...the first frontal gyrus [third frontal circonvolution according to modern nomenclature], which has motor function, acts as center for motor imagery; the first temporal gyrus, which is sensory in nature, may be regarded as the centre of acoustic images; the fibrae propriae, converging into the insular cortex, form the mediating arc reflex.*' He argued that '*aphasia may be caused by any disruption of this pathway, the clinical picture, however, may vary considerably and is related to the specific segment of the pathway involved.*' According to Wernicke, the '*production of spontaneous movement, that is, the consciously formulated word, would be brought about by the rearousal of the motor image through the associated memory image of the sound.*' Spontaneous speech, in his opinion, resulted from the interaction of distant cortical areas. Consequently, he interpreted the characteristic paraphasic speech of patients with conduction aphasia as the expression of the inability of temporal regions to monitor Broca's area speech output through subinsular connections. Wernicke's

model was the forerunner of current network models of cognition. His greatest merit was to anchor his ideas into the clinical-anatomical correlation method, where he coupled a careful description of the behavioural disturbances of his patients to the anatomical findings from post-mortem dissections. With him aphasiology became a discipline intimately concerned with the connective anatomy of the human brain.

In France, the associationist theories were popularized by Charcot who brought Wernicke's ideas to his medical trainees during his 'leçons du Mardi' at the Salpêtrière (Gelfand, 1999). However, it was Jules Dejerine who formulated the most elegant contribution of French neurology to the disconnection paradigm. He beautifully explained the occurrence of reading difficulties (i.e., pure alexia) in a patient with otherwise normal writing ability using a pure disconnection mechanism, which he was able to demonstrate with post-mortem dissections (Epelbaum et al., 2008, this issue).

Shortly after Wernicke's description of conduction aphasia, Lichtheim (1885) extended the disconnection paradigm to give a comprehensive account of different aphasic syndromes. He hypothesized that Broca's and Wernicke's areas are interconnected to an hypothetical "concept center" (not anatomically localized) and added to Wernicke's nomenclature two other forms of aphasia, i.e., transcortical sensory and transcortical motor aphasia, that he interpreted as resulting from the disconnection of the concept center from the motor and auditory language centers, respectively (Fig. 2). In transcortical sensory aphasia, heard words cannot reach the thought center leading to impairment in understanding words, in transcortical motor aphasia thoughts cannot be verbalised due to impaired transfer of inputs from the thought center to Broca's area.

Lichtheim translated Wernicke's ideas into simple and intuitive diagrams that became standard references for clinicians. However, Lichtheim also introduced hypothetical centers and connections backed by little supportive evidence. His diagrams served the purpose of fitting a theoretical framework that best explained clinical empirical observations without a necessary anatomical correspondence. These diagrams promoted a mechanical view of brain function where connections represented 'transferring devices' between stores of specialized information localized in individual cortical

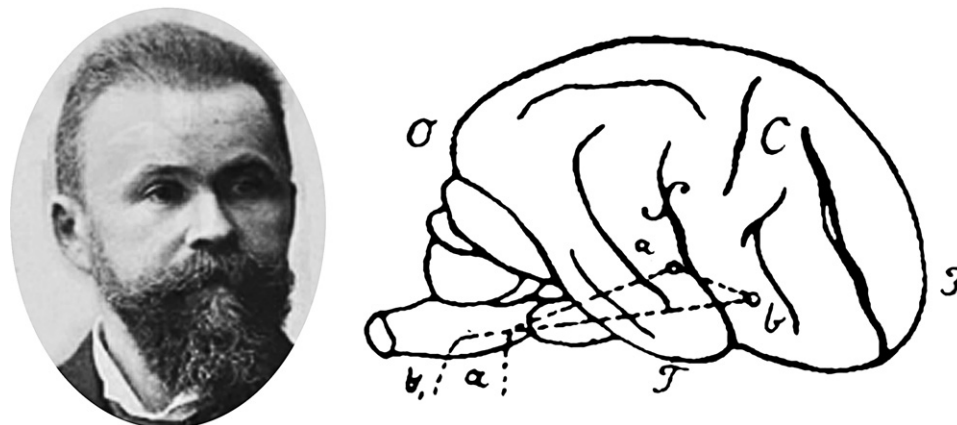


Fig. 1 – Carl Wernicke (1848–1905) and his representation of the language network from his 1874 MD thesis.

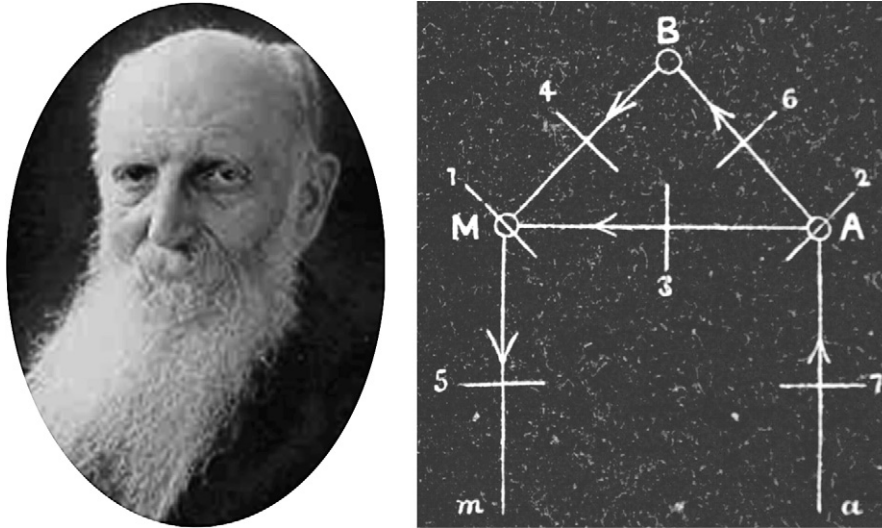


Fig. 2 – Ludwig Lichtheim (1845–1928) and his representation of the language network from his 1885 *Brain* paper.

