Research report

Beyond cortical localization in clinico-anatomical correlation

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ABSTRACT

Last year was the 150th anniversary of Paul Broca's landmark case report on speech disorder that paved the way for subsequent studies of cortical localization of higher cognitive functions. However, many complex functions rely on the activity of distributed networks rather than single cortical areas. Hence, it is important to understand how brain regions are linked within large-scale networks and to map lesions onto connecting white matter tracts. To facilitate this network approach we provide a synopsis of classical neurological syndromes associated with frontal, parietal, occipital, temporal and limbic lesions. A review of tractography studies in a variety of neuropsychiatric disorders is also included. The synopsis is accompanied by a new atlas of the human white matter connections based on diffusion tensor tractography freely downloadable on http://www.natbrainlab.com. Clinicians can use the maps to accurately identify the tract affected by lesions visible on conventional CT or MRI. The atlas will also assist researchers to interpret their group analysis results. We hope that the synopsis and the atlas by allowing a precise localization of white matter lesions and associated symptoms will facilitate future work on the functional correlates of human neural networks as derived from the study of clinical populations. Our goal is to stimulate clinicians to develop a critical approach to clinico-anatomical correlative studies and broaden their view of clinical anatomy beyond the cortical surface in order to encompass the dysfunction related to connecting pathways.

1. Introduction

The clinico-anatomical correlation method celebrates 150 years since Paul Broca brought it to existence in his seminal publication (Broca, 1861; Cubelli and De Bastiani, 2011; Lorch, 2011). To this day the method is still based on the circular reasoning that allows brain function to be inferred by studying the correspondence between clinical manifestations and lesion location. The validity of the method depends on: (i) the theoretical constructs and hypotheses being tested (e.g., psychological models); (ii) the level of sophistication of the methodology used for the patient's clinical characterization,

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and (iii) the resolution of the brain mapping methods (Damasio and Damasio, 1989; Catani and ffytche, 2010). In what follows we consider the evolution of the clinical-anatomical correlation method from the work of the pioneers to more recent neuroimaging approaches based on magnetic resonance imaging. The first part of our contribution is an historical introduction to the origin of the method, the ebb and flow of its fortune and the theoretical constructs derived from its application to neurological patients. In the second part we highlight the advantages of recent MRI methods to improve lesion localization and propose an atlas approach to extend the clinico-anatomical correlation to disorders affecting white matter tracts. In the final section we present a synopsis of the main clinical manifestations associated with lobe and tract lesions as a useful reference to guide the clinical and neuropsychological assessment of patients presenting with lesions to specific tracts.

2. Cortical localizationism and the origin of the clinico-anatomical correlation method

In April 1861, Ernest Auburtin (Fig. 1) presented at the meeting of the Société d'Anthropologie de Paris the case of Monsieur Cullerier, a patient who had shot himself in the head and was admitted to Saint-Louis hospital with an open wound in his forehead. The man remained conscious and possessed normal speech, but his anterior brain was exposed and Auburtin had the audacity to apply a light pressure with a blade to the wounded man's frontal lobe:

> […] the frontal bone was completely removed. The anterior lobes of the brain were exposed, but they were not damaged. Intelligence was intact as well as speech. This unfortunate survived several hours, and we could carry out the following observation. While he was interviewed the blade of a large spatula was placed on the anterior lobes; a light pressure was applied and speech suddenly terminated; a word that had been commenced was cut in two. The faculty of speech reappeared as soon as the compression ceased […] (Auburtin, 1861).

Among the audience was Paul Broca (Fig. 1), who felt that speech localization promoted by Auburtin, and many years before by his mentor and father-in-law Jean-Baptiste Bouillaud, was correct in principle but needed further experimental support. A few days after Auburtin's presentation, Broca admitted to his service Monsieur Leborgne, a 51 year-old man who had lost the use of speech since he was 30 years old. This patient presented with gangrene of the right leg and died a week later. Broca took this opportunity for testing the localization of speech hypothesis at the autopsy. Indeed, he found a lesion in the posterior third of the left inferior frontal gyrus (Fig. 1A). Broca presented his work to the Société d'Anthropologie and published his findings the same year (Broca, 1861). Broca's report, although certainly not the first on the topic (see, for example; Auburtin, 1863 for a review of the cases reported before Broca), served as a signpost for the beginning of the modern study of cerebral localization and encouraged clinicians to apply the clinico-anatomical method to other brain disorders. Within the language domain, for

example, Carl Wernicke (1874) described the centre for 'understanding words', Joseph Jules Dejerine (1892) the centre for 'reading' and Sigmund Exner (1881) the centre for 'writing' (Fig. 1B). In England, John Hughlings Jackson drew attention to the functions of the right hemisphere (Jackson, 1876) followed by others who argued for the existence of right localized centres for 'emotion' (Luys, 1881) and 'geography' (Dunn, 1895). The diffusion of the clinico-anatomical correlation method in the realm of neurology and psychiatry coincided with the rise of cortical localizationist theories of brain function (Fig. 2A and B). Localizationism had its roots in the phrenological theories of the 18th century, but its promoters found in the clinical-anatomical correlation a more valid empirical support than the flawed cranioscopy proposed by Gall and its followers (Gall and Spurzheim, 1810). Localizationist theories received further support from other respectable disciplines, in particular from cortical electrophysiology (Fritsch and Hitzig, 1870; Ferrier, 1875a, 1875b) and animal lesion studies (Ferrier, 1875a, 1875b). The resurgence of war conflicts at the dawn of the 20th century provided unique case series of wounded soldiers with localized cerebral lesions and partial deficits. This permitted Tatsuji Inouye (1909) in Japan and Gordon Holmes (1918) in England, for example, to produce accurate retinotopic maps of the calcarine cortex and correctly localize the foveal representation in the occipital pole (Campbell, 1905; Holmes, 1918; ffytche and Catani, 2005). Kleist (1934) went even as far as to map the entire human cortex and produce a complete cartography of brain functions based on human brain lesion studies. Kleist's work marked the acme of cortical localizationism but also the beginning of its fall (Catani and ffytche, 2005).

3. Holism and the abandonment of the clinico-anatomical correlation method

The clinico-anatomical approach based on a narrow cortical localizationism attracted criticism since its beginning. In England John Hughlings Jackson was one of the first to point out that localization of symptoms does not necessarily imply localization of function. He argued that it is entirely possible that some symptoms can be explained by a secondary effect of the damage on other regions, such as, for example, some positive symptoms resulting from a 'release' mechanism (Jackson, 1881, 1894; Catani, 2011). Furthermore he highlighted that many variables intervene in the correlative process, such as the 'depth of the dissolution'; the 'onset and rapidity of the process'; the 'kind of brain' in which the dissolution occurs, and the 'influence of external and internal circumstances' upon the patient (Jackson, 1894). Jackson's writings had little impact on his contemporaries, but were used some decades later as the ensign of the resurgent holistic movement (Head, 1926). Crucial to holism was the assumption that all areas are mutually interconnected through short- and long-range fibres (Fig. 2C and D). According to the holistic theory, this architectural property of the brain explains the ability of other parts of the cortex to take over functions within the competence of the damaged area, a property designated by Karl Lashley as 'equipotentiality' of the cortex. For Lashley, for example, the occipital region was important but not critical for vision

Ernest Auburtin
(1825-1893)

Paul Broca
(1824-1880)

Carl Wernicke
(1848-1904)

Joseph Jules Dejerine
(1849-1917)
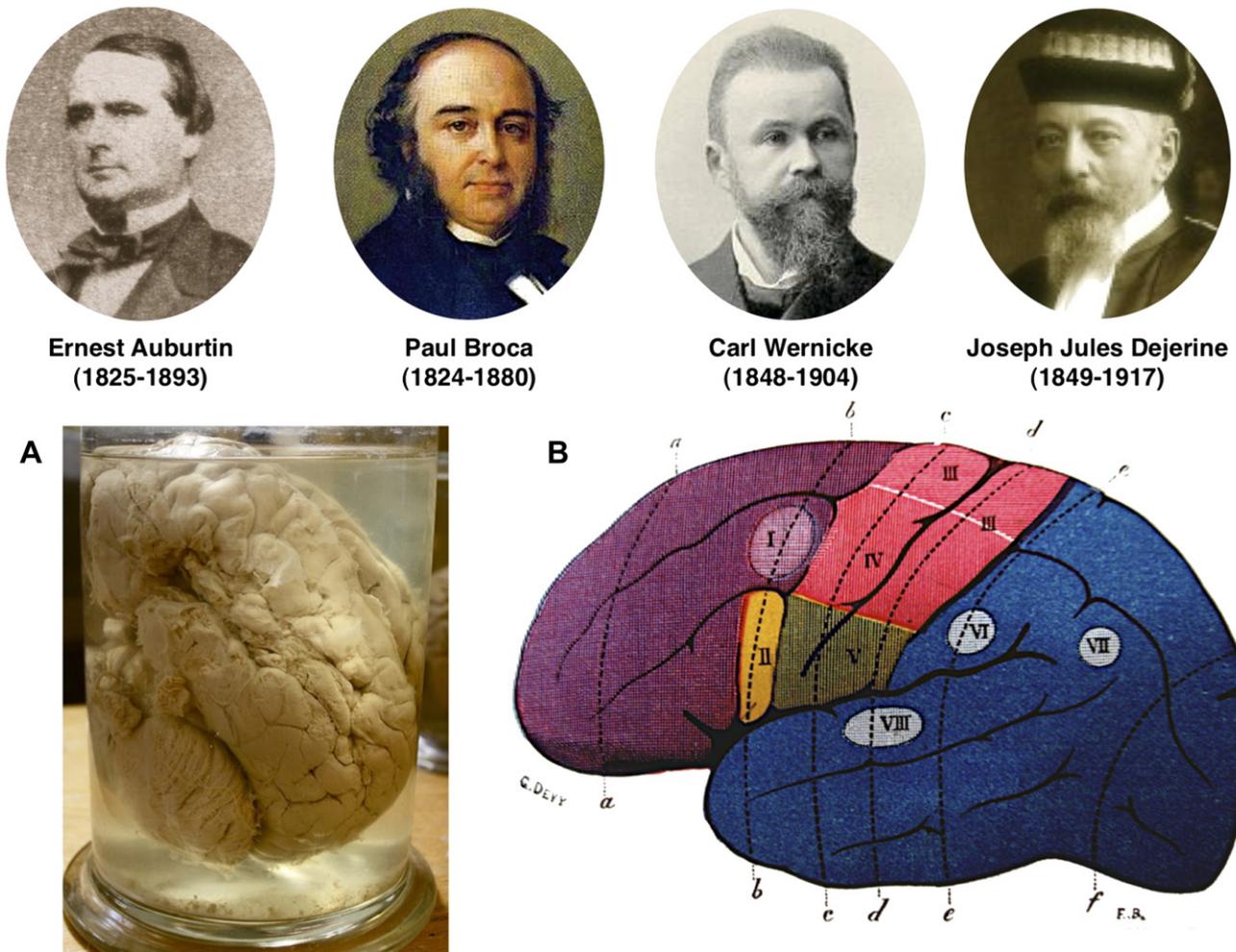
Fig. 1 — Pioneers of the clinical-anatomical correlation method (see text). (A) The brain of monsieur Leborgne, the first patient of Paul Broca, who presented with speech difficulties due to a lesion in the posterior third of the left inferior frontal convolution. The brain is preserved at the Dupuytren museum in Paris. (B) Representation of the cerebral centres in the human brain dedicated to higher cognitive functions (from Testut, 1897): I) writing centre of Exner; (II) Broca's centre for speech; (III) motor centre, lower limb; (IV) motor centre, upper limb; (V) motor centre, face and tongue; (VI–VII) Dejerine's centre for reading; (VIII) Wernicke's acoustic center for verbal comprehension. Blue and purple areas are respectively posterior and anterior zones of the association centres according to Flechsig (1901).

(Lashley, 1950). Hence, for the holistic approach localization of cortical damage is irrelevant, as lesions are more useful for inferring what the unaffected regions of the brain do without the lesioned area than what the lesioned area do when it is part of the intact brain. In the second half of the 20th century factors such as increased difficulty to obtain permission for post-mortem studies, a stagnating backwardness in methods to study human brain anatomy, and the use of more sophisticated standardised testing and group statistics reinforced the idea that the neuroanatomical understanding of the time was insufficient to capture the complexity of psychological functions (Catani and ffytche, 2010). A result of the holistic approach was that in the 1950s anatomy became largely irrelevant to the further development of psychological models of function and dysfunction and clinicians either completely abandoned the clinical-anatomical correlation method or limited its application mainly to surgical patients (e.g., in the

neuropsychology of leucotomised or split-brain patients) (Mettler, 1949; Sperry, 1974). In contemporary neuroscience holism is almost completely abandoned and replaced by a modern version of the associationist approach.

