

# Probabilistic map of critical functional regions of the human cerebral cortex: Broca's area revisited

Matthew C. Tate,<sup>1,2</sup> Guillaume Herbet,<sup>2,3</sup> Sylvie Moritz-Gasser,<sup>2</sup> Joseph E. Tate<sup>4</sup> and Hugues Duffau<sup>2,3</sup>

1 Department of Neurosurgery, Northwestern University, Feinberg School of Medicine, Chicago, Illinois 60611, USA

2 Department of Neurosurgery, Gui de Chauliac Hospital, Montpellier University Medical Centre, F-34295 Montpellier, France

3 INSERM U1051, Institute for Neuroscience of Montpellier, F-34091 Montpellier, France

4 Edward S. Rogers Sr. Department of Electrical and Computer Engineering, University of Toronto, Ontario M5S 3G4, Canada

Correspondence to: Prof. Hugues Duffau, MD, PhD,  
Department of Neurosurgery, Hôpital Gui de Chauliac,  
CHU Montpellier, 80 Avenue Augustin Fliche,  
34295 Montpellier, France  
E-mail: h-duffau@chu-montpellier.fr

The organization of basic functions of the human brain, particularly in the right hemisphere, remains poorly understood. Recent advances in functional neuroimaging have improved our understanding of cortical organization but do not allow for direct interrogation or determination of essential (versus participatory) cortical regions. Direct cortical stimulation represents a unique opportunity to provide novel insights into the functional distribution of critical epicentres. Direct cortical stimulation (bipolar, 60 Hz, 1-ms pulse) was performed in 165 consecutive patients undergoing awake mapping for resection of low-grade gliomas. Tasks included motor, sensory, counting, and picture naming. Stimulation sites eliciting positive (sensory/motor) or negative (speech arrest, dysarthria, anomia, phonological and semantic paraphasias) findings were recorded and mapped onto a standard Montreal Neurological Institute brain atlas. Montreal Neurological Institute-space functional data were subjected to cluster analysis algorithms (K-means, partition around medioids, hierarchical Ward) to elucidate crucial network epicentres. Sensorimotor function was observed in the pre/post-central gyri as expected. Articulation epicentres were also found within the pre/post-central gyri. However, speech arrest localized to ventral premotor cortex, not the classical Broca's area. Anomia/paraphasia data demonstrated foci not only within classical Wernicke's area but also within the middle and inferior frontal gyri. We report the first bilateral probabilistic map for crucial cortical epicentres of human brain functions in the right and left hemispheres, including sensory, motor, and language (speech, articulation, phonology and semantics). These data challenge classical theories of brain organization (e.g. Broca's area as speech output region) and provide a distributed framework for future studies of neural networks.

**Keywords:** brain mapping; language; Broca's area; direct cortical electrostimulation; probabilistic map

## Introduction

Initial studies of human brain function relied on correlating clinical outcomes with anatomic abnormalities discovered post-mortem, the classic example being Paul Broca's description of two patients with expressive aphasia after injury to the inferior frontal gyrus

(Broca, 1861a, b). The introduction of MRI allowed real-time correlation of anatomical abnormalities, such as a focal ischaemic episode, with neurological changes. Newer functional imaging modalities, including functional MRI (Logothetis, 2008; Carr *et al.*, 2010) and magnetoencephalography (Maess *et al.*, 2001; Hagan *et al.*, 2009), have contributed greatly to our

understanding of anatomical correlates of complex neural behaviours. In addition, connectivity measures and diffusion tensor imaging represent promising tools for discovering the pattern of cortical networks devoted to particular functions (Mori and Zhang, 2006; Hermundstad *et al.*, 2013; Mueller *et al.*, 2013). Although each of these modalities is non-invasive and can thus assess function in healthy and diseased states, the inability to directly interrogate the cerebral cortex and to distinguish essential cortical regions from those merely participating is a fundamental problem. Thus the essential functional anatomy of most basic brain processes remains to be elucidated. A more recent tool, transcranial magnetic stimulation (Devlin and Watkins, 2007; Tarapore *et al.*, 2012), theoretically overcomes some of these problems by allowing virtual lesioning of the cortex in healthy subjects. The 'gold standard' for assessing cortical function is direct cortical stimulation, first optimized by Wilder Penfield in his seminal work describing the somatotopic distribution of primary motor and sensory cortices in humans (Penfield and Boldrey, 1937). In addition to the ability to directly access the cortical surface, direct cortical stimulation allows for the determination of essential regions for a given function (Duffau *et al.*, 2005; Sanai *et al.*, 2008; Desmurget *et al.*, 2013). However, direct cortical stimulation is only applicable to patients undergoing surgical procedures for an underlying brain pathology, which limits the experimental time and interpretation of results. In addition, to investigate volitional behaviours, the patient must be under local anaesthesia (termed 'awake' craniotomy because the patient is able to interact with the examiner), which typically restricts analysis to the left hemisphere (given that most awake surgeries are for left-sided lesions adjacent to presumed language areas) and can limit the time window for studying cortical function.

In the present study, we used direct cortical stimulation in 165 consecutive patients undergoing awake craniotomy for initial resection of low-grade gliomas to assess several important functions in the human cortex: sensory, motor, and language (speech output, articulation, phonology, and semantics). Several features of the study design make this a novel approach for assessing fundamental brain networks. First, limiting the subjects to low-grade gliomas, which are intrinsic lesions that grow at a very slow rate, may minimize the alteration of normal brain networks relative to very aggressive lesions. For example, the spatial distribution of phonologic and semantic function in the current data set correlates well with a recent healthy volunteer functional MRI meta-analysis (Vigneau *et al.*, 2006). Second, the philosophy of the surgical team to maximize extent of tumour resection while preserving higher-order brain functions (e.g. semantic, phonological, visuo-spatial attention) in addition to more fundamental processes (motor, sensory, speech output) resulted in a significant proportion of patients with right hemisphere mapping, allowing the contribution of both hemispheres to be investigated at both the cortical and subcortical levels. Finally, the accrual of this large set of direct cortical data (165 patients, 712 stimulation points) over an 8-year interval overcomes many of the concerns regarding the variability inherent to the clinical realm while taking advantage of the efficiency of direct cortical stimulation to detect crucial network epicentres.