areas. This approach to brain function generated a wave of criticisms and the clinico-anatomical correlation method came under attack by many prominent investigators including Hughling Jackson, Von Monakow, Henry Head, Karl Lashley and Kurt Goldstein (for a review see Finger, 1994).

In many respects these authors brought forward important criticisms that are still valid in modern neuroscience. First, they warned that localization of symptoms and localization of function were not identical. For example, for John Hughlings Jackson, there was no doubt that verbal fluency is more likely to be affected by damage to the left hemisphere than the right hemisphere. Jackson had difficulty, however, with the belief that observable symptoms specified the locations of special centers for the affected functions. He argued that it was entirely possible that some symptoms could be due to secondary effects of the damage on other regions of the brain, a distant ‘hodological effect’ according to more recent terminology (Catani and ffytche, 2005; Catani, 2007). He also believed that lesions were more useful for finding out what the remaining unaffected parts of the brain did without the benefit of the damaged area than what the damaged area did when it was part of the intact brain (Finger, 1994).

This dialectic between the localizationists and their opponents lasted for several decades, until the work of Norman Geschwind in the 1960s. Geschwind brought new credibility to the localizationist approach by re-interpreting the functional role of connections and specialized cortical areas according to evidence arising from the new neuroscience of the 20th Century. He also extended the disconnection paradigm beyond white matter lesions to lesions of association cortex. In Geschwind’s (1965) model, even a lesion confined to association cortex could cause a disconnection syndrome, little distinction being made between such lesions and those restricted to white matter tracts (see also Glickstein and Berlucchi, 2008, this issue). He argued that ‘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).

Based on this broader view, Geschwind reappraised conduction aphasia as a disconnection syndrome resulting either from a lesion of the white matter connections or of the perisylvian cortex, the latter acting as relay station between Wernicke’s and Broca’s areas. In Geschwind’s view, Wernicke’s aphasia could also be conceptualized as a disconnection syndrome (Fig. 3). He argued for ‘the importance of the angular gyrus in acting as a region involved in cross-modal associations, particularly in cross-association between either vision, or touch and hearing. If 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’ (Geschwind, 1965). Wernicke’s aphasia could then result either from a lesion of Wernicke’s area or of its connections to the angular gyrus. But Geschwind admitted that his intuitions, pending experimental anatomical evidence, were to be regarded as ‘speculative’.

With the advent of new information arising from structural and functional imaging, it appeared that parts of the Geschwind–Wernicke model represented an over-simplification. Kempler et al. (1988), for example, showed that lesions to the arcuate fasciculus were associated with hypometabolism in Wernicke’s and Broca’s areas only in 50% of the patients, the remaining showing hypometabolism only in Wernicke’s area. Furthermore, the Geschwind–Wernicke model predicted that lesions at any point along the course of the arcuate fasciculus result in an identical aphasia. Yet, clinically, this emerged not to be the case with conduction aphasias forming a heterogeneous group ranging from “Broca-like” to “Wernicke-like” deficits (Levine and Calvanio, 1982). These studies began to raise questions concerning the validity of existing neurocognitive formulations of language.

The dilemma that aphasiologists in specific, and behavioural neurologists in general, had to face stemmed

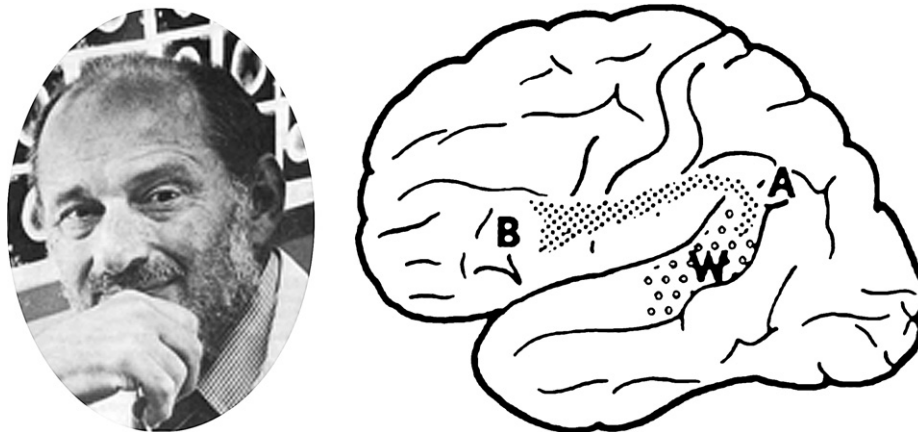


Fig. 3 – Norman Geschwind (1926–1984) and his representation of the language network from his 1970 *Science* paper.

principally from the lack of sufficient information on human neuroanatomy (see also Catani and Mesulam, 2008, *this issue*). In contrast to the giant strides made in unravelling the connectivity of the monkey brain, the details of connection pathways in the human brain remained stuck in the methodology of the 19th Century. In a scientific commentary in *Nature* Crick and Jones (1993) voiced these concerns to the scientific community: “to interpret the activity of the living human brains, their anatomy must be known in detail.” They urged the “development of new techniques since most of the methods used in the monkeys cannot be used on humans.” A year later, in 1994, Bassler et al. (1994) published their seminal paper where they describe for the first time DTI.