4.   Associationist theories and the disconnection syndromes

The discovery of long-range connections in the brain and their importance for a complete understanding of the mechanisms underlying brain function and its disorders predates of two centuries Broca's description of cortical localization of speech. In 1664 Thomas Willis was among the first to use sections of the brainstem to differentiate between ascending and descending tracts in the 'corpus striatum' and to speculate on possible associated motor and sensory functions:
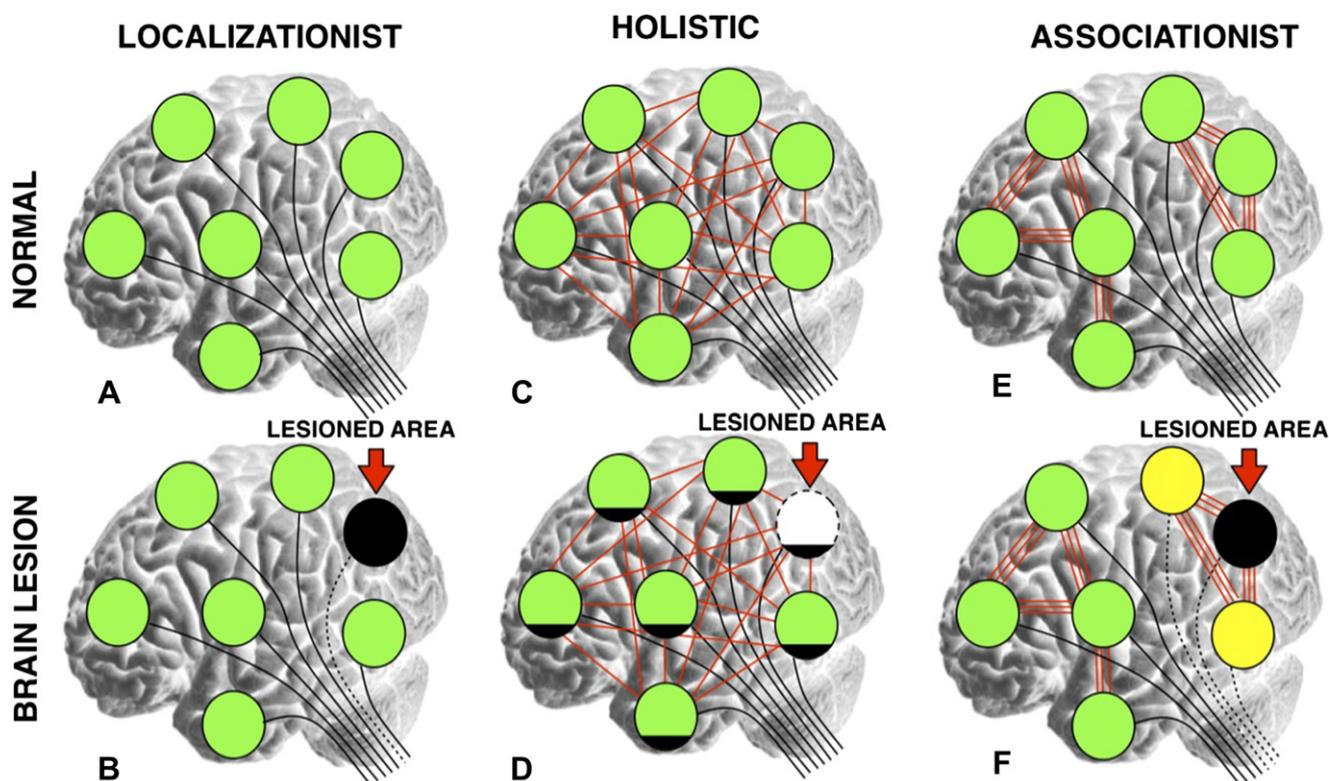
Fig. 2 — Theories of brain function and consequences of a discrete cortical lesion. (A and B) Localizationist models give little importance to interregional connections as each function is carried out by discrete independent regions, whose damage (black) results in a complete loss of a specific function leaving the others intact. Hence, localization of symptoms corresponds to localization of functions. (C and D) Holistic models consider all regions as mutually interconnected through a network of homogeneously distributed association fibres. Cognitive functions are the result of the simultaneous activity of all regions acting as a whole through the association pathways. In case of damage to one area (white), the network allows the redistribution of the lost function to the undamaged brain regions. It follows that for holistic approaches function cannot be localized with clinical-anatomical correlative methods, for the symptoms resulting form the loss of a "quantity" of cerebral cortex rather than a localized area. (E and F) Associationist models consider the brain organized in parallel distributed networks around cortical epicentres. Primary sensory and motor functions are localized (Penfield and Boldrey, 1937; Hatsopoulos, 2010; Plow et al., 2010) but higher cognitive functions are distributed within large-scale networks. Discrete lesions cause loss of specialised functions, whereas complex cognitive functions cannot be localized within single areas. A cortical lesion causes functional loss of the damaged area (black) and partial dysfunction of other interconnected regions (yellow).

The medulla oblongata seems a broad, almost a royal, highway into which the animal spirits [...] are carried into all the nervous parts of the body; when the spirits are disposed in order in this common passage or, so to speak diatasso in regular series, they serve two purposes, that is, either they may be directed outwards towards the nerves, at which time they exert the locomotive faculty; or flow inwards towards their sources when the acts of sensation, or rather perceptions of sensible things, are performed. (Willis, 1664)

Willis was also able to demonstrate the degeneration of the corpus striatum in a patient with severe paralyses. In the 19th century the continuous development of methods for preparing the brain for fibres dissection led to the identification of most of the association tracts of the human brain (Catani et al., 2010). The pioneer work of Johann Christian Reil, for example, based on the soaking of the brain in alcohol resulted in the first description of the course of most association bundles running beneath the cerebral convolutions (Reil, 1809). Karl Burdach in his Vom Baue und Leben (Burdach, 1822) not only confirmed Reil's findings but used a Latin terminology that has been adopted almost unchanged in the current international anatomical nomenclature (FCAT, 2000). In the second half of the 20th century the spread of associationist models of cognitive functions from the realm of psychology (Wundt, 1863; James, 1890) to that of neurology and psychiatry (Meynert, 1885) stimulated clinicians to adopt disconnection models for disorders of higher cognitive functions, such as conduction aphasia (Wernicke, 1874), visual agnosia (Lissauer, 1890), pure alexia (Dejerine, 1892) and apraxia (Liepmann, 1900) (Fig. 2E and F). The associationist theory originally elaborated by Meynert (1885) and Wernicke (1874), has been re-formulated in the last 50 years by Geschwind's neoassociationist school (Damasio and Damasio, 1989;

Geschwind, 1965a, 1965b; Mesulam, 1990; Ross, 2010) and has received further support in the recent years from functional imaging and diffusion magnetic resonance imaging tractography (Catani and ffytche, 2005; Catani, 2006). According to this theory large-scale networks in the human brain are dedicated to specific functions such as language, face-and-object recognition, executive function-comportment, spatial attention, and memory-emotion (Fig. 3) (Mesulam, 2000). The nodes of these networks can be divided into critical versus participating epicentres. Critical network epicenters constitute 'relays or integration centers, hubs, nexuses, sluices for convergence, divergence, feedback loops, feed-forward connections, and transition points from serial to parallel processing' (Catani and Mesulam, 2008a,b). Cognition and behaviour are considered as emergent properties of large-scale neural networks (Ross, 2010; Bartolomeo, 2011), where lesions to connections lead to the inability to transfer information from one node to another (as in the classical disconnection syndromes such as conduction aphasia) and a series of distant 'hodological' effects on each node of the network (as in the case of diaschisis) (von Monakow, 1914).

Recent advances in functional (Friston et al., 2003) and diffusion (Basser et al., 2000; Catani et al., 2002; Jones, 2008;

Dell'Acqua and Catani, in press) magnetic resonance imaging are important steps to gain insight into neuronal networks of the human brain. The diffusion tractography approach, for example, has demonstrated that the 'arcuate fasciculus' contains a direct and also an indirect component (Catani et al., 2005) and so added a new layer of understanding that is more in keeping with the parallel processing models of the language network (Mesulam, 2005). Unfortunately these advanced MRI methods are often not available to most clinicians, who frequently are the first to have the opportunity to study patients with unique neurological manifestations. Furthermore the lack of normalized white matter atlases of human brain connections based on diffusion tensor tractography and the limitations of currently available histological atlases in identifying association tracts hindered our ability to correctly localize damaged white matter pathways (Thiebaut de Schotten et al., 2011a). To fill this gap we propose in the following section a statistical atlas of human brain connections based on diffusion tensor imaging tractography. Together with a synopsis of the major lobe syndromes the atlas could help clinicians to include information on white matter anatomy in the clinico-anatomical correlative process.
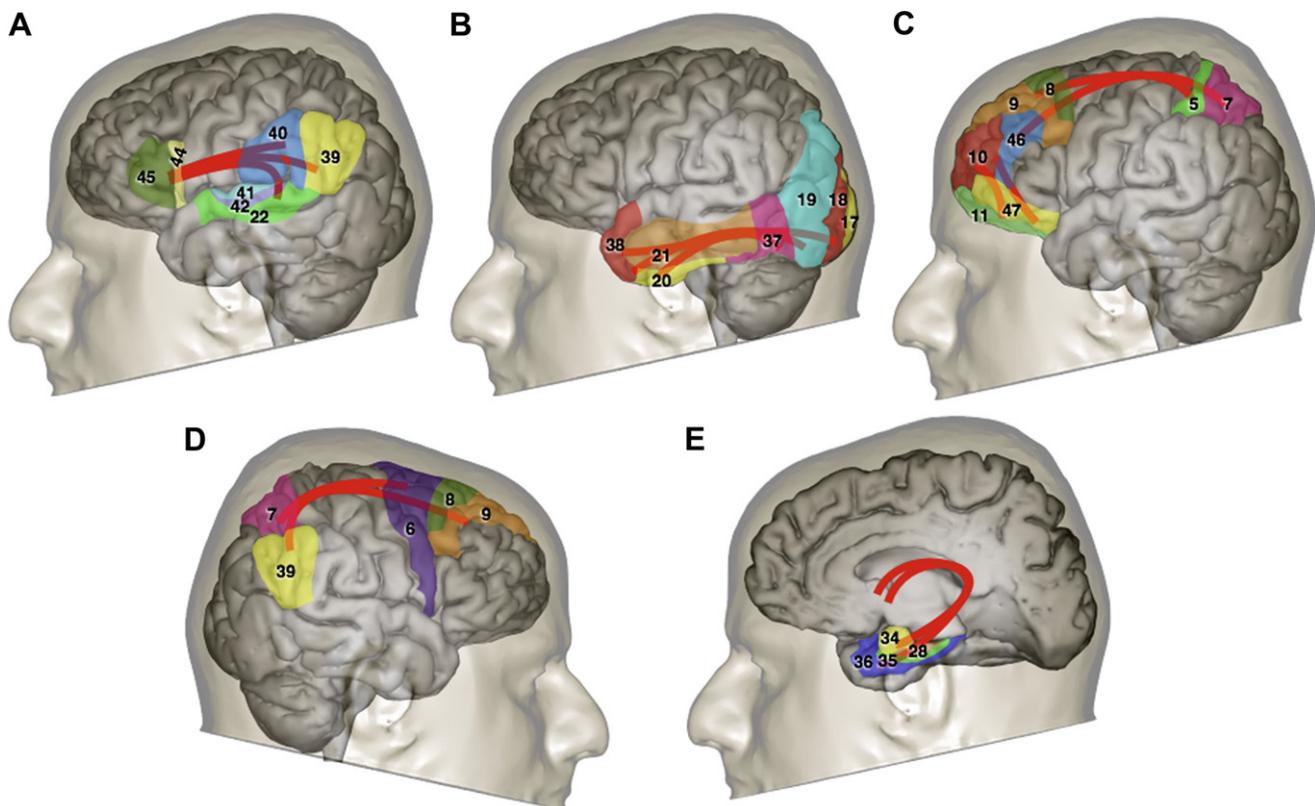
Fig. 3 – Large-scale networks for cognition and behaviour (Mesulam, 2000). (A) A left hemisphere-dominant language network with epicentres in Wernicke's and Broca's areas (Catani and Mesulam, 2008). (B) A face-object identification network with epicentres in occipito-temporal and temporopolar cortex (Fow et al., 2008). (C) An executive function-comportment network with epicentres in lateral prefrontal cortex, orbitofrontal cortex, and posterior parietal cortex (Zappala' et al., 2012). (D) A right hemisphere-dominant spatial attention network with epicentres in dorsal posterior parietal cortex, the frontal eye fields, and the cingulate gyrus (Doricchi et al., 2008). (E) A memory-emotion network with epicentres in the hippocampal-entorhinal regions and the amygdaloid complex (Park et al., 2010).

5. A tractography atlas for clinico-anatomical correlation

Brain atlases have always played an important part in understanding the anatomical basis of neurological and psychiatric disorders. Previous atlases were the offspring of methodological advancements available at that time (Dejerine, 1895; Campbell, 1905; Brodmann, 1909; Von Economo and Koskinas, 1925; Talairach and Tournoux, 1988). Most of these atlases contain detailed cortical maps with little information on the anatomy of underlying white matter. In this section we introduce a DTI-tractography atlas to facilitate the localization of white matter lesions to specific white matter tracts in neurological and psychiatric disorders (Thiebaut de Schotten et al., 2011a). Details of the method used to create the atlas can be found in the Supplementary material. Figs. 4–6 show selected axial, sagittal, and coronal composite maps of the principal white matter tracts of the human brain. The numbered grids indicate the MNI coordinates. The maps contain regions with complex white matter anatomy and show a high degree of overlap between tracts. Overall the origin, course and termination of the tracts have a good correspondence with classical textbooks of neuroanatomy and post-mortem dissections (Lawes et al., 2008; Thiebaut de Schotten et al., 2011a,b). Our maps also contain details on tracts (e.g., the three segments of the arcuate fasciculus) that are not provided by other atlases. The digital maps of the individual tracts can be downloaded as nifti image format files from the following link: http://www.natbrainlab.com.