# Materials and methods

## Participants

One hundred and sixty-five consecutive patients undergoing an initial resection for pathology-proven low grade glioma at CHU Gui de Chauliac (Montpellier, France) hospitals from 2004–12 were included. Patient characteristics and the anatomic location(s) of tumours are listed in Tables 1 and 2.

## Intraoperative cortical stimulation and functional map construction

The intraoperative mapping technique for cortical and subcortical function in patients undergoing awake craniotomy with local anaesthesia has been published previously by our group (Duffau *et al.*, 2002, 2005). Following craniotomy and reflection of the dura to expose

**Table 1** Characteristics of the study population and mapping details

Patients (n)	165
Age (years)	38.7 ± 10.4
Male:female ratio	1.23
Handedness (%)	
Right	84.42
Left	13.33
Ambidextrous	4.24
Hemisphere mapped (%)	
Right	32.12
Left	67.88
Contralateral	70.25
Ipsilateral	29.75
Stimulation current (mA)	2.36 ± 0.80
Positive mapping sites (n)	712

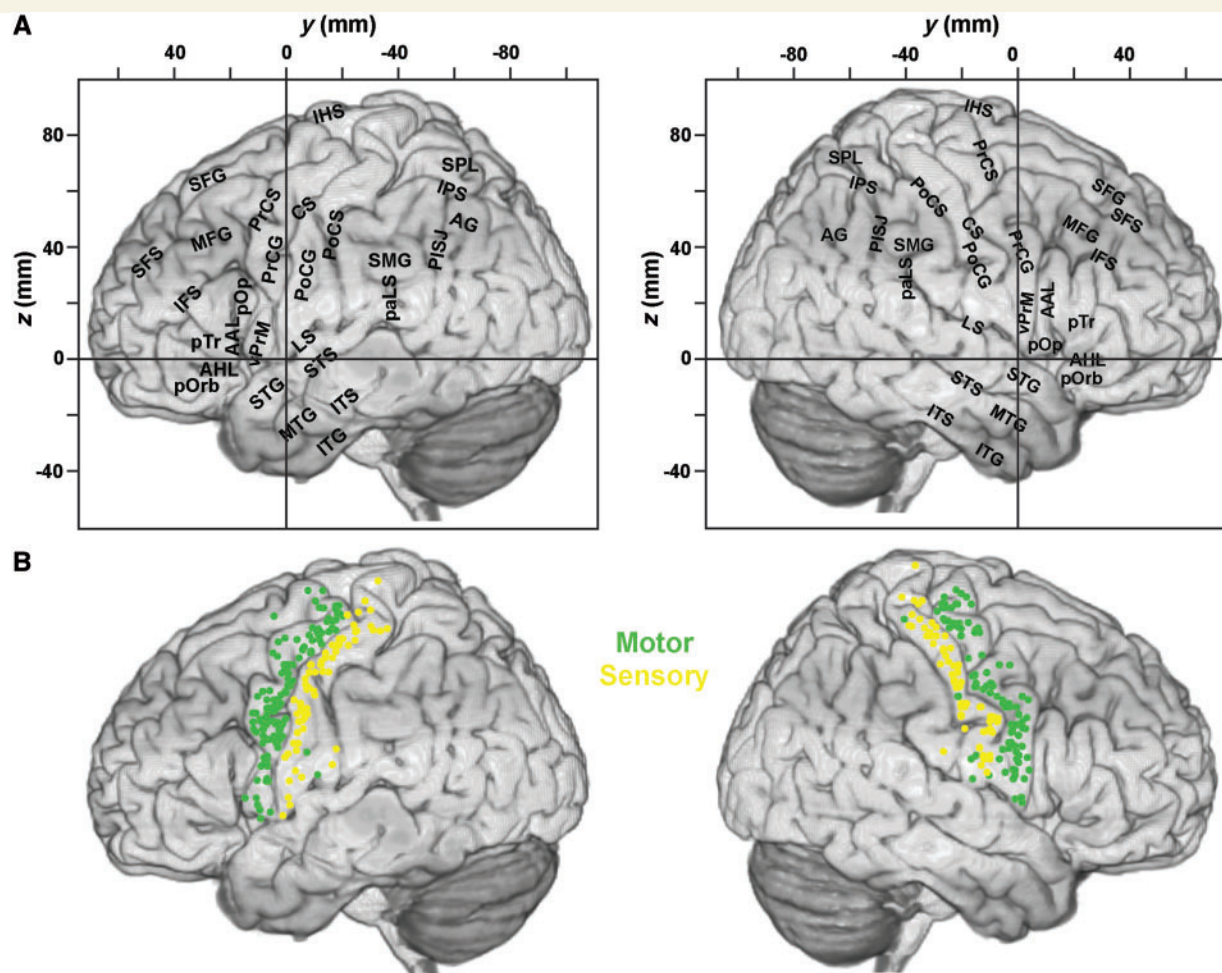
**Table 2** Details of the distribution of tumour location(s) in order of descending frequency

Tumour location	Patients (n)
F	43
T	25
FTI	23
P	22
FI	12
TI	12
I	8
FP	5
PT	5
TO	3
O	2
TPO	2
FITP	2
FT	1

F = frontal; I = insular; P = parietal; O = occipital; T = temporal.