DTI, coupled to tractography, offers a non-invasive technique that reconstructs white matter trajectories in the living human brain (see also Jones, 2008, *this issue*; Catani and Thiebaut de Schotten, 2008, *this issue*). By measuring the diffusivity of water along different directions and by tracing a pathway of least hindrance to diffusion, DTI tractography can visualise continuous pathways as inferred from the movement of water molecules subjected to a magnetic gradient (Basser et al., 2000; Le Bihan, 2003). Tractography findings are not necessarily equivalent to data obtained from post-

mortem dissections. Nevertheless, tractography results are likely to reflect highly reproducible features of the human brain anatomy (Catani et al., 2002; Wakana et al., 2004), and tractography-based dissections currently represent the only way to study the connective anatomy of language pathways in living subjects. As will be shown below, the anatomy of the arcuate fasciculus is one question that has been addressed very fruitfully by DTI tractography.

3. The anatomy of the arcuate fasciculus

Reil (1809, 1812) was the first to identify, almost two Centuries ago, a group of fibres running deeply into the white matter of the temporal, parietal and frontal regions located around the Sylvian fissure of each hemisphere (Fig. 4). In 1822 Burdach (1819–1826) described in detail this system of perisylvian fibres and named it the *Fasciculus Arcuatus* (*Arcuate fasciculus*), for the arching shape of its longest fibres. Subsequently, Dejerine (1895) confirmed the findings of the German neuroanatomists but attributed the discovery to Burdach. Dejerine also believed that the arcuate fasciculus was mainly composed of short associative fibres connecting

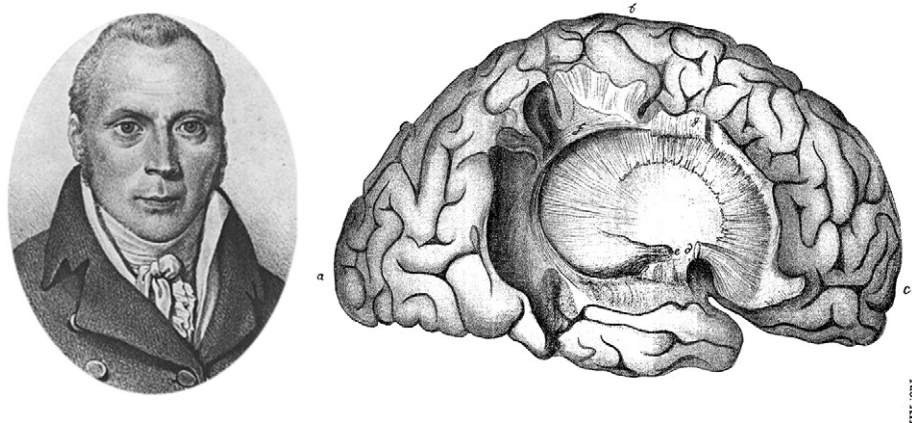


Fig. 4 – Johann Christian Reil (1759–1813) and his description of the arcuate fibres from his 1812 *Archiv für die Physiologie* paper.

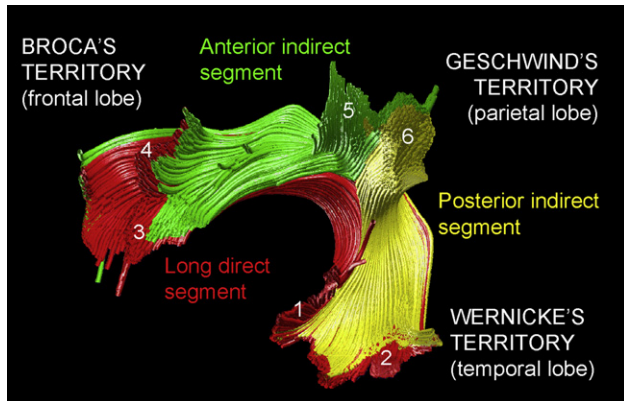


Fig. 5 – Tractography reconstruction of the arcuate fasciculus. Numbers indicate the cortical projections of the segments: 1, superior temporal lobe; 2, middle temporal lobe; 3, inferior frontal and precentral gyrus; 4, middle frontal and precentral gyrus; 5, supramarginal gyrus; 6, angular gyrus (mod. from Catani et al., 2005).

neighbouring perisylvian cortex. As we have seen above, Wernicke hypothesized that language relied on the integrity of a “psychic reflex arc” between temporal and frontal regions. But the arcuate fasciculus was not part of Wernicke’s original anatomical model (Wernicke, 1874). He thought that the temporal and frontal language areas were mutually interconnected by fibres passing through the external capsule and relaying in the cortex of the insula. It was Constantin Von Monakow who first identified the arcuate fasciculus as the tract connecting Broca’s and Wernicke’s areas, a view later accepted by Wernicke in 1908 (Geschwind, 1967). Von Monakow’s statement soon became a dogma in neurology and still today provides the backbone of anatomical models of language.