In clinical settings the atlas could help to identify the white matter tract positions on CT or MR images in individual patients with a wide range of pathologies including stroke, traumatic brain injury, multiple sclerosis, tumours, vascular malformations, leukoencephalopathies, and infectious diseases. An example of this application is shown in Fig. 7A. This is the case of a patient with a brain tumour who presented with language difficulties without a direct involvement of classical language areas. The localization of the lesion with
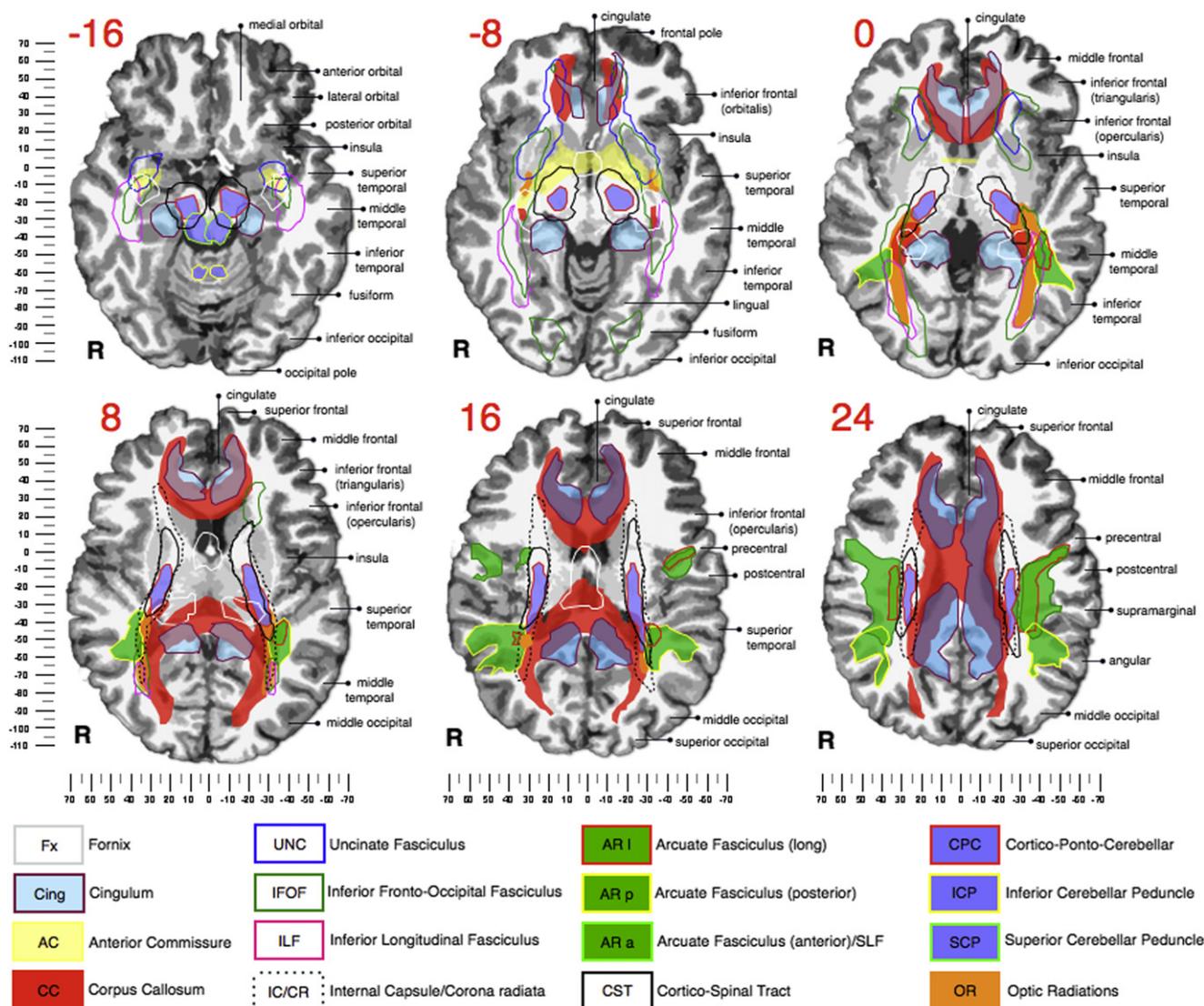
Fig. 4 – Axial maps. The red numbers indicate the MNI coordinates along the z-axis. The right side is indicated with the letter R. Note that when the internal capsule/corona radiata overlaps with the cortico-spinal tract only the latter is displayed.

Fx	Fornix	UNC	Uncinate Fasciculus	AR l	Arcuate Fasciculus (long)	CPC	Cortico-Ponto-Cerebellar
Cing	Cingulum	IFOF	Inferior Fronto-Occipital Fasciculus	AR p	Arcuate Fasciculus (posterior)	ICP	Inferior Cerebellar Peduncle
AC	Anterior Commissure	ILF	Inferior Longitudinal Fasciculus	AR a	Arcuate Fasciculus (anterior)/SLF	SCP	Superior Cerebellar Peduncle
CC	Corpus Callosum	IC/CR	Internal Capsule/Corona radiata	CST	Cortico-Spinal Tract	OR	Optic Radiations
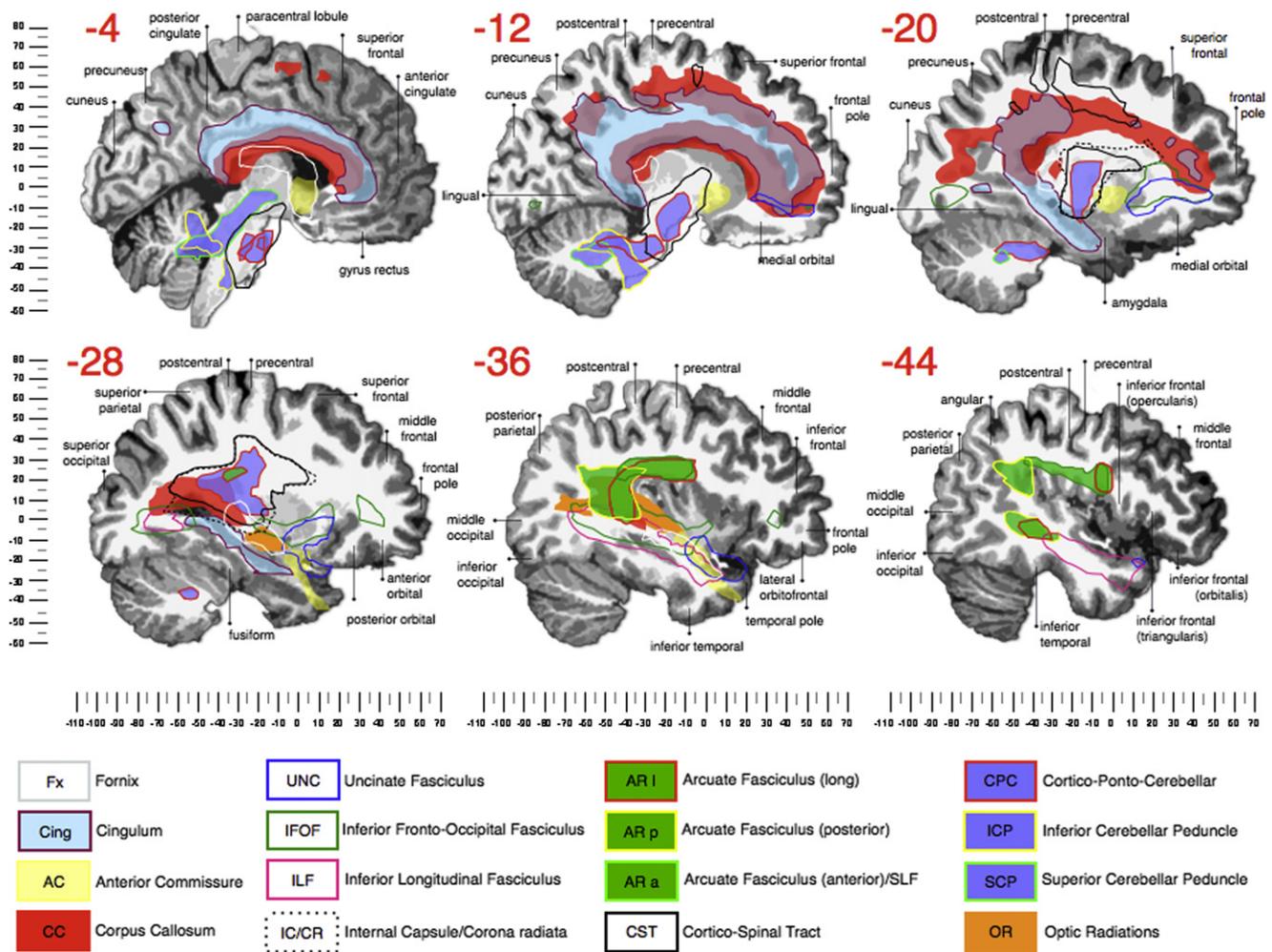
Fig. 5 — Sagittal maps. The red numbers indicate the MNI coordinates along the x-axis (only the left hemisphere is shown in this figure). Note that when the internal capsule/corona radiata overlaps with the cortico-spinal tract only the latter is displayed.

the atlas suggests an involvement of the anterior and long segments of the arcuate fasciculus. Hence, in this case an alternative hodological explanation to the classical cortical localization approach suggests that dysfunction of Broca's area can result from lesions of its connections with posterior parietal and temporal language regions.

The atlas could also be used in research studies to facilitate the localization of between-groups differences, for example in voxel-based morphometry studies (Radua et al., 2011) or correlative analysis (Rudrauf et al., 2008; Thiebaut de Schotten, 2008). An example of the application of the atlas to a meta-analysis of the voxel-based morphometry studies in autism is shown in Fig. 7B. This use of the atlas could help to expand the network approach beyond the neurology clinic to those disorders where the pathology is not 'visible' to the naked eye using conventional clinical imaging (e.g., schizophrenia, affective disorders, etc.).

To stimulate the transition from cortical localization to network mapping we review in the next section classical neurological manifestations, indicating whenever it is possible, the cortical and subcortical extension of the associated lesion.

6. A network approach to classical cerebral lobe syndromes

In this section we present a synopsis of the classical neurological syndromes based on classical textbooks or monographs (Mesulam, 2000; Salloway et al., 2001; Stuss and Knight, 2002; Cummings and Mega, 2003; Darby and Walsh, 2005), supplemented by more recent clinical diffusion tensor tractography studies in common neuropsychiatric disorders. Although the order of presentation follows a lobar division, our aim is to stimulate a broader view of these syndromes and ultimately promote a network approach to classical behavioural neurology and neuropsychiatry. In the accompanying images only the association tracts are displayed.

7. Frontal lobe

The principal subdivisions of the frontal lobe (Fig. 8) are: (i) precentral cortex (BA 4 and inferior 6); (ii) premotor cortex
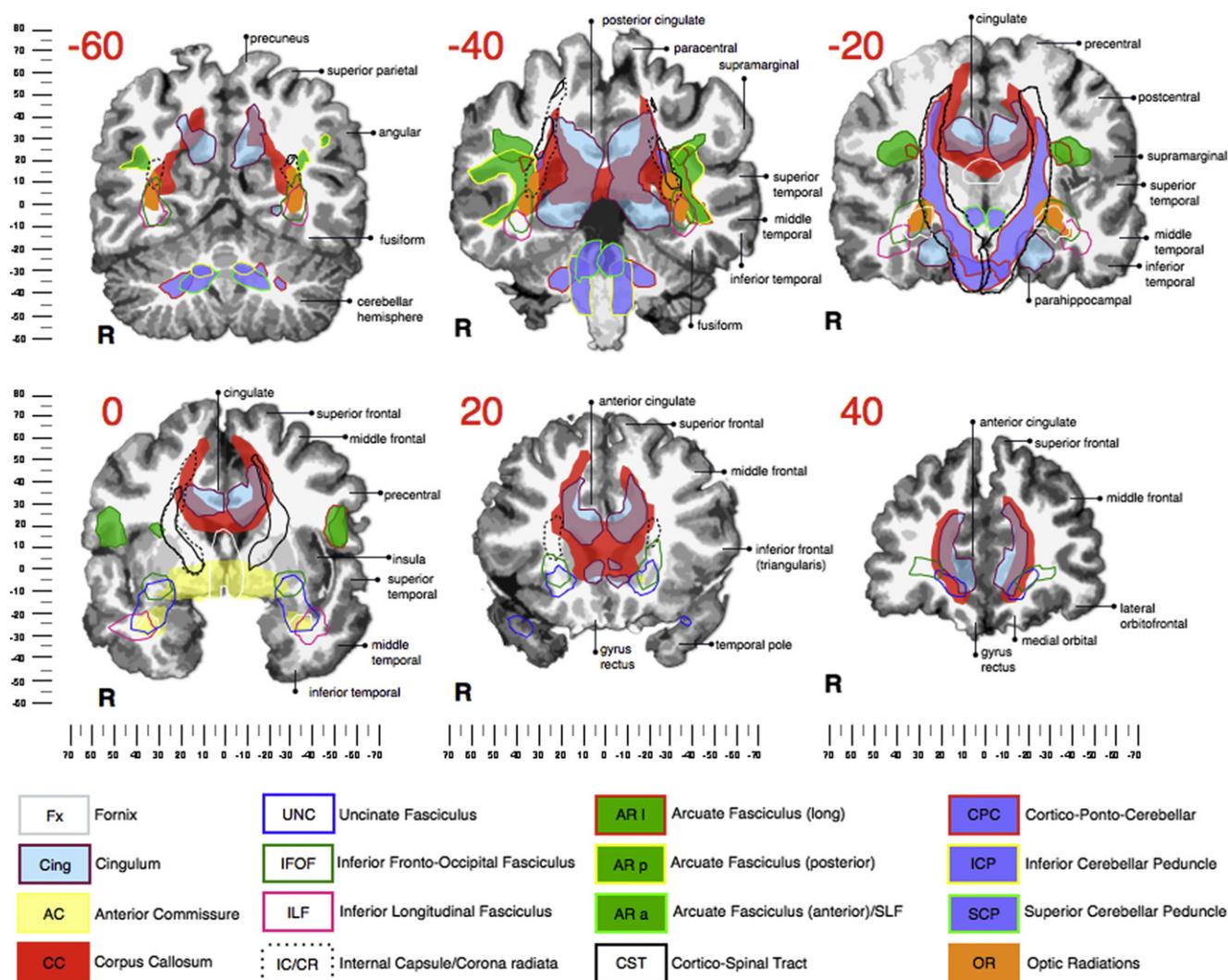
Fig. 6 — Coronal maps. The red numbers indicate the MNI coordinates along the y-axis. Note that when the internal capsule/corona radiata overlaps with the cortico-spinal tract only the latter is displayed.