the cortical surface, stimulation of the entire exposed cortical surface (between-stimulus spacing  $\sim 1$  cm) was performed using a bipolar electrode with 5 mm spacing (60 Hz, 1 ms pulse width, current amplitude 2–8 mA). First, after determining real-time tumour and sulcal/gyral anatomy with intraoperative ultrasound, motor and sensory mapping was performed starting at 2 mA and increasing up to a maximum of 8 mA until reliable motor and/or sensory changes were elicited. Once the sensorimotor threshold was determined, that amplitude was used for the remainder of the cortical and subcortical mapping. Intraoperative tasks included counting, DO-80 picture naming (Metz-Lutz *et al.*, 1991), and double-task (picture naming in concert with contralateral arm movement) while systematically stimulating throughout the entire exposed cortical surface. For the picture naming task, the patient was asked to start with 'This is a...' to distinguish anomia from speech arrest. The DO-80 picture naming

task is a set of 80 common black and white pictures that have been validated in clinical populations to assess anomias and naming impairment (Metz-Lutz *et al.*, 1991; Gagnon *et al.*, 2004). Intraoperative evaluation of patient function was assessed by a licensed speech therapist and/or neuropsychologist blinded to stimulation. Sites of stimulation that elicited errors in the aforementioned functional tasks were marked with tags on the cortical surface and the specifics of the error recorded (semantic paraphasia, speech arrest, dysarthria, etc.). After completion of cortical mapping, intraoperative images were taken and subsequently analysed offline. Each stimulation point (712 total cortical stimulation points for 165 patients) was manually plotted onto a digitized asymmetric human brain template [Montreal Neurological Institute (MNI) ICBM152, 1-mm resolution] using a combination of regional cortical landmarks (Fig. 1A),  $T_2$ -weighted MRI, and dictated operative reports. Three-dimensional coordinates ( $x$ ,  $y$ ,  $z$ ) in



**Figure 1** Study details and validation of mapping technique. (A) Left and right hemisphere projections from the human brain template (MNI ICBM152, asymmetric, 1 mm) used for mapping of positive intraoperative stimulation sites. Key cortical sulcus and gyrus landmarks are noted on both hemispheres. HIS = interhemispheric sulcus, SFG = superior frontal gyrus, SFS = superior frontal sulcus, MFG = middle frontal gyrus, IFS = inferior frontal sulcus, pOrb = pars orbitalis, AHL = anterior horizontal ramus of lateral (Sylvian) sulcus, pTr = pars triangularis, AAL = anterior horizontal ramus of lateral sulcus, pOp = pars opercularis, VPrM = ventral premotor cortex, PrCG = precentral sulcus, PrCG = precentral gyrus, CS = central sulcus, PoCG = postcentral gyrus, PoCS = postcentral sulcus, LS = lateral (Sylvian) fissure, STG = superior temporal gyrus, STS = superior temporal sulcus, MTG = middle temporal gyrus, ITS = inferior temporal sulcus, ITG = inferior temporal gyrus, SPL = superior parietal lobule, IPS = intraparietal sulcus, SMG = supramarginal gyrus, PISJ = primary intermediate sulcus of Jensen, AG = angular gyrus, PaLS = posterior ascending ramus of lateral sulcus. (B) Rendering of left and right hemisphere motor (green) and sensory (yellow) positive stimulation sites within the precentral and postcentral gyri.

MNI-space were recorded for each stimulation point for subsequent cluster analysis (Supplementary Table 2).

## Cluster and probability analysis

For a given function of interest, the MNI coordinates of all relevant stimulation points were imported into a spreadsheet and analysed using the statistical program R (version 2.15.13; <http://www.r-project.org/>). To determine whether a given data set should be represented as a single or multiple clusters, the Duda-Hart statistic was evaluated using three clustering techniques: k-means, partition-around-medioids and hierarchical Ward (Everitt, 2011). Only data sets with a Duda-Hart statistic >1.645 (corresponding to a significance level of 0.05) were subjected to formal cluster analysis, whereas those with Duda-Hart values <1.645 were reported as a single cluster of data points. For cluster analyses, all three methods (k-means,

partition-around-medioids, hierarchical Ward) were applied while varying the number of clusters from 2 to 10. The optimal number of clusters for each method was chosen based on the average silhouette width (Rousseeuw, 1987). To ensure conservative interpretation of the optimal cluster number for each data set, the smallest number of optimal clusters among the three methods was selected, and the corresponding method was then used for cluster reporting (in the case of ties, the method achieving the larger average silhouette width was used). Data are reported as centrions  $\pm$  standard deviations (SD) (Supplementary Table 1).

In addition to cluster analyses, the probability of a given function being located within a region of interest (precentral gyrus, pars opercularis, pars triangularis, dorsolateral prefrontal, ventral premotor cortex, postcentral gyrus, supramarginal gyrus, superior temporal gyrus, middle temporal gyrus) was calculated by dividing the total number of patients with at least one positive stimulation in that

**Table 3** Region of interest-based probability calculations

	Motor	Sensory	Anarthria arrest	Anomia	Dysarthria	Phonologic	Semantic
Left hemisphere							
PrG	0.63		0.22		0.18	0.02	
pOp			0.04	0.07		0.04	0.02
pTr				0.04		0.02	0.04
DLPF				0.10		0.07	0.05
VPrM			0.83				
PoG		0.25	0.13		0.09		
SMG			0.08	0.18			0.05
STG				0.44		0.04	0.09
MTG				0.11			
Right hemisphere							
PrG	0.84		0.35		0.18		
VPrM			0.55		0.06		
PoG	0.12	0.49			0.04		
STG				0.06			

Calculations of probability of a given function for relevant region of interest within the left hemisphere and right hemisphere regions.