4. Recent contribution from DTI tractography

Although the existence of the arcuate fasciculus has been confirmed in several post-mortem studies in humans, these methods (e.g., blunt dissections, axonal staining of degenerating axons, etc.) have not shed much light on the detailed anatomy of the relevant fibres. More powerful methods have been used to trace homologous axonal pathways in the monkey but the absence of language in non-human primates raises doubts on the possibility of translating connective anatomy of putative language pathways from animal to man.

Tractography studies are showing that the anatomy of the arcuate fasciculus is more complex than previously thought (Fig. 5) (Catani et al., 2005). In addition to the long direct segment connecting Wernicke’s area with Broca’s area, there is an indirect pathway consisting of two segments, an anterior segment linking Broca’s territory with the inferior parietal lobule and a posterior segment linking the inferior parietal lobule with Wernicke’s territory. This arrangement not only supports the more flexible architecture of parallel processing (Mesulam, 1990), but also is in keeping with some of the classical neurological models of aphasia, contemporary models of verbal working memory (Baddeley, 2003) and recent functional neuroimaging findings (Jung-Beeman, 2005; Sakai, 2005; Stephan et al., 2003). Additional support for the existence of the three perisylvian segments of the “arcuate fasciculus” comes from human intraoperative electrocorticography (Matsumoto et al., 2004), functional connectivity (Schmithorst and Holland, 2007), post-mortem dissections (Lawes et al., 2008), and experiments in homologous parts of the monkey brain (Deacon, 1992).

Another unexpected finding derived from the tractography dissections of the arcuate fasciculus is the extension of its putative cortical terminations beyond the classical limits of Broca’s and Wernicke’s areas to include part of the middle and precentral frontal gyrus and the posterior middle temporal gyrus, respectively (Catani et al., 2005).

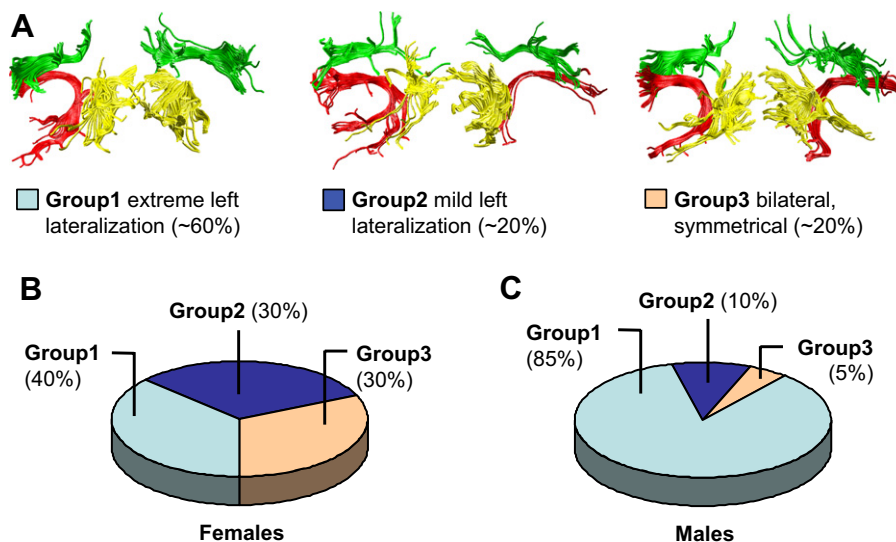


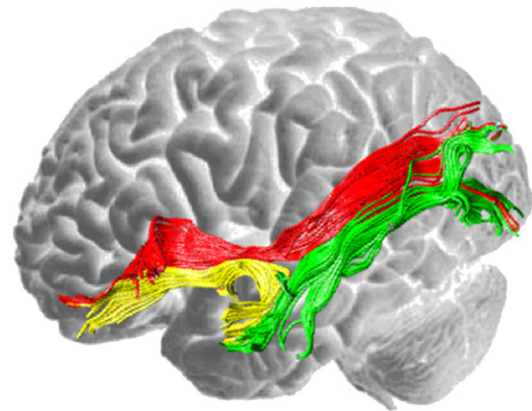
Fig. 6 – Distribution of the pattern of lateralization of the long segment in the normal population and between genders (mod. from Catani et al., 2007).

Hemispheric asymmetry is a key feature of the language network. Differences in the arcuate fasciculus between left and right hemispheres have been demonstrated by microscopic examination of post-mortem specimens (Galuske et al., 2000), by structural T1 MRI (Paus et al., 1999) and by DTI (Buchel et al., 2004; Hagmann et al., 2006; Nucifora et al., 2005; Powell et al., 2006; Catani et al., 2007). Tractography analysis of the degree of lateralization of the three segments (as measured by an indirect index of segment volume) showed an extreme degree of leftward lateralization in ~60% of the normal population (Fig. 6A) (Catani et al., 2007). The remaining ~40% of the population shows either a mild leftward lateralization (~20%) or bilateral, symmetrical pattern (~20%). An extreme degree leftward lateralization is observed in 40% of the female population (Fig. 6B), whereas 85% of males appear to be extremely left lateralised (Fig. 6C). The overall prevalence of leftward asymmetry (Groups 1 and 2 in Fig. 6) in the direct segment of the arcuate fasciculus in the right-handed population is higher (~80%) than that reported for the planum temporale (~65%), the region of the posterior superior temporal gyrus classically associated with language lateralization (Geschwind and Levitsky, 1968). Considering that the prevalence of left functional 'dominance' for language is >90%, asymmetry of the direct segment may represent a more critical anatomical substrate for language lateralization than planum temporale asymmetry (Catani et al., 2007).