(BA 6, 8, 44, 45) (iii) prefrontal cortex (BA 9, 10, 46, 47); and (iv) orbitofrontal cortex (BA 11, 47). The clinical manifestations commonly associated with frontal lobe lesions can be grouped into four syndromes (Table 1).

7.1. Motor syndrome

The primary motor cortex located in the posterior part of the precentral gyrus (Hatsopoulos, 2010) gives origin to almost 50% of the fibres of the cortico-spinal tract. Lesions to the primary motor cortex and its connections manifest with contralateral motor deficits of the limbs or face (e.g., hemiparesis or complete hemiplegia) (Newton et al., 2006). In patients with left hemisphere damage, the extension of the lesion to the anterior segment of the arcuate fasciculus may impair the ability to execute or carry out learned purposeful movements (i.e., apraxia) of the left arm and face in addition to hemiparesis of the right arm (see also disorders of motility in parietal syndromes) (Heilman and Watson, 2008; Ramayya et al., 2010). Anterior to the primary motor cortex at the

junction between the precentral gyrus and the superior frontal sulcus, is the frontal eye field (Muggleton et al., 2010). Lesions to the frontal eye field and its connections manifest with gaze abnormalities (Anderson et al., 2011). The anarchic hand syndrome (one hand acting autonomously as if having its own will) is a rare condition associated with lesions of the dorso-medial frontal lobe and its callosal or intralobar connections (Marchetti and Della Sala, 1998; Berlucchi, 2012; Catani et al., 2012). Finally, abnormal neuronal activity within the precentral and premotor cortex manifest with motor seizures (O'Muircheartaigh and Richardson, 2012).

7.2. Cognitive syndrome

The dorsolateral prefrontal cortex is connected to the parietal cortex, temporal lobe and basal ganglia by the cingulum, superior longitudinal fasciculus, arcuate fasciculus and internal capsule (i.e., fronto-striatal connections) (Yeterian et al., 2012; Krause et al., 2012; Thiebaut de Schotten et al., 2012; Catani et al., 2012). Patients with dorsolateral lesions
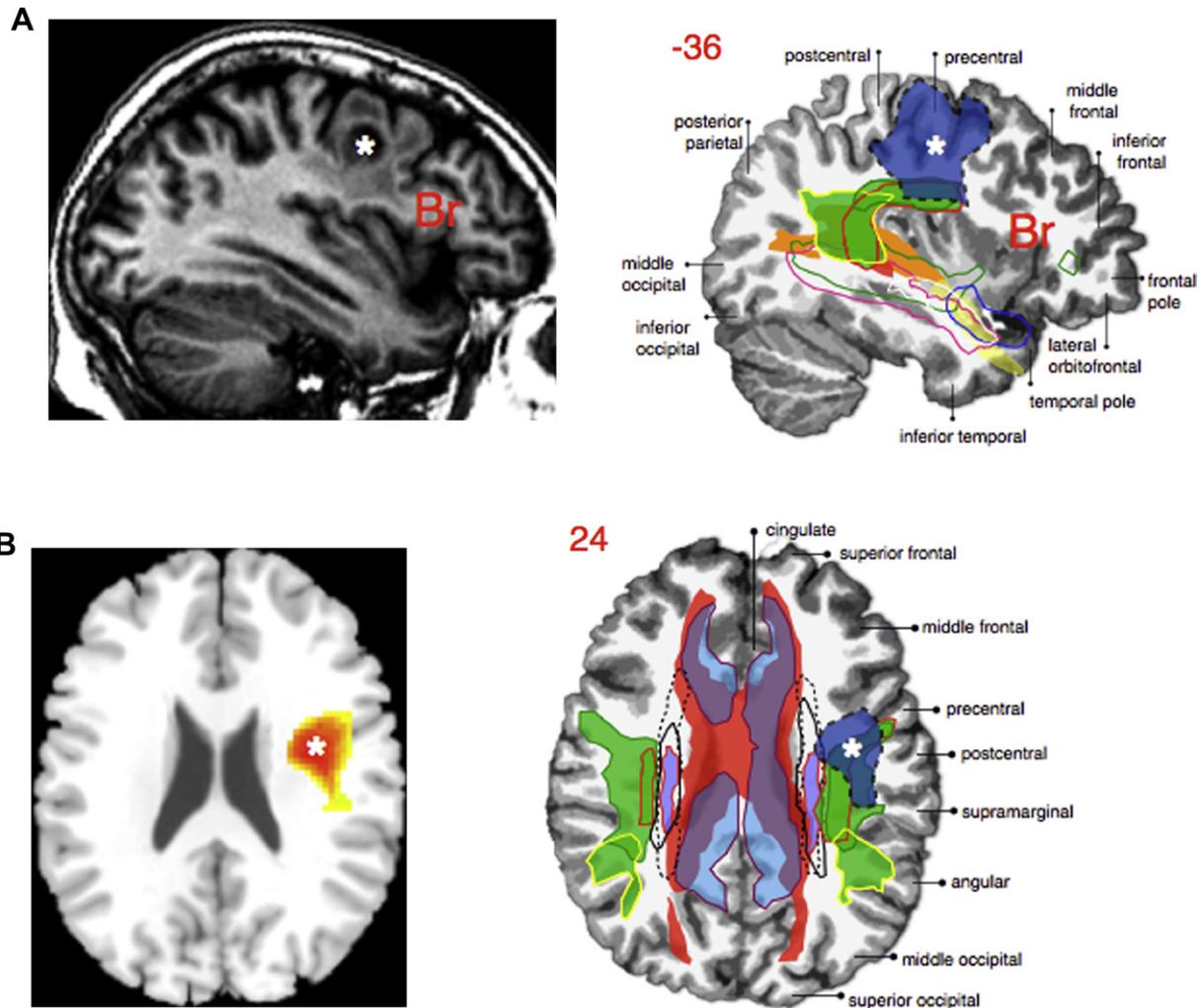
Fig. 7 – Two examples of the possible applications of the atlas to clinical populations. (A) The first example refers to the use of the atlas for localizing white matter lesions in individual patients, in this case a 72 years old right-handed female with moderate language impairment characterized by reduced verbal fluency and repetition deficits. This clinical profile is usually indicative of a lesion to Broca's area (Br), which in this case was intact. The MRI shows a tumour (asterisk) localized in the precentral gyrus with perilesional oedema extending into adjacent parietal and frontal white matter. In the right panel the area of the tumour and oedema is indicated in blue and overlaid onto the corresponding sagittal image of the atlas to identify the affected white matter tracts (i.e., anterior and long segment of the arcuate fasciculus). Hence, in this case the language deficits can be attributed to a lesion of the connections between Broca's area and more posterior language areas in the parietal and temporal lobe. (B) This second example refers to the use of the atlas to facilitate the interpretation of group analysis, in this case the results of a meta-analysis of voxel-based morphometry (VBM) studies in autism spectrum disorder. The meta-analysis, which included thirteen datasets comprising 246 patients with ASD and 237 healthy controls (Radua et al., 2011), suggests decreased white matter volume in a discrete region that the atlas identified to include the anterior and long segment of the arcuate fasciculus (right).

show cognitive impairment characterized by memory deficit, altered serial motor sequencing, poor response inhibition, impaired cognitive estimation and abnormal abstract thinking (Baddeley, 2007; Catani et al., 2012; Thiebaut de Schotten et al., 2012). Executive functions for goal-directed behaviour (planning, rule learning, focusing, hierarchical organization, switching, monitoring, etc.) are also affected (Stuss and Knight, 2002). These patients are often easily distracted and show impaired mental flexibility and motor perseveration (Zappala' et al., 2012). Some cognitive

symptoms are lateralized. For example, impaired ability to convey meaning and emotions through the modulation of speech intonation, rhythm, and gestural expression (i.e., anterior affective-aprosodia) (Ross, 1981) and unilateral neglect (see also disorders of spatially-directed attention in the parietal lobe) (Husain et al., 2000; Redding and Wallace, 2010; Bultitude and Rafal, 2010) often occur with lesions of the right inferior frontal gyrus, while apraxia (Heilman and Watson, 2008) and Broca's aphasia (Catani and Mesulam, 2008a,b Berthier et al., 2012; Bizzi et al., 2012) are more
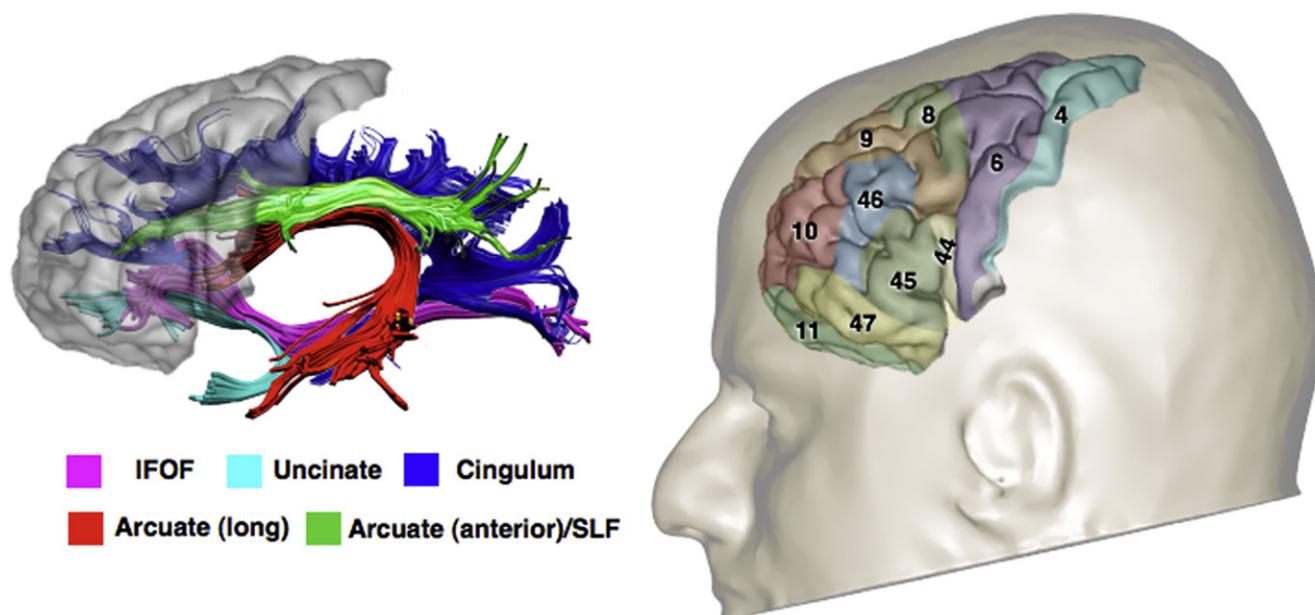
Fig. 8 – The cortical anatomy of the frontal lobe and its main associative connections. Numbers indicate cytoarchitectonic areas according to Brodmann's nomenclature. The major association pathways of the frontal lobes are the cingulum for the medial surface, the uncinate and inferior fronto-occipital fasciculus (IFOF) for the ventral surface and the anterior and long segments of the arcuate fasciculus for the lateral surface. The dorso-lateral frontal cortex is also connected by the superior longitudinal fasciculus, which is difficult to visualize with current diffusion tensor tractography studies.

frequent in left inferior frontal lesions. Cognitive 'frontal lobe' symptoms are also observed in patients with lesions to the cerebellum (Budisavljevic and Ramnani, 2012) and basal ganglia (Krause et al., 2012).

7.3. Abulic syndrome

The medial prefrontal cortex is connected to the medial parietal, occipital and temporal lobe by the cingulum. Lesions

Table 1 – Clinical syndromes, white matter tracts and cortical areas of the frontal lobes.