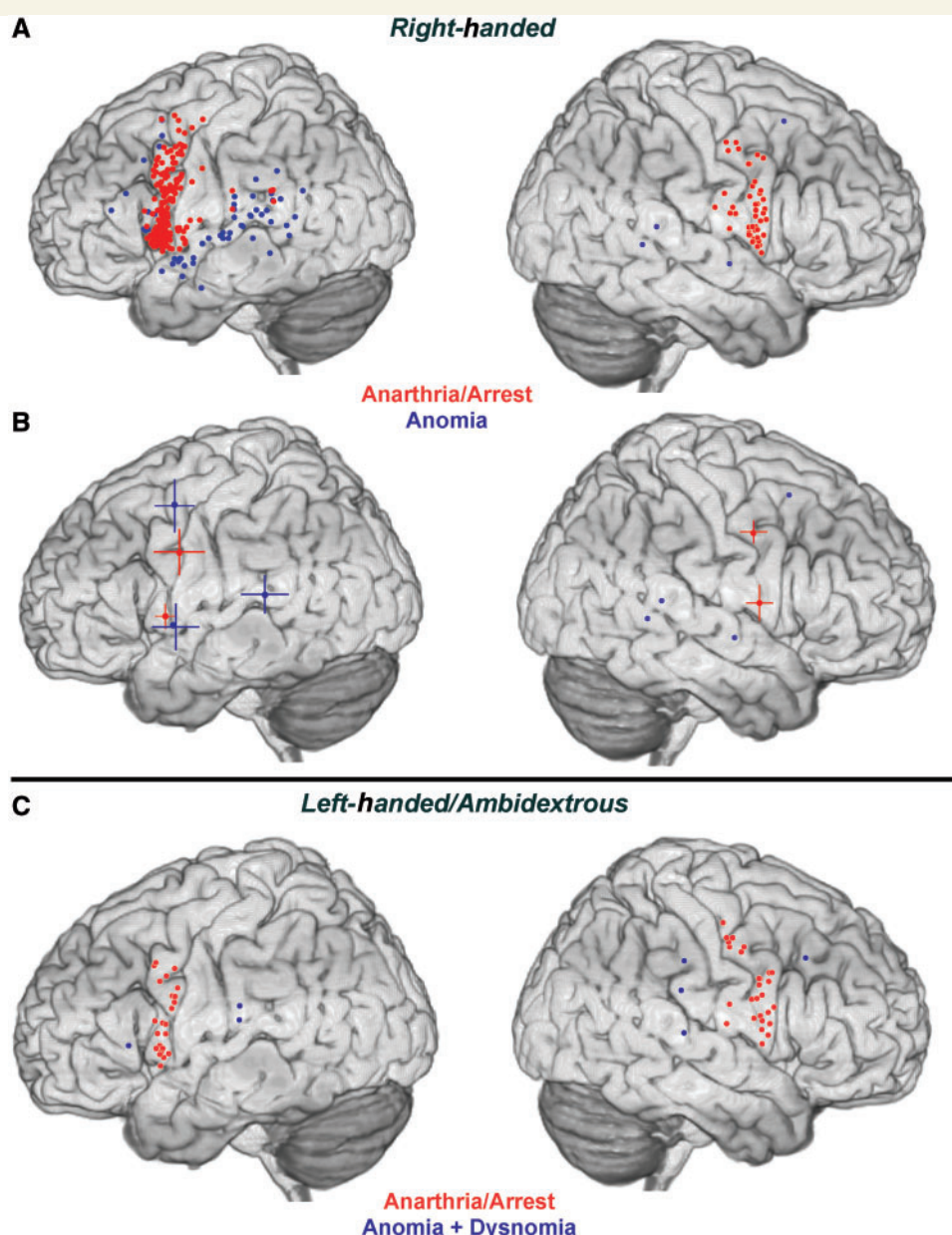
PrG = precentral gyrus; pOp = pars opercularis; pTr = pars triangularis; DLPF = dorsolateral prefrontal; VPrM = ventral premotor cortex; PoG = postcentral gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus; MTG = middle temporal gyrus.

**Table 4** Probability of anomia and anarthria/arrest for various region of interest as a function of tumour location (frontal, parietal, temporal)

	Anomia			Anarthria/arrest		
	Frontal	Parietal	Temporal	Frontal	Parietal	Temporal
PrG	0.05			0.35	0.18	
pOp	0.27					
pTr	0.16					
DLPF	0.23					
VPrM				0.7	0.82	0.88
PoG						0.21
SMG		0.18	0.15			
STG		0.83	0.76			

PrG = precentral gyrus; pOp = pars opercularis; pTr = pars triangularis; DLPF = dorsolateral prefrontal; VPrM = ventral premotor cortex; PoG = postcentral gyrus; SMG = supramarginal gyrus; STG = superior temporal gyrus.