Surprisingly, the extreme left lateralization of the direct long segment is associated with worse performance on a complex verbal memory task that relies on semantic clustering for retrieval (i.e., California Verbal Learning Test, CVLT). These findings suggest that lateralization of language to the left hemisphere is a key aspect of human brain organization. Paradoxically less than extreme lateralization might ultimately be advantageous for certain cognitive functions (Catani et al., 2007) (see also Doron and Gazzaniga, 2008, this issue).

5. Beyond the arcuate fasciculus: the ventral pathways

The arcuate fasciculus belongs to the core perisylvian circuitry underlying language. Functional imaging experiments and clinicopathological observations of a language-based neurodegenerative syndrome known as primary progressive aphasia (PPA) have been expanding the boundaries of this core circuitry (for a recent review see Mesulam, 2007). One of the most interesting developments has been the demonstration that areas in the medial, inferior and anterior temporal cortices, traditionally considered outside the canonical language network, may play crucial roles in semantic processing. The interaction of these additional areas with the canonical perisylvian language network may be mediated by a set of ventral tracts such as the inferior longitudinal fasciculus, the uncinata fasciculus, and the inferior fronto-occipital fasciculus (Fig. 7) (for an anatomical description of these tracts see Catani and Thiebaut de Schotten, 2008, this issue). The inferior longitudinal fasciculus carries visual information from occipital areas to the temporal lobe (Catani et al., 2003a) and



- Inferior Fronto-Occipital Fasciculus
- Inferior Longitudinal Fasciculus
- Uncinate Fasciculus

Fig. 7 – Tractography reconstruction of the ventral pathways of the left hemisphere.

it is likely to play an important role in visual object recognition, and in linking object representations to their lexical labels (Mummery et al., 1999). The uncinata fasciculus interconnects the anterior temporal lobe to the orbitofrontal area, including the inferior frontal gyrus (Catani et al., 2002), and may play an important role in lexical retrieval, semantic associations, and aspects of naming that require connections from temporal to frontal components of the language network (e.g., the naming of actions) (Grossman et al., 2004; Lu et al., 2002). The inferior fronto-occipital fasciculus is arguably the only direct connection between occipital and frontal cortex in the human brain (Catani, 2007). It is considered as part of the mirror neuron system and there is preliminary evidence suggesting that this tract is not present in monkey. The relevance of this fasciculus to language is not fully understood but may involve reading and writing (for other functional aspects of these three segments see Gaffan and Wilson, 2008, this issue; Fox et al., 2008, this issue; Ross, 2008, this issue; Epelbaum et al., 2008, this issue; Doricchi et al., 2008, this issue; Raudruff et al., 2008, this issue; Catani and Thiebaut de Schotten, 2008, this issue). These ventral pathways are linked to the perisylvian network at least in two different regions, posteriorly, through short U-shaped fibres connecting Wernicke's area to lateral temporo-occipital cortex and anteriorly through intralobar fibres connecting lateral orbitofrontal cortex to Broca's area.

6. Additional directions for DTI and tractography

As illustrated in Fig. 8, information on the anatomy of connections can potentially help to resolve dilemmas posed by cases that superficially appear to defy established neurocognitive