Clinical manifestations	White matter tracts	Cortical Brodmann areas
Motor syndromes:		
- Hemiparesis or hemiplegia	Cortico-spinal tract	4, 6
- Apraxia	Superior longitudinal fasciculus	6, 8
- Eye gaze abnormalities	Superior longitudinal fasciculus, cingulum	9, 46
- Anarchic hand syndrome	Anterior body of the corpus callosum/superior longitudinal fasciculus	8, 9
Cognitive syndromes:		
- Memory deficits/impaired abstract thinking and inhibition	Superior longitudinal fasciculus, uncinate, internal capsule (i.e., fronto-striatal projections)	8, 9, 47
- Dysexecutive symptoms	Internal capsule (i.e., fronto-striatal projections)	6, 8, 9
- Affective-aprosodia	Arcuate fasciculus	6, 44, 45
- Neglect	Superior longitudinal fasciculus	6
- Apraxia (ideomotor or limb kinetic)	Superior longitudinal fasciculus, corpus callosum	6, 8
- Broca's aphasia	Arcuate fasciculus	6, 44, 45
Abulic syndromes:		
- Blunt affect, reduced interests	Subgenual cingulum	10, 11, 24, 32, 33
- Lack of motivation, reduced concentration	Anterior cingulum, internal capsule	8, 9, 10, 24, 32, 33
- Limb akinesia, mutism	Dorsal cingulum, superior longitudinal fasciculus	6, 8, 9, 24, 32
Behavioural syndromes:		
- Personality changes, imitation and utilization behaviour, grasping, emotional lability, disinhibition	Uncinate, inferior fronto-occipital fasciculus, internal capsule (i.e., fronto-striatal projections)	10, 11, 47
Other neuropsychiatric syndromes		
- Schizophrenia	Genu, arcuate, uncinate fasciculus, anterior thalamic projections, cortico-spinal tract	4, 6, 8, 9, 10, 11, 44, 45, 47
- Autism	Genu, arcuate, uncinate fasciculus, cingulum	6, 8, 9, 10, 11, 44, 45, 47
- Stuttering	Anterior thalamic projections	44, 45, 6

to the medial frontal lobe manifest with apathy, whose central features are blunt affect, loss of motivation and reduced goal-directed movements (Mesulam, 2000). Apathy has affective, cognitive and motor components (Mega et al., 1997). Affective aspects of apathy manifest with blunt affect and absence of interests. The cognitive aspects of apathy include decreased engagement with usual activities, lack of curiosity and interest in learning, impoverished generative thinking and reduced ability to sustain effort. These affective and cognitive aspects of abulia are usually associated with anterior medial frontal lesions extending into the anterior cingulate cortex (Rankin et al., 2006; Zappala' et al., 2012). Finally, motor symptoms of apathy are characterized by marked reduction of spontaneous movements (i.e., limb akinesia and mutism) and are usually associated with more posterior lesions of the medial aspect of the superior frontal lobe (i.e., supplementary and pre-supplementary motor areas) (Mega et al., 1997).

7.4. Behavioural syndrome

The orbitofrontal cortex is connected to the anterior temporal and ventral temporo-occipital cortex through the uncinate and inferior fronto-occipital fasciculus, respectively. The most medial portion of the orbitofrontal cortex is also connected to the medial dorsolateral prefrontal region through the cingulum. Patients with orbitofrontal lesions present with personality changes characterized by disinhibition, social inappropriateness and sexual preoccupation. Other frontal lobe signs that frequently accompany the behavioural syndrome are related to automatic motor behaviour. Patients, for example, automatically imitate the examiner's movements without being told to do so (i.e., imitation behaviour), grip objects (i.e., grasping) or use tools (i.e., utilization behaviour) presented to them (Mesulam, 2000; Salloway et al., 2001; Rosen et al., 2005). Neuropsychiatric manifestations are also frequently described in these patients. These include reduced empathy, impulsivity, distractibility, emotional lability, depression, and more rarely hypomania or mania. Cognitive deficits are not frequent in patients with behavioural symptoms (Mega et al., 1997).

7.5. Tractography studies in neurodevelopmental and psychiatric disorders

Diffusivity changes have been reported in the frontal connections of patients with schizophrenia. In particular reduced fractional anisotropy has been consistently documented in the genu of the corpus callosum (Kanaan et al., 2006), uncinate fasciculus (Kubicki et al., 2002), arcuate fasciculus (Jones et al., 2006), anterior thalamic projections (Oh et al., 2009) and cortico-spinal tract (Douaud et al., 2009). In autism spectrum disorder in vivo anatomical differences are reported for the corpus callosum (Alexander et al., 2007, Thomas et al., 2011) and the arcuate fasciculus (Kumar et al., 2010). Kumar et al. (2010) found that in young children with autism spectrum disorder the average length of the long segment of the arcuate fasciculus is greater in the right compared to the left hemisphere. This pattern of asymmetry is different to those of children with neurotypical development, which show a more symmetrical distribution. In adolescents with high functioning autism the long segment of the arcuate fasciculus has increased radial diffusivity, suggesting that anatomical abnormalities of the axonal membrane and/or myelin persist later in life (Fletcher et al., 2010). Dysfunction of the ventral anterior thalamic nucleus and its connections to frontal areas have been reported in developmental stuttering (Watkins et al., 2008).

8. Parietal lobe

The parietal lobe includes: (i) post-central gyrus (BA 3, 1, 2); (ii) superior parietal lobule (BA 5, 7); (iii) inferior parietal lobule (BA 39, 40); (iv) precuneus (medial BA 5, 7); and (v) posterior parietal gyrus (BA 19) (Fig. 9). The parietal syndromes can be divided into five groups (Table 2).

8.1. Disorders of somatosensory and tactile function

The post-central gyrus is connected to neighbouring regions by U-shaped fibres and receives direct projections from the thalamus (Catani et al., 2012). Lesions to the post-central gyrus and its connections can manifest with either isolated or combined impaired sensation for pain, temperature, touch, and vibration. Sensation can be absent (i.e., anaesthesia), reduced (i.e., hypoaesthesia), or increased (i.e., hyperaesthesia). If more than one modality is altered (either reduced or increased), the patient reports multiple symptoms such as tingling, burning, numbness, feeling of pins and needles (i.e., dysaesthesia) (Bassetti et al., 1993). Proprioception (i.e., the ability to detect joint motion and limb position) can also be impaired in isolation or in combination with other somatosensory modalities. Spontaneous tactile sensation can present in the form of tactile perseveration (i.e., persistence of touch sensation after cessation of the stimulus), polyaesthesia (i.e., a single tactile stimulus is reported as several), and hallucination of touch (i.e., tactile sensation in the absence of any stimulus) (ffytche et al., 2010). Other forms of sensation require higher integration and are associated with more extensive lesions of the parietal lobe (Frassinetti et al., 2010). These include impaired tactile recognition of three-dimensional objects (i.e., astereognosis) or letters (i.e., agraphaesthesia), inability to localize sensory stimuli (i.e., atopaesthesia), and failure to detect the stimulus on one side of the body when touched simultaneously on both sides (i.e., extinction) (Critchley, 1953).

8.2. Disorders of motility

The parietal regions posterior to the post-central gyrus connect extensively with the occipital lobe through U-shaped fibres and project to the frontal lobes through the arcuate and superior longitudinal fasciculus system (Thiebaut de Schotten, 2011b; Yeterian et al., 2012; Thiebaut de Schotten et al., 2012; Catani et al., 2012, Catani et al., in press). Patients with lesions of the precuneus and superior parietal lobe may present uncoordinated voluntary movements that lack speed, smoothness, and appropriate direction (i.e., ataxia). Ataxia is not related to disorders of motor, sensory or visual function. Some patients are impaired solely in reaching
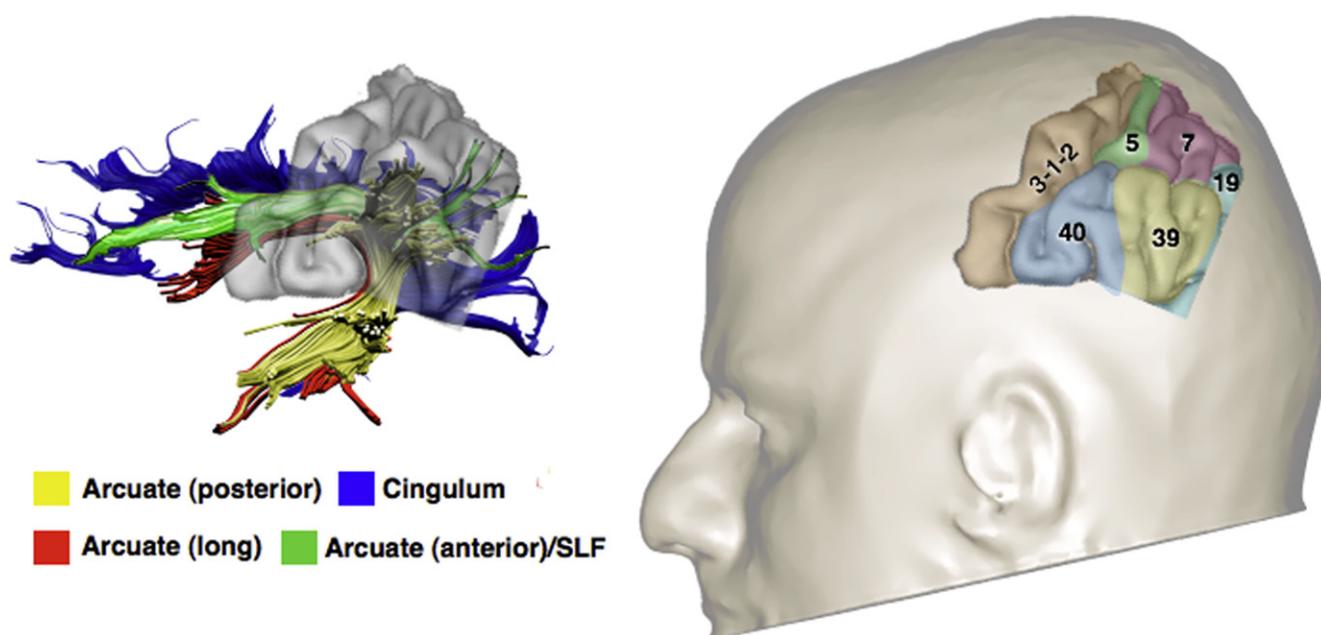
Fig. 9 − The cortical anatomy of the parietal lobe and its main associative connections. Numbers indicate cytoarchitectonic areas according to Brodmann's nomenclature. The major association pathways of the parietal lobes are the cingulum, the superior longitudinal fasciculus (SLF) and the anterior and posterior long segments of the arcuate fasciculus. The long segment of the arcuate, which courses through the parietal lobe without sending projections to the parietal cortex, is often damaged in lesions extending into the deep white matter of the inferior parietal lobule.

Table 2 − Clinical manifestations, white matter tracts and cortical areas of the parietal lobes.		
Clinical manifestations	Tract	Cortical areas (Brodmann areas)
Somatosensory and tactile syndromes:		
- Hypoaesthesia, hyperaesthesia, dysaesthesia	Internal capsule (i.e., superior thalamic projections)	3, 1, 2
- Tactile perseveration, polyaesthesia, tactile hallucinations	Internal capsule (i.e., superior thalamic projections)	3, 1, 2, 5, 40
- Astereognosis, agraphaesthesia, atopaesthesia, extinction	Superior longitudinal fasciculus, internal capsule (i.e., superior thalamic projections)	5, 7, 40
Motor syndromes:		
- Limb ataxia, optic ataxia	Cingulum, superior longitudinal fasciculus	5, 7, 19
- Apraxia (limb kinetic, constructional, ideomotor)	Superior longitudinal fasciculus, arcuate fasciculus, body of the corpus callosum	5, 7, 39, 40
- Oculomotor apraxia	Superior longitudinal fasciculus	5, 7
Visuospatial syndromes:		
- Motor, somatosensory, visual neglect	Arcuate (anterior segment), superior longitudinal fasciculus	39, 40
Symbolic thought and memory syndromes:		
- Acalculia	Arcuate (anterior segment)	39, 40
- Alexia	Arcuate (anterior and posterior segment)	39, 40
- Agraphia	Arcuate (anterior segment)	39, 40
- Conduction aphasia, reduced comprehension, impaired verbal working memory, anomia	Arcuate fasciculus	39, 40
Complex visual syndromes:		
- Impaired visual imagery, de-realization, out-of-body experience	Thalamic projections (superior and posterior peduncle), arcuate fasciculus	39, 19
- Balint syndrome	Cingulum, superior longitudinal and arcuate fasciculus	5, 7, 19
- Gerstmann syndrome	Arcuate fasciculus (anterior and posterior segment)	39, 40
Other neuropsychiatric syndromes:		
- Dyslexia	Arcuate fasciculus (anterior and posterior segments)	39, 40
- Dyscalculia	Arcuate fasciculus (anterior segment)	39, 40

and grasping for objects (i.e., optic ataxia) (Shallice et al., 2010). In these cases the lesion can be located more posterior in the precuneus and posterior parietal gyrus (Karnath and Perenin, 2005). More frequently patients with parietal lesions present with the inability to carry out complex movements despite intact coordination, and preserved sensory, visual, and motor functions (i.e., apraxia). Apraxic patients seem to have lost the ability to initiate and perform previously learned skilled movements involving the use of tools (i.e., limb kinetic apraxia). Other patients have difficulties in putting together one-dimensional units so as to form two-dimensional figures or patterns (i.e., constructional apraxia) (Heilman and Watson, 2008; Capruso and Hamsher, 2011). More rarely a dissociation between intact spontaneous execution of a motor act and the inability to imitate or pantomime the act occurs (i.e., ideomotor apraxia) (Alexander et al., 1992). Apraxias occur with left-sided lesions of the inferior parietal lobule and their connections to the occipital and frontal lobes through the superior longitudinal fasciculus, arcuate fasciculus or callosal fibres (Heilman and Watson, 2008; Glickstein and Berlucchi 2008; Ramayya et al., 2010). Oculomotor apraxia is a disorder of gaze in which subjects are unable to disengage fixation to move gaze from one object to another and is associated with dorsal parieto-occipital lesions.

8.3. Disorders of spatially-directed attention

Lesions to the right inferior parietal lobule can present with a range of spatial disorders. Patients can manifest reduced awareness of parts of their body (i.e., motor and somatosensory neglect), the space close to their body (i.e., peripersonal neglect) or the visual stimuli from one hemifield (i.e., visuospatial neglect) (van Kessel et al., 2010; Olk et al., 2010). Neglect can affect motor, somatosensory and visual modalities together or separately.