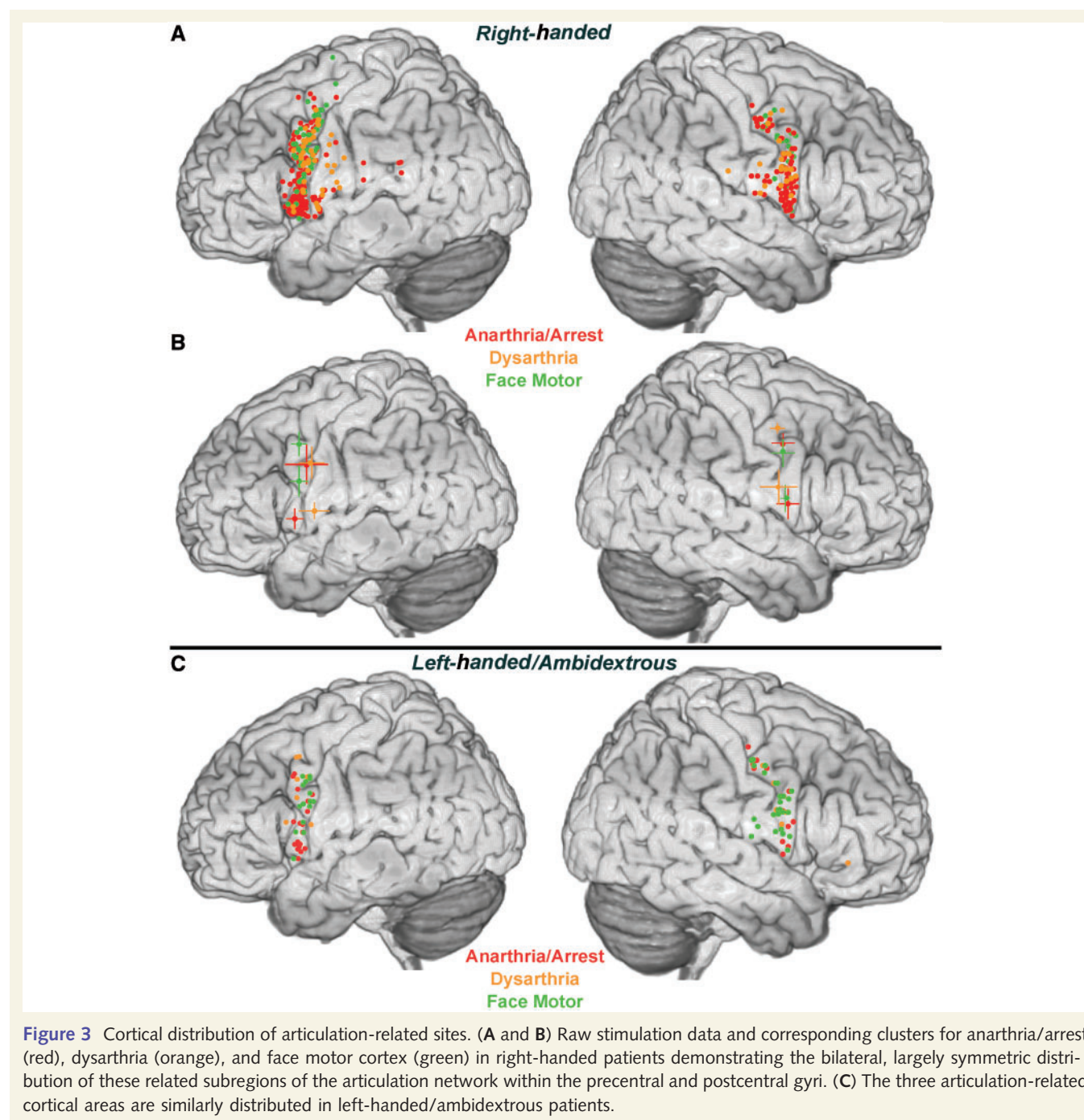




**Figure 2** Critical regions of speech output and naming in the human cortex. (A and B) Raw stimulation data (A) and corresponding clusters (B) determined by formal unbiased classification algorithms (plotted as centroid  $\pm$  SD in the MNI  $y$ - $z$  plane; see Supplementary Table 1 for exact values) for speech arrest (red) and anomia (blue) in the right and left hemispheres of right-handed patients. These data illustrate two crucial epicentres for speech output in the bilateral precentral gyri: ventral premotor cortex ( $n = 106$  sites in left hemisphere,  $n = 34$  sites in right hemisphere) and region of face motor cortex ( $n = 67$  sites in left hemisphere,  $n = 11$  sites in right hemisphere). Three epicentres necessary for naming were identified in the hemisphere of the right-handed patients: junction of supramarginal and posterior superior temporal gyri ( $n = 29$ ), peri-Sylvian cortices at junction of precentral and superior temporal gyri ( $n = 21$ ), and dorsolateral prefrontal cortex ( $n = 6$ ). Data from patients demonstrating crossed aphasia (anomia elicited within the right hemisphere of right-handed patients;  $n = 4$ ) demonstrate a similar pattern within the three regions defined by the left-hemisphere analysis. (C) Stimulation data in the right and left hemispheres of left-handed/ambidextrous patients also suggests an analogous pattern of speech output and naming to right-handed patients.

region of interest by the total number of patients for which that region of interest was exposed during the surgical mapping. For example, the probability of finding stimulation-induced movement in the precentral gyrus of left hemispheric tumour patients was 0.63 (70 patients with positive motor stimulation in the precentral gyrus/111 patients that

had stimulation of the precentral gyrus). These region of interest-based functional probabilities were calculated for both right and left hemispheres (Table 3). In addition, similar calculations were performed for two language functions (anomia, arrest) as a function of tumour location (frontal, parietal, temporal) (Table 4).



**Figure 3** Cortical distribution of articulation-related sites. (A and B) Raw stimulation data and corresponding clusters for anarthria/arrest (red), dysarthria (orange), and face motor cortex (green) in right-handed patients demonstrating the bilateral, largely symmetric distribution of these related subregions of the articulation network within the precentral and postcentral gyri. (C) The three articulation-related cortical areas are similarly distributed in left-handed/ambidextrous patients.

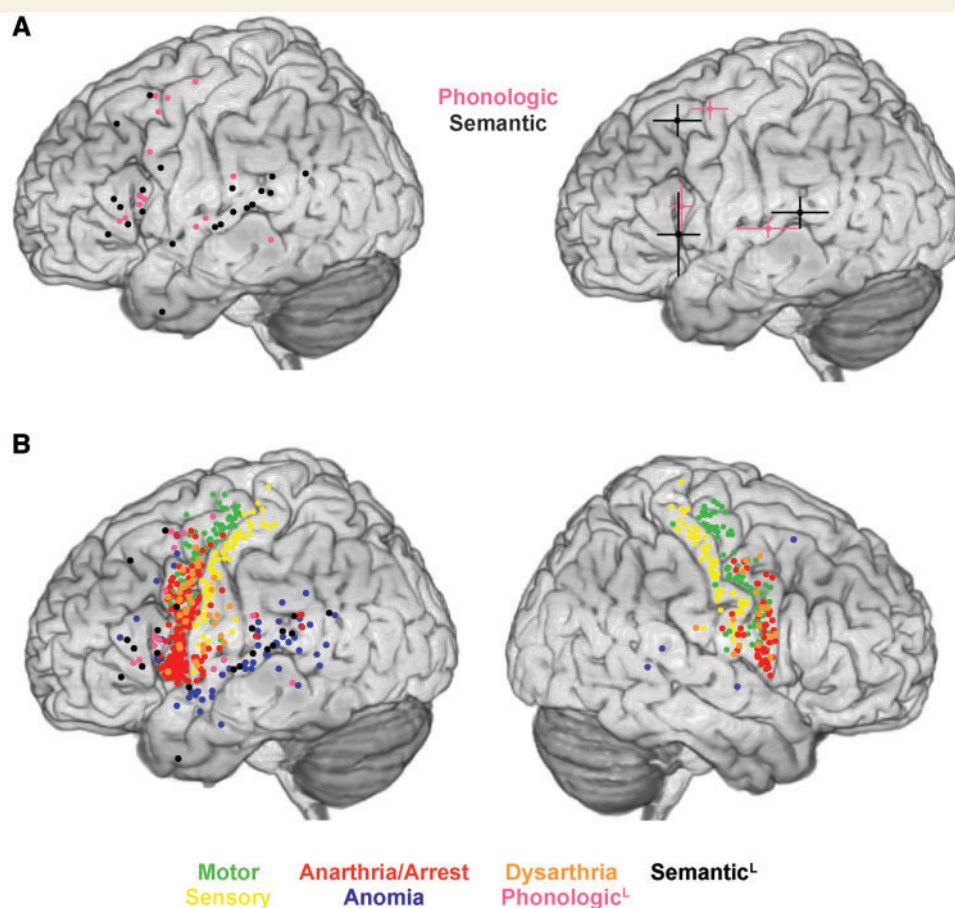
## Results

### Patient characteristics and sensorimotor function

The details of the 165 newly-diagnosed low grade glioma undergoing awake craniotomy for elective resection are included in Tables 1 and 2, and Fig. 1. The most common regions involved were frontal ( $n = 43$ , 26%), temporal ( $n = 25$ , 15%), frontal-temporal-insular ( $n = 23$ , 14%), and parietal ( $n = 22$ , 13%) (Tables 1