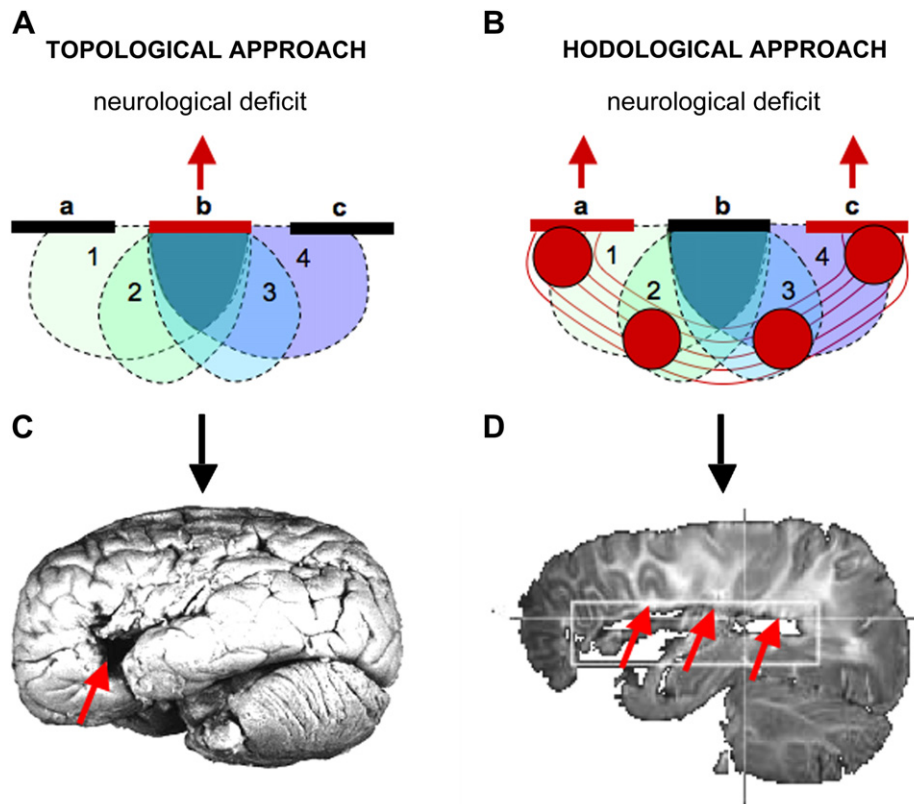


Fig. 8 – Topological and hodological approaches in clinico-anatomical correlation studies. In the upper row an example of a lesion overlap study for clinico-anatomical correlation is represented where four patients present with similar neurological deficits and their respective brain images are overlapped in order to identify a common anatomical substrate. Here we want to highlight that the conclusion that one may draw from this type of studies depends on the hypothesis that is tested and the general framework adopted. (A) A strict topological approach considers brain functions as localized in specific cortical regions. Within this framework the critical area for the same neurological deficit manifested by a group of stroke patients (four in the example, where each area, from 1 to 4, represents the extension of the lesion for each patient) is located at the cortical region of maximum lesion overlap (region b in the example). (B) The hodological (network) approach to brain-behaviour correlation includes a consideration of brain pathways that pass through the damaged area. Within this framework, the neurological deficit could also be attributed to a disconnection between a and c because all lesions affect the same a to c pathway at different levels (red circle). Note that A and B represent the same experiment (i.e. same patients and image analysis), however the conclusions are opposite due to the different approach. (C) Image of the brain of Broca's aphasic patient showing a lesion to the inferior frontal cortex. Broca, who worked within a topological framework, considered that his patient's speech deficit was the consequence of the cortical lesion in the inferior frontal lobe. (D) Sagittal MRI image (mod. from Dronkers et al., 2007) of the same brain shown in (C). Clearly the lesion extends into the white matter of the arcuate (red arrows) of the left hemisphere. If Broca had worked within a hodological framework and performed dissections of his patient's brain it is probable that he would have attributed the speech deficit to a lesion of the arcuate fasciculus.

models. For example, the site of maximal lesion overlap for a specific syndrome may extend into axonal pathways that interconnect a different set of remote areas, raising the possibility that the critical factor is not necessarily the destruction in the cortical area of overlap but a disconnection of the two remote areas (Fig. 8).

DTI tractography also has the potential of detecting pathway changes at early stages of neurodegenerative processes affecting language function so that the effects of such changes upon the resultant aphasias can be studied (Catani, 2006). In primary progressive aphasia, for example, the loss of cortical neurons is accompanied by axonal degeneration along specific white matter pathways (Fig. 9) (Catani et al., 2003b;

Borrioni et al., 2007). Up to now, morphometric work on PPA had focused on the relationship of cortical degeneration to details of the language impairment. An equally interesting development would be to use DTI to measure microstructural changes in specific tracts and to correlate them with the symptom profile (Catani, 2006).

Individual differences in the asymmetry of the arcuate fasciculus detected by DTI could conceivably also help to assess recovery potential in aphasias. It is not unreasonable to assume that greater symmetry is likely to lead to better recovery following stroke or neurosurgery. This is an assumption that can be tested experimentally with currently available methodology.

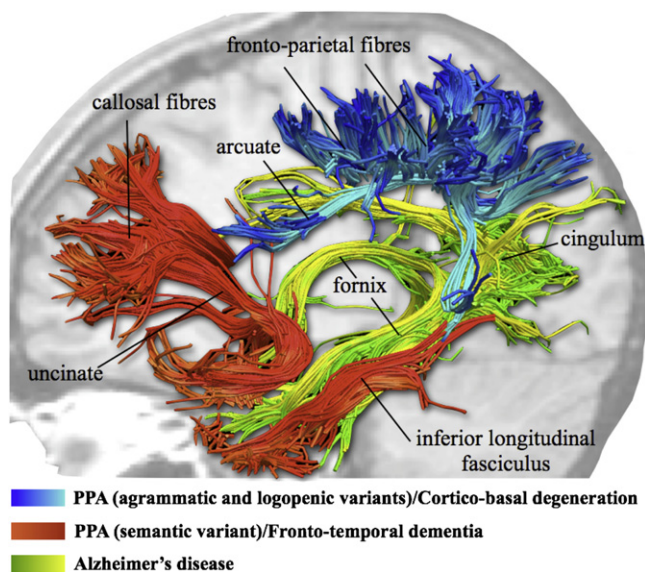


Fig. 9 – Tractography reconstruction of the white matter pathways involved in the most frequent neurodegenerative disorders, some of which affect language function.

7. Concluding remarks and future directions

In this review we have tried to highlight the merits of the hodological (pathway-based) approach to behavioural neurology and its modern pursuit with DTI tractography as applied to language and the arcuate fasciculus. We realize, of course, that mapping symptoms onto single tracts is subjected to the same criticisms directed to narrow cortical localizationism, that our knowledge of human white matter anatomy is still very limited, and that giant strides are needed to reach the level of pathway characterization that has been obtained in the monkey. Nonetheless, DTI tractography applied to the arcuate fasciculus and other pathways is likely to offer productive insights into the connectivity of the human brain and to reconfirm our belief that the disconnection paradigm has still a lot to offer to neurology and psychiatry.

Acknowledgements

MC is funded by the Medical Research Council (UK), the AIMS network MM is funded by the National Institute of Deafness and Communication Disorders (DC008552), National Institute on Aging (AG13854).