Pure motor neglect is characterized by a spontaneous underutilization of one side of the body, with a normal utilization of this side on command. These patients show no defects of strength, reflexes or sensibility of the neglected side (Laplane and Degos, 1983).

Pure somatosensory neglect is a rare condition in patients without sensorial defects who fail to detect somatosensory stimulations on one side of the body (Vallar et al., 1993).

Visual neglect has several degrees, from reduced space-directed attention to one side for simultaneous bilateral stimulation (extinction) (Riddoch et al., 2010; Cubelli et al., 2011) to complete unawareness of one half of the space. Neglect is frequently associated with lesions of the right inferior parietal lobe and its connections to the frontal and temporal lobes through the arcuate fasciculus and superior longitudinal fasciculus (Husain et al., 2000, Doricchi et al., 2008, Thiebaut de Schotten et al., 2005, Thiebaut de Schotten et al., 2011b).

8.4. Disorders of symbolic thought and memory

Disorders such as impaired manipulation of numbers in mathematical operations (i.e., acalculia), impaired reading (i.e., alexia) or writing (i.e., agraphia) are frequently associated with lesions of the left inferior parietal lobule and its connections through the arcuate fasciculus. Other disorders observed in patients with inferior parietal lobule damage include impaired repetition of words (i.e., conduction aphasia), reduced comprehension of words (i.e., Wernicke's aphasia), deficits in verbal working memory (Baddeley, 2007; Charlton et al., 2010), and more rarely anomia for colors, objects, faces (Critchley, 1953) and agnosia for mirror stimuli (Priftis et al., 2003).

8.5. Complex visual defects

The inferior parietal lobule and posterior parietal gyrus are connected to visual areas of the temporal and occipital lobes through U-shaped fibres. Damage to these cross-modal transition zones can produce defects in the ability to integrate memory, vision and proprioception. Patients may report an inability to revisualize objects or scenes (disorders of mental imagery), the feeling that experiences, typically visual, seem strange or unreal (i.e., derealization) or out-of-body experiences (ffytche et al., 2010). Other complex visual syndromes have been attributed to lesions of the parietal lobe. Balint syndrome, characterized by simultagnosia (the inability to perceive simultaneous stimuli), optic ataxia, and oculomotor apraxia, is due to bilateral degeneration of the parieto-occipital cortex. The pseudothalamic syndrome manifests with a combination of somatosensory loss, astereognosis, tactile extinction, hemiplegia, and focal sensory epilepsy. Finally, Gerstmann's syndrome is associated with a left parietal lesion manifesting with finger agnosia, left/right disorientation, acalculia, and pure agraphia (Vallar, 2007; Rusconi et al., 2010). A neurodevelopmental Gerstmann's syndrome has also been described in children (Benson and Geschwind, 1970) but its anatomical correlates remain to be identified.

8.6. Tractography studies in neurodevelopmental and psychiatric disorders

Children with dyslexia show reduced fractional anisotropy in the left anterior segment of the arcuate fasciculus that correlates with the severity of reading difficulties (Rimrodt et al., 2010). White matter tracts of the parietal lobe are also involved in arithmetic skills as suggested by recent studies reporting a correlation between the microstructural properties of the left anterior segment of the arcuate fasciculus and arithmetic approximation skills in normal developing children (Tsang et al., 2009) and reduced fractional anisotropy of the parietal connections in children with developmental dyscalculia (Rykhlevskaia et al., 2009).

9. Occipital lobe

The occipital lobe is divided into a primary visual cortex (BA17), also designated as striate cortex, and a much more extended extrastriate cortex, which corresponds to the occipital visual association areas (BA 18, 19) (Fig. 10). Disorders associated with occipital lobe lesions can be grouped into three categories (Table 3).
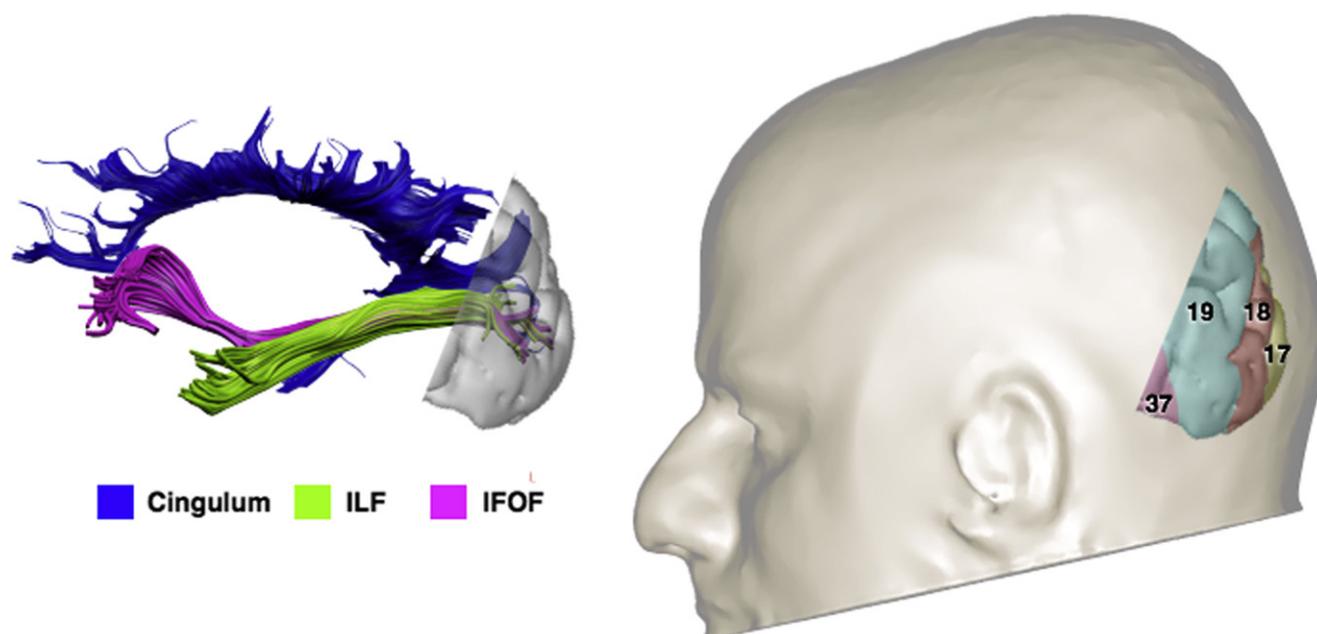
Fig. 10 — The cortical anatomy of the occipital lobes and its main associative connections. Numbers indicate cytoarchitectonic areas according to Brodmann's nomenclature. The major association pathways of the occipital lobes are the cingulum for the medial surface, the inferior longitudinal fasciculus (ILF) and the inferior fronto-occipital fasciculus (IFOF) for the ventral surface.

9.1. Disorders of simple visual perception

The primary visual cortex receives inputs from the lateral geniculate nucleus and connects via U-shaped fibres directly with neighbouring extrastriate cortex. Patients with lesions to the primary visual area or the optic radiations may present with an area of altered vision (scotoma). The loss of vision can extend to a quadrant (i.e., quadranopia), an entire hemifield

Table 3 — Clinical manifestations, white matter tracts and cortical areas of the occipital lobes.		
Clinical manifestations	Tract	Cortical areas (Brodmann areas)
Primary visual syndromes:		
- Visual field deficits (scotome, quadranopia, hemianopia, cerebral blindness)	Optic radiations	17
- Simple hallucinations (phosphenes)	Optic radiations	17
Dorsal visual stream syndromes:		
- Akinetopsia	Superior longitudinal fasciculus	19
- Alloaesthesia	Superior longitudinal fasciculus	19
- Optic ataxia	Cingulum, superior longitudinal fasciculus	18, 19
- Motion hallucinations	Superior longitudinal fasciculus	19
Ventral visual stream syndromes:		
- Object agnosia, achromatopsia, prosopagnosia, alexia	Inferior longitudinal fasciculus	18, 19, 37
- Object, colour, face, text hallucinations	Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus	18, 19, 37
Complex visual syndromes:		
- Reduplicative phenomena (Capgras syndrome; Fregoli syndrome)	Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus	18, 19, 37
- Visual hypoemotionality, visual amnesia	Inferior longitudinal fasciculus	18, 19, 37
- Fregoli syndrome, post-traumatic stress disorder	Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus	18, 19, 37
- Anton's syndrome	Inferior longitudinal fasciculus	18, 19
Other neuropsychiatric syndromes:		
- Schizophrenia	Inferior longitudinal fasciculus	18, 19
- Congenital prosopagnosia	Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus	18, 19
- Autism	Inferior longitudinal fasciculus	18, 19

(i.e., homonymous hemianopia) or to both hemifields (i.e., complete cerebral blindness) if the lesion is bilateral (Cavézian et al., 2010). Hallucinations linked to primary visual cortex pathology are of simple featureless forms and colours (i.e., phosphenes) (ffytche et al., 2010).

9.2. Disorders of the dorsal stream

The associative occipital cortex is composed of several regions linked through multiple, parallel, cortico-cortical connections divided into a dorsal and a ventral pathway stream. The dorsal stream is related to spatial aspects of vision (the 'where' stream) (Ungerleider and Mishkin, 1982) including spatial working memory, visually guided action and navigation (Kravitz et al., 2011). Patients with dorsal stream lesions present with selective loss of motion vision (i.e., akinetopsia). In visual alloaesthesia the world is perceived in an incorrect orientation, for example, inverted, tilted or right-left reversed. Optic ataxia is a disturbance of limb guidance such that subjects are unable to reach for objects in an otherwise intact visual field. Increased activity in the dorsal occipital regions can cause motion hallucinations.

9.3. Disorders of the ventral stream

The ventral stream is composed of associative interconnected cortical areas specialised for colour, face, object, and letter vision (the 'what' stream) (Ungerleider and Mishkin, 1982). Patients with an impairment of the ventral cortex and its connections present with selective loss of colour vision (i.e., achromatopsia) (Zeki, 1990), face perception (i.e., proso-pagnosia) (Fox et al., 2008; Ramon and Rossion, 2010; Tree and Wilkie, 2010; Grüter et al., 2011; Tree, 2011), object perception (i.e., visual object agnosia) (Catani et al., 2003, Germine et al., 2011), and words (i.e., alexia) (Cohen et al., 2000). Similarly colour, object, and text or letter-string hallucinations are each linked to pathology causing hyperfunctioning of their respective region of cortical specialisation. Face hallucina-tions and illusions characterized by distorted facial features (i.e., prosopometamorphopsia) are likely to relate to a region specialised for face features on the lateral convexity of the occipital lobe (i.e., occipital face area) while hallucinations of normal faces or facial intermetamorphosis (a change in the visually perceived identity of a face) are likely to relate to activity within an area specialised for faces on the ventral occipito-temporal surface (i.e., fusiform face area) (ffytche and Howard, 1999).

9.4. Complex visual syndromes

In some patients the involvement of long association tracts connecting the occipital lobe to more anterior regions lead to complex visual syndromes. Reduplicative phenomena are thought to relate to disconnection between visual, affective and memory regions due to lesions of the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus (ffytche et al., 2010). In these disorders familiar people, places and objects are perceived as duplicates that have replaced the real person, place, or object. The disorder is termed Capgras syndrome when involving a person. Similar disconnection

accounts are given of disorders manifesting with reduced emotional tone to visual experience (i.e., visual hypo-emotionality) (Bauer, 1982), impaired registering of visual experiences in short term memory (i.e., visual amnesia) (Ross, 1980, 2008) or feelings that experiences, typically visual, seem strange or unreal (i.e., derealization) (Sierra et al., 2002). The Fregoli syndrome in which unfamiliar people are perceived as familiar (typically as a person in disguise with malevolent intent) can be interpreted as a hyperconnection between visual, emotional and memory networks. Similarly, the strong affective and imagery components of flashbacks in post-traumatic stress disorder suggest hyperconnection between visual, emotional and memory regions (ffytche et al., 2010). Patients with cortical blindness due to extensive occipital lesions can sometime deny their visual impairment (Anton's syndrome) (Anton, 1889). Patients with Anton's syndrome may also report visual experiences, that traditionally have been interpreted as confabulations (a false memory or false report of visual perceptual experience) or as spontaneous visual imagery. Anton's syndrome can be conceptualised as a disconnection of visual cortex from body schema repre-sentations in the parietal lobe (ffytche et al., 2010).

9.5. Tractography studies in neurodevelopmental and neuropsychiatric disorders

Altered microstructural integrity (i.e., reduced fractional anistotropy) of the inferior longitudinal fasciculus in adoles-cents with schizophrenia has been reported, especially in those subjects with a history of visual hallucinations (Ashtari et al., 2007). In patients with congenital prosopagnosia, where conventional structural imaging is usually normal, the frac-tional anisotropy of the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus is reduced and this reduc-tion correlates significantly with performances on face pro-cessing tasks (Thomas et al., 2009). Conversely an increased number of streamlines in the inferior longitudinal fasciculus has been reported in subjects with high functioning autism (Thomas et al., 2011) and Asperger syndrome (Pugliese et al., 2009).

10. Temporal lobe

The main divisions of the temporal lobe include the: (i) primary auditory cortex (BA41); (ii) auditory association cortex (BA42, 22); (iii) visual association cortex (BA20, 21, 37); (iv) tempor-opolar cortex (BA38) (Fig. 11). Lesions to each of the above regions cause four distinct temporal lobe syndromes (Table 4).