and 2). Sites of positive intraoperative stimulation ( $n = 712$ , mean 4.32 sites/brain) were plotted onto a non-symmetric MNI template brain space using regional anatomic landmarks (Fig. 1A). In all cases, at least one site of positive stimulation was elicited. Using this method, motor and somatosensory maps for the right and left hemisphere were constructed (Fig. 1B). Demonstration of the expected localization of motor and somatosensory function within the precentral and postcentral gyri served as a positive control for the mapping methodology used. The probability of eliciting motor and sensory phenomena in the precentral and postcentral gyri are listed in Table 3.





**Figure 4** Linguistic components of naming and summary map of cortical stimulation data. (A) Raw stimulation data and corresponding clusters for phonological (pink) and semantic (black) aspects of naming in right-handed patients. Phonological epicentres were located in the middle superior temporal gyrus, pars opercularis, and junction of precentral gyrus/dorsolateral prefrontal cortex. Three semantic nodes were identified: junction of posterior superior temporal gyrus and supramarginal gyrus, pars triangularis/opercularis, and dorsolateral prefrontal cortex. (B) Compilation of all stimulation data ( $n = 771$  stimulation sites) in the right and left hemisphere demonstrating the wide distribution of cortical representation within and between critical functions of the human brain: motor (green), sensory (yellow), anarthria/arrest (red), anomia (blue), dysarthria (orange), phonologic (pink), semantic (black). L = left hemisphere only.

## Speech arrest

We next analysed the cortical regions necessary for speech production, analogous to the classically described Broca's area. Stimulations causing a complete cessation of speech output (anarthria/arrest) in right-handed patients localized to the precentral gyrus of the right and left hemispheres, suggesting a bilateral cortical requirement for speech output (Fig. 2). Within the precentral gyrus of each hemisphere, cluster analysis revealed two foci, a higher probability region within the ventral premotor cortex ( $n = 106$  and  $34$  for left and right hemisphere, respectively) and lower probability epicentre at the level of face motor cortex ( $n = 67$  and  $11$  for left and right hemisphere, respectively). A similar pattern of speech output within the precentral gyrus was identified bilaterally in left-handed/ambidextrous patients. Notably, lack of speech output was rarely accomplished with stimulation of the classical Broca's area (pars opercularis and pars triangularis;  $n = 5$ , 2.9% of all speech arrest sites). Probability calculations demonstrated similar findings, with only a 4% chance of speech

arrest with left pars opercularis stimulation compared with an 83% chance with stimulation of ventral premotor cortex (Table 3). This probability of speech arrest with stimulation of ventral premotor cortex was maintained despite tumour location, with rates of 70%, 82%, and 88% for frontal, parietal, and temporal tumours, respectively (Table 4). These data are consistent with recent functional MRI data in brain tumour patients demonstrating that speech deficits are more common with infiltration of ventral premotor cortex than the classical Broca's area (Bizzi *et al.*, 2012) and reports of patients with normal speech function following removal of Broca's area (Benzagmout *et al.*, 2007; Plaza *et al.*, 2009). Together, these data suggest that the combined function of the right and left ventral premotor cortex serve as the final common output for motor speech plans.

## Articulation

After establishing the final common output of speech output through the ventral premotor cortex, the distribution of relevant

associated cortices were evaluated to understand the networks in modulating the mechanical aspects of speech output, i.e. articulation. In particular, stimulation sites causing overt facial muscle contraction (face motor cortex) and dysarthria (improper articulation of speech with retention of verbal output) were analysed. For right-handed patients, face motor cortex representation within both hemispheres was located within a more restricted extent of the precentral gyrus compared to zero output states (arrest) (Fig. 3A). In contrast, dysarthria-related stimulation sites were more broadly distributed within the lateral precentral and postcentral gyri, reflecting a role for sensory data in modulating articulatory output. A similar pattern of articulation-related regions was observed in left-handed/ambidextrous patients (Fig. 3B). Probabilistic data demonstrated a 9% and 18% rate of dysarthria with stimulation of left postcentral and precentral gyri, respectively, with similar rates in the right hemisphere. Taken together, these data suggest that proper articulation during speech output is a bilateral process involving bidirectional motor, sensory, and supramodal integration within the precentral and postcentral gyri to ensure completion of the intended acoustic output, which is in agreement with a recent study demonstrating somatotopically arranged speech-articulator representations in the ventral precentral and postcentral gyri of humans (Bouchard *et al.*, 2013).

## Anomia

Anomia was also assessed using an object naming task. Importantly, during the picture naming task (see 'Materials and methods' section), patients were asked to begin the naming of an individual picture with 'This is a/an', followed by the name of the presented picture. Such a task allows differentiation of frank speech arrest (zero verbal output) from an anomia, where the patient is able to say 'This is a...' but cannot complete the sentence with the correct name of the presented picture. In right-handed patients, stimulation-induced anomia lateralized to the left-hemisphere (Fig. 2), with only rare observations of crossed anomia, in agreement with previous data (Sanai *et al.*, 2008). Cluster analyses indicated that in addition to an epicentre in the posterior superior temporal gyrus/inferior parietal lobule of the left hemisphere corresponding to the classical Wernicke's area ( $n = 29$ ), two additional epicentres crucial to naming were observed. One such area is located more anteriorly within the superior temporal gyrus at its junction with the inferior precentral gyrus at the Sylvian fissure ( $n = 21$ ). A third epicentre is located at the junction of the posterior middle frontal and precentral gyri, which is also the junction of the dorsal premotor and ventral premotor cortices within Brodmann area 6 ( $n = 6$ ). Although few patients ( $n = 4$ , 2.9%) exhibited crossed anomia (naming error elicited by stimulation of the right hemisphere in right-handed patients), the pattern of cortical representation was similar to that observed in the left hemisphere (posterior superior temporal gyrus/inferior parietal lobule, mid-superior temporal gyrus, posterior middle frontal gyrus). Anomia maps in left-handed/ambidextrous patients were also similar to right-handed counterparts (Fig. 2B). Probability calculations illustrated the following region of interest-based rates of anomia: superior temporal gyrus (44%), supramarginal gyrus (18%), middle temporal gyrus