REFERENCES

Baddeley A. Working memory: looking back and looking forward. *Nat Reviews Neuroscience*, 4: 829–839, 2003.
 Bassler PJ, Mattiello J, and LeBihan D. MR diffusion tensor spectroscopy and imaging. *Biophysical Journal*, 66: 259–267, 1994.

Basser PJ, Pajevic S, Pierpaoli C, Duda J, and Aldroubi A. In vivo fiber tractography using DT-MRI data. *Magnetic Resonance in Medicine*, 44: 625–632, 2000.
 Borroni B, Brambati SM, Agosti C, Gipponi S, Bellelli G, Gasparotti R, Garibotto V, Di Luca M, Scifo P, Perani D, and Padovani A. Evidence of white matter changes on diffusion tensor imaging in frontotemporal dementia. *Archives of Neurology*, 64: 246–251, 2007.
 Buchel C, Raedler T, Sommer M, Sach M, Weiller C, and Koch MA. White matter asymmetry in the human brain: a diffusion tensor MRI study. *Cerebral Cortex*, 14: 945–951, 2004.
 Burdach K. *Vom baue und leben des gehirns und rückenmarks*. Leipzig: Dyk, 1819–1826.
 Catani M. Diffusion tensor magnetic resonance imaging tractography in cognitive disorders. *Current Opinion In Neurology*, 19: 599–606, 2006.
 Catani M. From hodology to function. *Brain*, 130: 602–605, 2007.
 Catani M, Allin M, Husain M, Pugliese L, Mesulam M, Murray R, and Jones DK. Symmetries in human brain language pathways predict verbal recall. *Proceedings of the National Academy of Sciences of the United States of America*, 104: 17163–17168, 2007.
 Catani M and ffytche DH. The rises and falls of disconnection syndromes. *Brain*, 128: 2224–2239, 2005.
 Catani M, Howard RJ, Pajevic S, and Jones DK. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *Neuroimage*, 17: 77–94, 2002.
 Catani M, Jones DK, Donato R, and ffytche DH. Occipito-temporal connections in the human brain. *Brain*, 126: 2093–2107, 2003a.
 Catani M, Piccirilli M, Cherubini A, Tarducci R, Sciarra T, Gobbi G, Pelliccioli G, Petrillo SM, Senin U, and Mecocci P. Axonal injury within language network in primary progressive aphasia. *Annals of Neurology*, 53: 242–247, 2003b.
 Catani M, Jones DK, and ffytche DH. Perisylvian language networks of the human brain. *Annals of Neurology*, 57: 8–16, 2005.
 Catani M and Thiebaut de Schotten M. A diffusion tensor tractography atlas for virtual in vivo dissections, *Cortex*, 2008, [this issue](#).
 Catani M, Mesulam MM. What is a disconnection syndrome? *Cortex*, 2008, [this issue](#).
 Crick F and Jones E. Backwardness of human neuroanatomy. *Nature*, 361: 109–110, 1993.
 Deacon TW. Cortical connections of the inferior arcuate sulcus cortex in the macaque brain. *Brain Research*, 573: 8–26, 1992.
 Dejerine J. *Anatomie des centres nerveux*. Paris: Rueff et Cie, 1895.
 Dronkers NF, Plaisant O, Iba-Zizen MT, and Cabanis EA. Paul broca's historic cases: high resolution MR imaging of the brains of leborgne and lelong. *Brain*, 130: 1432–1441, 2007.
 Doron KW and Gazzaniga MS. Neuroimaging techniques offer new perspectives on callosal transfer and interhemispheric communication, *Cortex*, 2008, [this issue](#).
 Doricchi F, de Thiebaut de Schotten M, Tomaiuolo F and Bartolomeo P. White matter (dis)connections and gray matter (dys)functions in visual neglect: Gaining insights into the brain networks of spatial awareness. *Cortex*, 2008, [this issue](#).
 Epelbaum S, Pinel P, Gaillard R, Delmaire C, Perrin M, Dupont S, Dehaene S and Cohen L. Pure alexia as a disconnection syndrome: New diffusion imaging evidence for an old concept. *Cortex*, 2008, [this issue](#).
 Finger S. *Origins of neuroscience*. New York: Oxford University Press, 1994.
 Fox CJ, Iaria G and Barton JJS. Disconnection in prosopagnosia and face processing. *Cortex* 2008, [this issue](#).
 Galuske RA, Schlote W, Bratzke H, and Singer W. Interhemispheric asymmetries of the modular structure in human temporal cortex. *Science*, 289: 1946–1949, 2000.
 Gelfand T. Charcot's brains. *Brain and Language*, 69: 31–55, 1999.