10.1. Cortical deafness for sounds and words

The primary auditory cortex receives projections of the acoustic radiations from both medial geniculate nuclei and connects to adjacent areas through U-shaped fibres. Lesions to the left primary auditory area impair the ability to recognise words (i.e., 'word deafness' or sensory aphasia), while right-sided lesions impair recognition of non-verbal sounds (i.e., 'sound deafness' or acoustic agnosia) (Suarez et al., 2010).
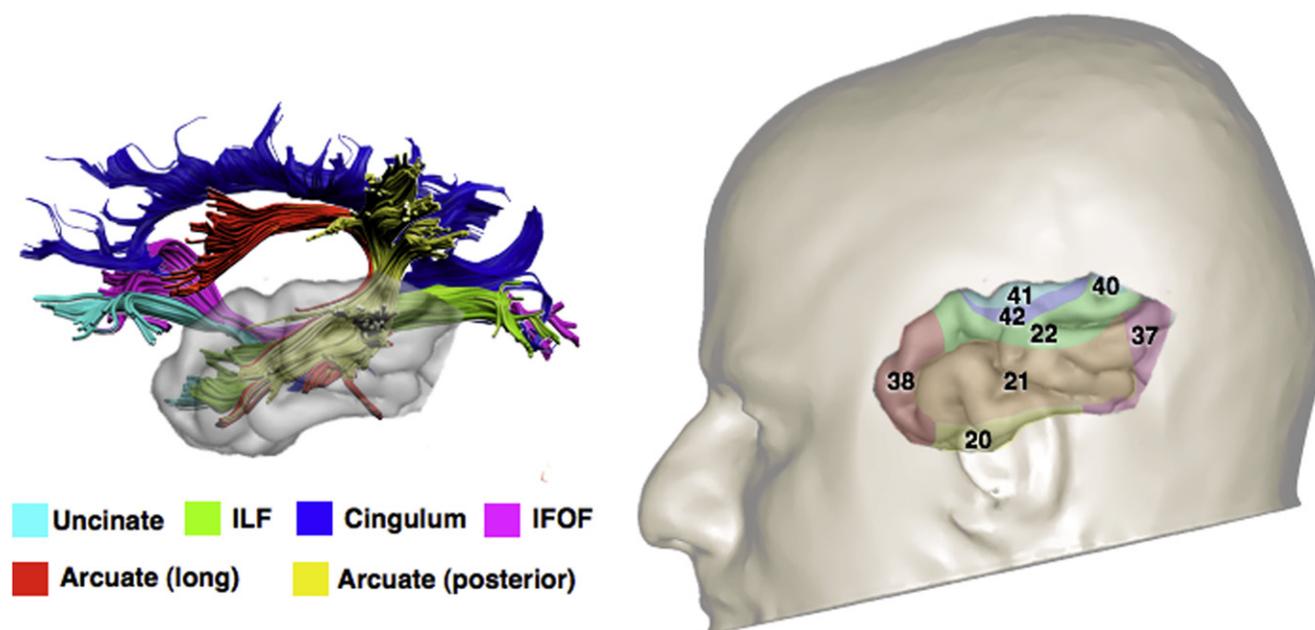
Fig. 11 — The cortical anatomy of the temporal lobe and its main associative connections. Numbers indicate cytoarchitectonic areas according to Brodmann's nomenclature. The major association pathways of the occipital lobes are the cingulum for the medial surface, the uncinate for the anterior temporal region, the inferior longitudinal fasciculus (ILF) for the ventral and lateral surface, the long and posterior segments of the arcuate fasciculus for the posterior temporal regions. The inferior fronto-occipital fasciculus (IFOF), which courses through the temporal lobe without sending projections to the temporal cortex, is often damaged in lesions extending deep into the white matter of the temporal lobe.

10.2. Disorders of language

The auditory association cortex extends along the superior and part of the middle temporal gyrus and connects to the inferior parietal lobe and the posterior frontal lobe through the posterior and long segments of the arcuate fasciculus, respectively (Catani et al., 2005). The most frequent syndrome associated with lesions to the posterior part of this region in

Clinical manifestations	Tract	Cortical areas (Brodmann areas)
Table 4 — Clinical syndromes, white matter tracts and cortical areas of the temporal lobes.		
Auditory perception syndromes:		
- Cortical deafness for sounds or words	Acoustic radiations	41
Language syndromes:		
- Wernicke's aphasia	Arcuate fasciculus (posterior and long segment)	42, 22, 37
- Transcortical sensory aphasia	Arcuate fasciculus (posterior segment)	22, 37
- Conduction aphasia	Arcuate fasciculus (long segment)	42, 22, 37
- Receptive aprosodia	Arcuate fasciculus (posterior and long segment)	42, 22, 37
- Nominal aphasia	Arcuate fasciculus (posterior and long segment), inferior longitudinal fasciculus	21, 22, 37, 42
Multimodal visual syndromes:		
- Macropsia, micropsia, pelopsia, teleopsia	Inferior longitudinal fasciculus, thalamic projections	21, 37
- Autoscopy	Inferior longitudinal fasciculus, thalamic projections	21, 37
- Prosopagnosia	Inferior longitudinal fasciculus, inferior fronto-occipital fasciculus	20, 37
- Alexia	Arcuate fasciculus (posterior segment), inferior longitudinal fasciculus	22, 37
Memory and behavioural syndromes:		
- Semantic dementia	Uncinate fasciculus, inferior longitudinal fasciculus	20, 21, 38
- Reduced verbal fluency	Uncinate fasciculus	38
- Impaired naming	Uncinate fasciculus, inferior longitudinal fasciculus	21, 22, 38
Other neuropsychiatric syndromes:		
- Schizophrenia	Arcuate fasciculus (posterior and long segment)	42, 22, 37
- Congenital amusia	Arcuate fasciculus (long segment)	42, 22, 37

the left hemisphere is Wernicke's aphasia, characterized by impaired auditory comprehension and repetition with normal verbal fluency (Hillis et al., 2002). Equivalent lesions in the right hemisphere may cause impairment in understanding emotional aspects of language (i.e., receptive aprosodia) (Ross, 1981) or music (Dellacherie et al., 2011; Gosselin et al., 2011). The auditory association cortex is also connected to more posterior visual occipital regions and more anterior temporal areas through the inferior longitudinal fasciculus and U-shaped fibres. Patients with lesions to the above connections may show difficulty in using words to name objects (i.e., nominal aphasia), or inability to repeat a series of words with normal repetition of single words (i.e., auditory amnesic aphasia). Auditory hallucinations are also frequently observed with lesions or stimulation (e.g., intraoperative cortical stimulation) of the auditory association cortex.

10.3. Disorders of multimodal visual processing

The visual association cortex is located in the middle and inferior temporal gyrus and connects to the occipital lobes through the inferior longitudinal fasciculus and the frontal lobe through the long segment of the arcuate fasciculus and the uncinate fasciculus. Its most posterior part is connected to the inferior parietal through the posterior segment of the arcuate fasciculus. Objects appearing larger (i.e., macropsia), smaller (i.e., micropsia), nearer (i.e., pelopsia) or further (i.e., teleopsia) have been attributed to a dysfunction of object constancy within this posterior region of the temporal lobe. Autoscopic phenomena describe a range of experiences in which the self is duplicated in external space. In autoscopy, visual perspective remains in the physical body (the duplicate self is seen in the external world). In out-of-body experience the physical body is seen from the perspective of the external self (Blanke et al., 2002). In the autoscopy perspective changes between the external self and physical self in rapid alternation. These phenomena are thought to relate to the disintegration of visual, proprioceptive, tactile and vestibular modalities and have been linked to transient dysfunction in the region of the temporoparietal junction (ffytche et al., 2010). Lesions to the ventral aspect of the temporo-occipital (fusiform) gyrus cause prosopagnosia (Fox et al., 2008), mainly for lesions in the right hemisphere, and pure alexia (Epelbaum et al., 2008; Starrfelt et al., 2010) or pathological orthographic processing (Tsapkini and Rapp, 2010) in the left hemisphere.

10.4. Disorders of memory and behaviour

The temporopolar region morphologically belongs to the temporal lobe but functionally is considered as part of the limbic system. It is connected to more posterior temporal and occipital regions through the inferior longitudinal fasciculus and U-shaped fibres and to the frontal lobe via the uncinate fasciculus. Semantic dementia is a memory disorder characterized by a progressive inability to associate meaning to sensorial perception (Laisney M, 2011). These patients show marked atrophy of the anterior temporal lobe and its main connections (Agosta et al., 2010). Lesions to the uncinate fasciculus may also present with reduced verbal fluency and naming deficits, especially for famous faces (Papagno et al.,

2011). Other complex syndromes associated with anterior temporal dysfunction are discussed in the section on limbic disorders.

10.5. Tractography studies in neurodevelopmental and neuropsychiatric disorders

In schizophrenia altered microstructural integrity of the arcuate segments originating or projecting to the posterior temporal auditory regions have been reported using diffusion tensor tractography (Jones et al., 2005). These findings are bilateral and more significant in patients with auditory hallucinations (Catani et al., 2011). In subjects with tone-deafness (i.e., congenital amusia) a reduced fractional anisotropy and volume of the right long segment of the arcuate fasciculus has been reported using diffusion tensor imaging tractography (Loui et al., 2009). Disorders of the anterior temporal lobe are reviewed in the next section.

11. Limbic lobe

The limbic system includes a core subcortical network (centred around the hippocampus and thalamus) formed by the fornix and mammillo-thalamic tract, and a group of paralimbic cortical areas connected through the cingulum and uncinate fasciculus (Fig. 12). Other tracts, such as the inferior longitudinal fasciculus and inferior fronto-occipital fasciculus connect the limbic regions to visual and auditory areas. The limbic lobe syndromes are divided into three distinct groups (Table 5).

11.1. Disorders of the hippocampal-hypothalamic division

Lesions to the hippocampal-thalamic centred division of the limbic system cause severe amnesia for events before (retrograde) and after (anterograde) the onset of the lesion (Markowitsch, 2000). Retrograde amnesia is more severe for recent than remote events, while anterograde amnesia affects explicit learning of new events but leaves implicit procedural memory for motor and perceptual tasks intact. Amnesia is more often associated to other symptoms. Degeneration of the medial temporal lobe structures is a feature of Alzheimer's disease, a form of dementia where memory deficits are accompanied by at least two other cognitive problems (e.g. language deficits, apraxia, etc.). Korsakoff disease is a severe amnesia with confabulation commonly due to alcoholic degeneration of the mammillo-thalamic tracts (Markowitsch, 2000). Some patients with amnesia may also present difficulties in spatial orientation due to the inability to derive directional information from landmark cues in familiar and new environments (Aguirre and D'Esposito, 1999). This form of spatial memory dysfunction (i.e. topographical amnesia) can also present as an isolated problem and is often associated with stroke lesions to the posterior parahippocampal, retrosplenial cingulate cortex and posterior precuneus (Vann et al., 2009, Valenstein et al., 1987).
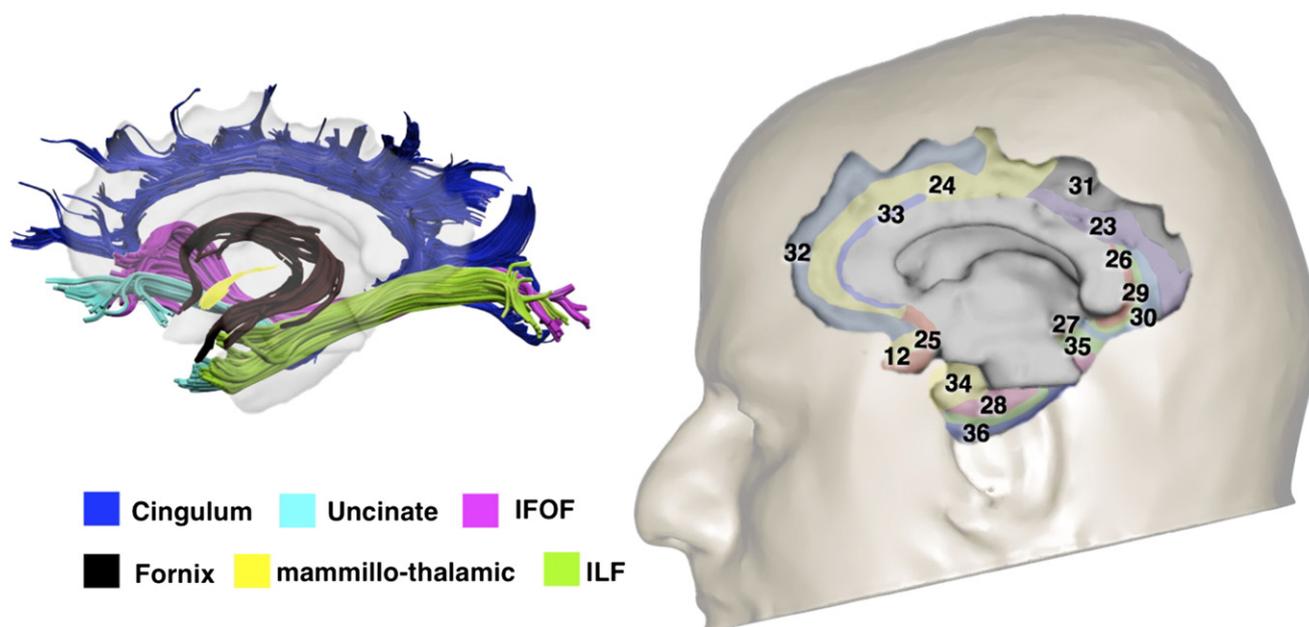
Fig. 12 – The cortical anatomy of the limbic lobe and its main associative connections. Numbers indicate cytoarchitectonic areas according to Brodmann's nomenclature. The major association pathways of the limbic lobes are the cingulum for the medial surface, the uncinate for the anterior temporal region, the inferior longitudinal fasciculus (ILF), the inferior fronto-occipital fasciculus, the mammillo-thalamic tract, and the fornix.