(11%), dorsolateral prefrontal (10%), pars opercularis (7%), and pars triangularis (4%) (Table 3). Similar anomia probabilities were observed for the superior temporal and middle temporal gyri for patients with parietal versus temporal tumours (Table 4). Together, these data suggest that while speech output is bilaterally distributed within the ventral premotor cortex, circuits responsible for naming in right-handed patients predominately resides in the left hemisphere as a network connecting frontal, temporal and parietal nodes.

## Phonology and semantics

After the confirmation of the cortical regions responsible for anonomias, we sought to define regions crucial to processing of two major linguistic categories—phonological and semantic output (Fig. 4A). Broadly, semantic sites were widely distributed throughout the cortex of the left hemisphere, including the posterior frontal lobe, superior temporal lobe, and inferior parietal lobule. Three semantic nodes were identified by cluster analysis: the junction of posterior superior temporal gyrus and supramarginal gyrus, pars triangularis/pars opercularis, and dorsal premotor cortex. Similarly, phonological sites were widely distributed throughout the cortex of the left hemisphere, including the posterior frontal lobe, superior temporal lobe and inferior parietal lobule. Cluster analysis yielded three statistical epicentres: the middle superior temporal gyrus, pars opercularis, and junction of dorsal premotor and ventral premotor cortices. Table 3 lists the relevant probability calculation for phonologic and semantic function within spatially diverse left hemisphere regions of interest. In summary, at the cortical level, phonological and semantic processing consists of both adjacent and overlapping epicentres, and the frontal lobe sites of anomia described earlier in this report may be the functional consequence of superimposed disruption of shared semantic/phonological regions. Further, the location of semantic and phonological sites in the classical Broca's area suggest that this region is involved in higher-order tuning of language versus global speech output, which the current study suggests resides in the ventral premotor cortex. Finally, the spatial distribution of linguistic category data at the cortex in the present study is remarkably similar to that reported in a recent meta-analysis of functional MRI data in normal patients (Vigneau *et al.*, 2006), supporting the robustness of our findings.

## Discussion

Direct cortical stimulation in awake patients provides a reliable method for examining cortical and subcortical function in humans. In contrast to other functional assays such as functional MRI, PET and magnetoencephalography, that indicate cortical regions involved in a particular function, direct cortical stimulation enables determination of the regions that are absolutely required for a given function. In the present study, direct cortical stimulation was used to assess multiple functions in both the left and right cerebral hemispheres: sensory, motor, and language (speech output, articulation, naming, phonology, semantics). Sensorimotor function was localized as expected to the precentral



and postcentral gyri, respectively, confirming the specificity of the technique (Desmurget *et al.*, 2013).

With respect to language function, one of the major findings of the current study is that the final common pathway for speech output reliably localizes to ventral premotor cortex in the right and left hemispheres. Broca's area, along with the dorsal premotor cortex, was noted to be involved in modulating higher-order aspects of language such as semantic and phonological content. Thus, in agreement with recent studies on motor speech output (Dronkers, 1996), our findings support the fact that Broca's area would be more involved in cognitive functions, as lexical retrieval, phonological assembly, verbal working memory, sequential processing or cognitive control, as a supramodal hierarchical processor (Tettamanti and Weniger, 2006), and challenge the prevailing notion of Broca's area as a motor area, *per se*.

In addition, even though our current data are consistent with some aspects of both classical language models (e.g. importance of posterior superior temporal gyrus in naming), they support the modern 'dual stream' theory of language anatomy (Hickok and Poeppel, 2007; Saur *et al.*, 2008; Hickok, 2012; Schwartz *et al.*, 2012; Duffau *et al.*, 2013, 2014): indeed, phonological foci have been essentially found in a more dorsal localization (at/near premotor and supramarginal gyrus). On the other hand, our cluster-based analyses demonstrate overlapping and adjacent anatomic epicentres for phonologic and semantics, suggesting the presence of amodal or supramodal language network hubs in the posterior superior temporal gyrus, frontal operculum, and dorsolateral prefrontal cortex. Finally, a hierarchical local network within the precentral and postcentral gyri important for optimizing the mechanical aspects of speech articulation was directly demonstrated. Limitations of our analysis include: (i) spatial biasing due to non-random distribution of tumours and subsequent cortical exposure at surgery; (ii) the presence of tumours in the study population; and (iii) time constraints of surgery limiting the number of stimulation trials.

In summary, the present study provides the first bilateral probabilistic map for essential cortical functions in the right and left hemisphere of humans. In addition to pragmatic benefits, such as allowing neurosurgeons to better predict the relationship between functional circuits and a tumour to be resected, these data are relevant to future investigations of the normal functional anatomy in the human brain. For example, described epicentres could be included as seeding points or regions of interest for diffusion tensor imaging and functional MRI-based connectivity measures, respectively. These types of studies will allow further specification of the anatomical organization or cortical/subcortical epicentres and the dynamic interactions between these brain regions.

## Funding

American Association of Neurological Surgeons, Association pour la Recherche sur le Cancer (France). This work was also supported by the Van Wagenen Fellowship of the American Association of Neurological Surgeons (AANS) to M.T. G.H. is supported by the Association pour la Recherche sur le Cancer (grant number: DOC20120605069).

## Supplementary material

Supplementary material is available at *Brain* online.