- Geschwind N. Disconnexion syndromes in animals and man. I. *Brain*, 88: 237–294, 1965.
- Geschwind N. Wernicke's contribution to the study of aphasia. *Cortex*, 3: 449–463, 1967.
- Geschwind N. The organization of language and the brain. *Science*, 170: 940–944, 1970.
- Geschwind N and Levitsky W. Human brain: left–right asymmetries in temporal speech region. *Science*, 161: 186–187, 1968.
- Grossman M, McMillan C, Moore P, Ding L, Glosser G, Work M, and Gee J. What's in a name: voxel-based morphometric analyses of mri and naming difficulty in Alzheimer's disease, frontotemporal dementia and corticobasal degeneration. *Brain*, 127: 628–649, 2004.
- Glickstein M and Berlucchi G. Classical disconnection studies of the corpus callosum, *Cortex*, 2008, [this issue](#).
- Gaffan D and Wilson CRE. Medial temporal and prefrontal function: Recent behavioural disconnection studies in the macaque monkey, *Cortex* 2008, [this issue](#).
- Hagmann P, Cammoun L, Martuzzi R, Maeder P, Clarke S, Thiran JP, and Meuli R. Hand preference and sex shape the architecture of language networks. *Human Brain Mapping*, 27: 828–835, 2006.
- Jung-Beeman M. Bilateral brain processes for comprehending natural language. *Trends in Cognitive Sciences*, 9: 512–518, 2005.
- Jones DK. Studying connections in the living human brain with diffusion MRI, *Cortex*, 2008, [this issue](#).
- Kempler D, Metter EJ, Jackson CA, Hanson WR, Riege WH, Mazziotta JC, and Phelps ME. Disconnection and cerebral metabolism. The case of conduction aphasia. *Archives of Neurology*, 45: 275–279, 1988.
- Lawes IN, Barrick TR, Murugam V, Spierings N, Evans DR, Song M, and Clark CA. Atlas-based segmentation of white matter tracts of the human brain using diffusion tensor tractography and comparison with classical dissection. *Neuroimage*, 39: 62–79, 2008.
- Le Bihan D. Looking into the functional architecture of the brain with diffusion mri. *Nature Reviews Neuroscience*, 4: 469–480, 2003.
- Levine D and Calvanio R. *Conduction aphasia*. Lisse: Swets and Zeitlinger, 1982.
- Lichtheim L. On aphasia. *Brain*, 7: 433–484, 1885.
- Lu LH, Crosson B, Nadeau SE, Heilman KM, Gonzalez-Rothi LJ, Raymer A, Gilmore RL, Bauer RM, and Roper SN. Category-specific naming deficits for objects and actions: semantic attribute and grammatical role hypotheses. *Neuropsychologia*, 40: 1608–1621, 2002.
- Matsumoto R, Nair DR, LaPresto E, Najm I, Bingaman W, Shibusaki H, and Luders HO. Functional connectivity in the human language system: a cortico-cortical evoked potential study. *Brain*, 127: 2316–2330, 2004.
- Mesulam MM. Imaging connectivity in the human cerebral cortex: the next frontier? *Annals of Neurology*, 57: 5–7, 2005.
- Mesulam MM. Large-scale neurocognitive networks and distributed processing for attention, language, and memory. *Annals of Neurology*, 28: 597–613, 1990.
- Mesulam MM. Primary progressive aphasia: a 25-year retrospective. *Alzheimer Disease and Associated Disorders*, 21: S8–S11, 2007.
- Mummery CJ, Patterson K, Wise RJ, Vandenberghe R, Price CJ, and Hodges JR. Disrupted temporal lobe connections in semantic dementia. *Brain*, 122: 61–73, 1999.
- Nucifora PG, Verma R, Melhem ER, Gur RE, and Gur RC. Leftward asymmetry in relative fiber density of the arcuate fasciculus. *Neuroreport*, 16: 791–794, 2005.
- Paus T, Zijdenbos A, Worsley K, Collins DL, Blumenthal J, Giedd JN, Rapoport JL, and Evans AC. Structural maturation of neural pathways in children and adolescents: in vivo study. *Science*, 283: 1908–1911, 1999.
- Powell HW, Parker GJ, Alexander DC, Symms MR, Boulby PA, Wheeler-Kingshott CA, Barker GJ, Noppeney U, Koeppe MJ, and Duncan JS. Hemispheric asymmetries in language-related pathways: a combined functional mri and tractography study. *Neuroimage*, 32: 388–399, 2006.
- Reil JC. Die Sylvische Grube oder das Thal, das gestreifte grobe hirnganglium, dessen kapsel und die seitentheile des grobn gehirns. *Archiv für die Physiologie*, 9: 195–208, 1809.
- Reil JC. Die vördere commissur im groben gehirn. *Archiv für die Physiologie*, 11: 89–100, 1812.
- Ross ED. Sensory-specific amnesia and hypoemotionality in humans and monkeys: Gateway for developing a hodology of memory. *Cortex*, 2008, [this issue](#).
- Rudrauff D, Mehta S and Grabowski T. Disconnection's renaissance takes shape: Formal incorporation in group-level lesion studies, *Cortex*, 2008, [this issue](#).
- Sakai KL. Language acquisition and brain development. *Science*, 310: 815–819, 2005.
- Schmithorst VJ and Holland SK. Sex differences in the development of neuroanatomical functional connectivity underlying intelligence found using bayesian connectivity analysis. *Neuroimage*, 35: 406–419, 2007.
- Stephan KE, Marshall JC, Friston KJ, Rowe JB, Ritzl A, Zilles K, and Fink GR. Lateralized cognitive processes and lateralized task control in the human brain. *Science*, 301: 384–386, 2003.
- Wakana S, Jiang H, Nagae-Poetscher LM, van Zijl PC, and Mori S. Fiber tract-based atlas of human white matter anatomy. *Radiology*, 230: 77–87, 2004.
- Wernicke C. *Der aphasische symptomcomplex*. Ein psychologische studie auf anatomischer basis. Breslau: Cohn & Weigert, 1874.