11.2. Disorders of the orbitofrontal-amygdala division

Patients with lesions of the anterior temporal lobe, including the amygdala and its connections to olfactory and orbito-frontal cortices, present with symptoms reminiscent of the Klüver–Bucy syndrome described in monkeys (Klüver and Bucy, 1939). The syndrome is characterized by abnormal emotional placidity (i.e., absence of reaction), hyperorality (i.e., strong oral tendency in examining objects), hyper-metamorphosis (i.e., tendency to attend and react to visual stimuli), altered dietary preferences, increased sexual activity and visual agnosia (Terzian and Ore, 1955). In patients with isolated amygdala lesion the autonomic responses normally associated with learning and recall is

Table 5 – Clinical syndromes, white matter tracts and cortical areas of the limbic lobe.

Clinical manifestations	Tract	Cortical areas (Brodmann areas)
Hippocampal-hypothalamic syndromes:		
- Amnesias	Fornix, mammillo-thalamic tract	28
- Alzheimer's disease (early)	Fornix, posterior cingulum	23, 26, 28, 29, 30, 35
- Korsakoff disease	Mammillo-thalamic tract	
- Topographical disorientation	Cingulum, inferior longitudinal fasciculus	26, 29, 30, 35
Orbitofrontal-amygdala syndromes:		
- Klüver-Bucy syndrome	Uncinate, inferior longitudinal fasciculus	28, 34, 36, 38
- Visual hypoemotionality	Inferior longitudinal fasciculus	28, 34, 36, 38,
- Personality changes	Uncinate, cingulum	11, 32, 33, 34
Paralimbic syndromes:		
- Pain asymbolia	Anterior cingulum, thalamic projections	24, 32, 33
- Altered olfaction (increased or decreased)	Cingulum	12, 25, 32
- Apathy	Anterior cingulum	24, 32, 33
- Mood changes (depression, irritability)	Subgenual cingulum	24, 25, 32, 33
- Semantic dementia	Uncinate, inferior longitudinal fasciculus	36, 38
- Right olfactory anomia	Rostral callosum, anterior commissure	12, 25, 32
Other neuropsychiatric syndromes:		
- Schizophrenia	Uncinate, fornix, cingulum, anterior thalamic	11, 23, 24, 26, 28, 29, 30, 32, 33, 35, 38
- Autism	Uncinate, inferior longitudinal fasciculus, cingulum	24, 32, 33
- Depression and bipolar disorder	Subgenual cingulum, uncinate, anterior thalamic	24, 25, 32, 33
- Temporal lobe epilepsy	Fornix, uncinate	28, 34, 36, 38
- Mild cognitive impairment	Posterior cingulum	23, 26, 29, 30, 31
- Psychopathy	Uncinate	11, 34, 38

abolished. Lesions confined to the amygdalae are extremely rare in humans and result in mildly impaired modulation of social behaviour and abnormalities in the visual examination of faces (Adolphs et al., 1994). In patients with temporolimbic epilepsy a wide range of acute and chronic psychiatric symptoms have been observed, from panic attacks to aggressive outbursts, depression, and psychosis (Waxman and Geschwind, 1974; Flügel et al., 2006). Personality changes are often associated with abnormalities in the orbitofrontal cortex, medial anterior cingulate, amygdala and their reciprocal connections through the uncinate fasciculus, corpus callosum and anterior commissure (Zappala' et al., 2012; Berlucchi, 2012).

11.3. Disorders of the paralimbic areas

The paralimbic areas include the temporopolar region, insula, cingulate gyrus, orbitofrontal cortex, and parahippocampal gyrus. Lesions to paralimbic regions may present with emotional indifference to pain (i.e., pain asymbolia), altered olfaction, impaired ability to express emotions, reduced attention and motivation (Sprengelmeyer et al., 2010; Reker et al., 2010). Severe apathy and personality changes are frequently associated with orbitofrontal and anterior cingulate pathology (Shamay-Tsoory et al., 2010). Degeneration of the anterior temporal and posterior orbitofrontal cortex is frequently observed in patients with semantic dementia, alteration in personality and behaviour, and mood changes. The anterior temporal and orbitofrontal cortex are commonly affected in traumatic brain injury (Zappala' et al., 2012). Stimulation of the cingulate and parahippocampal cortices causes memory flashbacks, dreamlike states, and mood alterations. Obsessive-compulsive disorder has been associated with increased activity in the cingulate cortex causing 'rigid hyperattentiveness' to thoughts and emotions.

Reduced olfactory sensation is commonly observed in patients with Alzheimer's disease and Parkinson's disease. Anomia for olfactory stimuli presented to the right nostril (right olfactory anomia) (Gordon and Sperry, 1969) and memory deficits (Zaidel and Sperry, 1974) have been described in split-brain patients with complete commissurotomy (complete severing of the corpus callosum and anterior and posterior commissure) but not in those with intact anterior commissure (Ledoux et al., 1977; Risse et al., 1978). The right olfactory anomia in these patients is due to a disconnection between the right olfactory cortex and the left fronto-temporal language areas.

11.4. Tractography studies in neurodevelopmental and neuropsychiatric disorders

Limbic dysfunction underlie many symptoms of other psychiatric conditions, including schizophrenia, affective disorders, psychopathy and autism. Voxel-based and tractography diffusion tensor imaging approaches have been used to examine the integrity of limbic white matter connections in schizophenia, with microstructural differences reported in the cingulum (Fujiwara et al., 2007), uncinate fasciculus (McIntosh et al., 2008), fornix (Kuroki et al., 2006, Takei et al., 2008), and the anterior thalamic radiations (McIntosh et al.,

2008). A recent tractography study in adolescents with major depressive disorder reported lower fractional anisotropy in the white matter tract connecting the subgenual cingulate region to the amygdala in the right hemisphere (Cullen et al., 2010). In adults with bipolar affective disorder tractography showed increased tract volume of the subgenual-amygdala connections (i.e., subpopulation of uncinate fibres) (Houenou et al., 2007) and reduced fractional anisotropy in the uncinate and anterior thalamic projections (McIntosh et al., 2008).

Diffusion imaging tractography studies in patients with unilateral temporal lobe epilepsy reported diffuse damage to the limbic white matter tracts such as the fornix (Concha et al., 2005) and the uncinate fasciculus (Diehl et al., 2008) often extending contralaterally from the side of the suspected seizure. In temporal lobe epilepsy patients with mesial hippocampal sclerosis, decrease in fractional anisotropy of the fornix fibres is probably due to reduced axonal diameter and myelin content (Concha et al., 2010). Such changes have an impact on cognitive abilities as demonstrated by the correlation between the diffusivity measures of the uncinate fasciculus and the severity of delayed recall deficits (Diehl et al., 2008). Preliminary data also suggest, that in patients with temporal lobe epilepsy undergoing surgery, the pre-operative tractography assessment of the temporal tracts can help in predicting naming deficits after the operation (i.e., patients with more leftward asymmetry showed worse post-operative deficits) (Powell et al., 2008). Correlations between fractional anisotropy levels and verbal fluency performances before and after anterior temporal resection have also been reported (Yogarajah et al., 2010).

In patients with mild cognitive impairment a combined cortical morphometry and diffusion tensor imaging study found reduced cortical thickness and white matter abnormalities of the retrosplenial regions (Acosta-Cabronero et al., 2010). Craig et al. (2009) reported a significantly reduced fractional anisotropy in the uncinate fasciculus of psychopaths compared to healthy subjects with similar age and intelligence. A correlation between measures of antisocial behaviour and anatomical differences in the uncinate fasciculus was also described. A tractography study showed that compared to healthy controls, adults with Asperger's syndrome had a significantly higher number of streamlines in the cingulum bilaterally and a lower number of streamlines in the right uncinate (Pugliese et al., 2009). Diffusivity changes in the inferior longitudinal fasciculus have been reported in autistic subjects with impaired ability to recognise faces (Conturo et al., 2008).

12. Discussion and conclusions

In this study we provide a new digital atlas of white matter tracts based on diffusion tensor imaging tractography to facilitate the anatomical localization of deep white matter lesions. The atlas is accompanied by a synopsis of the major lobe syndromes to help correlating white matter lesions with clinical manifestations. The atlas has three main features: (i) it provides normalized maps in a reference space (i.e., MNI); (ii) it is derived from a statistical analysis at a group level and, therefore, it is

representative of the average anatomy; (iii) the maps of the single tracts are provided in a digital format (i.e., nifti).

The atlas reference space (MNI) will facilitate the overlay of the tracts onto normalized neuroradiological images. Some of the white matter tracts reported in the atlas have been described only in recent years and are not available in previously published histological or tractography atlases (e.g., the three segments of the arcuate fasciculus). For other tracts, such as the corpus callosum, uncinate and cingulum, the atlas shows anatomical features that are close to classic post-mortem blunt dissections and post-mortem histology (Thiebaut de Schotten et al., 2011a).

Our presentation of the white matter tracts as a single composite map may help explain findings that in clinico-anatomical correlation studies may sometimes appear incongruent. For example, it has been reported that hemianopia, a symptom commonly associated with lesions to the optic radiations, occur in patients with lesions of the parietal lobe (Critchley, 1953). Although inputs from the visual thalamus (i.e., pulvinar) reach the parietal cortex whose damage has been suggested as a possible mechanism for the visual deficits in these patients, in our opinion a more likely explanation would be an involvement of the optic radiations that run deeply in the white matter of the parietal lobe, which can be easily appreciated on the coronal slices of our atlas (e.g., slice −40 of Fig. 6 shows in orange the optic radiations deep in the white matter of the parietal lobe). Lesions to the parietal lobe extending deep into the white matter could therefore affect the optic radiations and cause hemianopia. Furthermore a network approach in clinico-anatomical correlation studies offers the advantage of explaining how symptoms classically attributed to damage of a cortical area (e.g., non fluent aphasia with lesions to Broca's area) can manifest also in patients with lesions outside that area. For example, empirical evidence suggests that in 15% of patients with Broca's aphasia the lesion is outside Broca's area, often encompassing post-Rolandic parietal regions (Basso et al., 2000) or deep white matter tracts (Bizzi et al., 2012). This is the case of the patient with brain tumour presented in Fig. 7A, where the atlas suggests an involvement of the anterior and long segment of the arcuate fasciculus without direct damage to Broca's area. In this case an alternative hodological explanation to the classical cortical localization approach suggests that dysfunction of Broca's area can result from lesions of its connections with posterior parietal and temporal language regions.

We realize, of course, that mapping symptoms onto single tracts is subject to the same criticisms directed to narrow cortical localizationism and that often complex syndromes clearly seem to result from a dysfunction of an extended network of cortical and subcortical areas connected by several tracts. Unilateral neglect, for example, has been described in association with lesions of the superior longitudinal fasciculus, inferior longitudinal fasciculus, inferior fronto-occipital fasciculus and the overlying parietal, temporal, occipital and frontal cortex (Doricchi et al., 2008). Hence, a hodological approach to clinico-anatomical correlation should not underestimate the role of the cortex and it should certainly refrain from considering the effects of cortical lesions as equivalent to those of lesions to subcortical tracts. Furthermore different mechanisms act for cortical and subcortical

lesions, which may influence the severity of symptoms and their recovery. The clinical manifestations commonly seen in patients with multiple sclerosis are a clear example. Here, even with extensive subcortical lesions, the observation of classical syndromes commonly seen with other pathologies (e.g., Wernicke's aphasia in stroke patients) is extremely rare.

For some tracts (e.g., inferior occipito-frontal fasciculus and arcuate fasciculus) the atlas has an advantage over histological approaches by providing more accurate anatomical reconstructions (Thiebaut de Schotten et al., 2011a). This may reflect the difficulty of using post-mortem myelin staining methods to trace tracts with a longitudinal course (Bürgel et al., 2006). In contrast, compared to histological maps, the atlas presents only a partial reconstruction of the lateral projections of the cortico-spinal tract and the terminal projections of most of the tracts. This is most likely due to the limitations of current diffusion tensor model in resolving fibre crossing. Future in vivo studies of tracts such as these may be aided by other diffusion methods such as diffusion spectrum imaging (DSI) (Schmahmann et al., 2007) or spherical deconvolution (Tournier et al., 2004, 2008; Dell'Acqua et al., 2007, 2010, 2012; Dell'Acqua and Catani, 2012; Catani, Bode and Dell'Acqua, in press) that can, in part, overcome the limitations of the tensor model. This is also the reason for the absence of the first and second branch of the superior longitudinal fasciculus (Catani et al., in press) and many short U-shaped fibres that are often difficult to dissect reliably with DTI tractography (Catani et al., 2012).

An atlas-based approach can be problematic in disorders where the presence of oedema or mass effect alters the anatomy of the tracts (Clark et al., 2003). In these cases findings from the atlas could be difficult to interpret or could sometimes be misleading. Finally, our atlas is based on people from a relatively young and narrow age range, and therefore the results of our study may not be representative of white matter anatomy across the lifespan. Future atases will need to take into account age-related changes in diffusion measurements (Verhoeven et al., 2010, Lebel et al., 2008, 2010) and how these changes affect the results of fibre tracking.

In conclusion after 150 years the clinical-anatomical correlation method still occupies a prominent role in contemporary neuroscience. Anatomical atlases have always played an important part in the process of correlating lesions to symptoms and understanding the neuroanatomical basis of neurological and psychiatric disorders. We hope that our new atlas will help to capture the excitement of 21st century anatomy and will help clinicians to understand the role of many tracts whose functions remain unknown empirical contributions to come.

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Appendix A. Supplementary material

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.cortex.2012.07.001.

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