## References

- Benzagmout M, Gatignol P, Duffau H. Resection of World Health Organization Grade II gliomas involving Broca's area: methodological and functional considerations. *Neurosurgery* 2007; 61: 741–52; discussion 52–3.
- Bizzi A, Nava S, Ferre F, Castelli G, Aquino D, Ciaraffa F, et al. Aphasia induced by gliomas growing in the ventrolateral frontal region: assessment with diffusion MR tractography, functional MR imaging and neuropsychology. *Cortex* 2012; 48: 255–72.
- Bouchard KE, Mesgarani N, Johnson K, Chang EF. Functional organization of human sensorimotor cortex for speech articulation. *Nature* 2013; 495: 327–32.
- Broca P. Nouvelle observation d'aphémie produite par une lésion de la troisième circonvolution frontale. *Bull Soc Anat Paris* 1861a; 6: 398–407.
- Broca P. Perte de la parole: ramollissement chronique et destruction partielle du lobe antérieur gauche du cerveau. *Bull Soc Anthropol* 1861b; 2: 235–8.
- Carr VA, Rissman J, Wagner AD. Imaging the human medial temporal lobe with high-resolution fMRI. *Neuron* 2010; 65: 298–308.
- Desmurget M, Song Z, Mottolese C, Sirigu A. Re-establishing the merits of electrical brain stimulation. *Trends Cogn Sci* 2013; 17: 442–9.
- Devlin JT, Watkins KE. Stimulating language: insights from TMS. *Brain* 2007; 130 (Pt 3): 610–22.
- Dronkers N. A new brain region for coordinating speech articulation. *Nature* 1996; 384: 159–61.
- Duffau H, Capelle L, Sichez N, Denvil D, Lopes M, Sichez JP, et al. Intraoperative mapping of the subcortical language pathways using direct stimulations. An anatomo-functional study. *Brain* 2002; 125 (Pt 1): 199–214.
- Duffau H, Gatignol P, Mandonnet E, Peruzzi P, Tzourio-Mazoyer N, Capelle L. New insights into the anatomo-functional connectivity of the semantic system: a study using cortico-subcortical electrostimulations. *Brain* 2005; 128 (Pt 4): 797–810.
- Duffau H, Herbet G, Moritz-Gasser S. Toward a pluri-component, multi-modal, and dynamic organization of the ventral semantic stream: lesson from stimulation mapping in awake patients. *Front Syst Neurosci* 2013; 7: 44.
- Duffau H, Moritz-gasser S, Mandonnet E. A re-examination of neural basis of language processing: proposal of a dynamic homotopical model from data provided by brain stimulation mapping during picture naming. *Brain Lang* 2014; 131: 1–10.
- Everitt B. Cluster analysis. 5th edn. Chichester, West Sussex, UK: Wiley; 2011.
- Gatignol P, Capelle L, Le Bihan R, Duffau H. Double dissociation between picture naming and comprehension: an electrostimulation study. *Neuroreport* 2004; 15: 191–5.
- Hagan CC, Woods W, Johnson S, Calder AJ, Green GG, Young AW. MEG demonstrates a supra-additive response to facial and vocal emotion in the right superior temporal sulcus. *Proc Natl Acad Sci USA* 2009; 106: 20010–5.
- Hermundstad AM, Bassett DS, Brown KS, Aminoff EM, Clewett D, Freeman S, et al. Structural foundations of resting-state and task-based functional connectivity in the human brain. *Proc Natl Acad Sci USA* 2013; 110: 6169–74.
- Hickok G, Poeppel D. The cortical organization of speech processing. *Nat Rev Neurosci* 2007; 8: 393–402.
- Hickok G. Computational neuroanatomy of speech production. *Nat Rev Neurosci* 2012; 13: 135–45.
- Logothetis NK. What we can do and what we cannot do with fMRI. *Nature* 2008; 453: 869–78.

- Maess B, Koelsch S, Gunter TC, Friederici AD. Musical syntax is processed in Broca's area: an MEG study. *Nat Neurosci* 2001; 4: 540–5.
- Metz-Lutz M, Kremin H, Deloche G. Standardisation d'un test de dénomination orale: contrôle des effets de l'âge, du sexe et du niveau de scolarité chez les sujets adultes normaux. *Rev Neuropsychol* 1991; 1: 73–95.
- Mori S, Zhang J. Principles of diffusion tensor imaging and its applications to basic neuroscience research. *Neuron* 2006; 51: 527–39.
- Mueller S, Wang D, Fox MD, Yeo BT, Sepulcre J, Sabuncu MR, et al. Individual variability in functional connectivity architecture of the human brain. *Neuron* 2013; 77: 586–95.
- Penfield W, Boldrey E. Somatic motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 1937; 60: 55.
- Plaza M, Gatignol P, Leroy M, Duffau H. Speaking without Broca's area after tumor resection. *Neurocase* 2009; 15: 294–310.
- Rousseeuw PJ. Silhouettes: a graphical aid to the interpretation and validation of cluster analysis. *J Comp Appl Math* 1987; 20: 53–65.
- Sanai N, Mirzadeh Z, Berger MS. Functional outcome after language mapping for glioma resection. *N Engl J Med* 2008; 358: 18–27.
- Saur D, Kreher BW, Schnell S, Kummerer D, Kellmeyer P, Vry MS, et al. Ventral and dorsal pathways for language. *Proc Natl Acad Sci USA* 2008; 105: 18035–40.
- Schwartz MF, Faseyitan O, Kim J, Coslett HB. The dorsal stream contribution to phonological retrieval in object naming. *Brain* 2012; 135 (Pt 12): 3799–814.
- Tarapore PE, Tate MC, Findlay AM, Honma SM, Mizuiri D, Berger MS, et al. Preoperative multimodal motor mapping: a comparison of magnetoencephalography imaging, navigated transcranial magnetic stimulation, and direct cortical stimulation. *J Neurosurg* 2012; 117: 354–62.
- Tettamanti M, Weniger D. Broca's area: a supramodal hierarchical processor? *Cortex* 2006; 42: 491–4.
- Vigneau M, Beaucois V, Herve PY, Duffau H, Crivello F, Houde O, et al. Meta-analyzing left hemisphere language areas: phonology, semantics, and sentence processing. *Neuroimage* 2006; 30: 1414–32.