



Contents lists available at ScienceDirect

NeuroImage

journal homepage: [www.elsevier.com/locate/ynimg](http://www.elsevier.com/locate/ynimg)

## Connectivity constraints on cortical reorganization of neural circuits involved in object naming

Costanza Papagno<sup>a,\*</sup>, Marcello Gallucci<sup>a</sup>, Alessandra Casarotti<sup>a,b</sup>, Antonella Castellano<sup>c</sup>, Andrea Falini<sup>c</sup>, Enrica Fava<sup>b</sup>, Carlo Giussani<sup>b</sup>, Giorgio Carrabba<sup>b</sup>, Lorenzo Bello<sup>b</sup>, Alfonso Caramazza<sup>d,e</sup>

<sup>a</sup> Dipartimento di Psicologia, Università di Milano Bicocca, Piazza dell'Ateneo Nuovo 1, Edificio U6, 20126 Milano, Italy

<sup>b</sup> Dipartimento di Scienze Neurologiche, Università degli Studi di Milano, via Francesco Sforza 35, 20122 Milano, Italy

<sup>c</sup> Dipartimento di Neuroradiologia and CERMAC, Scientific Institute and Università Vita-Salute San Raffaele, via Olgettina 60, 20132 Milano, Italy

<sup>d</sup> CIMeC—Center for Mind/Brain Sciences, Università di Trento, Corso Bettini 31, 38068 Rovereto, Italy

<sup>e</sup> Harvard University, Cambridge (MA) 02138, USA

### ARTICLE INFO

#### Article history:

Received 18 October 2010

Revised 28 December 2010

Accepted 4 January 2011

Available online xxx

#### Keywords:

Awake surgery

Direct electrical stimulation

Tractography

Object naming

### ABSTRACT

The brain's plasticity in response to sensory deprivation and other perturbations is well established. While the functional properties of the reorganized areas are under vigorous investigation, the factors that constrain cortical reorganization remain poorly understood. One factor constraining such reorganization may be long-distance subcortical connectivity between relevant cortical regions—reorganization attempts to preserve the functionality of subcortical connections. Here we provide human neurophysiological evidence for the role of the subcortical connections in shaping cortical reorganization of the networks involved in object naming following perturbation of normal function. We used direct electrical stimulation (DES) during surgical removal of gliomas to identify the sites that are involved in naming different categories of objects. The sites that were selectively inhibited in naming either living or non-living objects were displaced relative to those observed with other subject populations, possibly reflecting cortical reorganization due to slowly evolving brain damage. Subcortical DES applied to the white matter underlying these regions also led to category-specific naming deficits. The existence of these subcortical fiber pathways was confirmed using diffusion tensor tractography. These results constitute the first neurophysiological evidence for the critical role of subcortical pathways as part of the neural circuits that are involved in object naming; they also highlight the importance of subcortical connectivity in shaping cortical reorganization following perturbations of normal function.

© 2011 Elsevier Inc. All rights reserved.

### Introduction

Neuropsychological and functional neuroimaging research indicates neural specificity for a small number of semantic categories in the human brain. Reports of patients with disproportionate naming impairment for one category of objects relative to other semantic categories (Caramazza and Shelton, 1998; Hillis and Caramazza, 1991; Sartori and Job, 1988; Tranel et al., 1997; Warrington and Shallice, 1984; see review in Capitani et al., 2003; Gainotti, 2000), as well as functional brain imaging studies (Damasio et al., 1996; Kriegeskorte et al., 2008; Martin et al., 1996; Rogers et al., 2005) and single cell recordings in humans (Kreiman et al., 2000; Quiroga et al., 2005) have helped chart some of the cortical networks involved in processing different categories of objects, but this issue is not without controversy (see Lambon Ralph et al. (2007) for arguments against

the existence of category-specific deficits). The distinction between animate and inanimate objects has emerged as one of the principal dimensions of the organization of object knowledge. Neuroimaging studies have suggested that the major areas involved for naming animals include the left inferior temporal gyrus (IITG) and bilateral fusiform gyri; the regions involved in naming tools and other artifacts include the left posterior middle temporal gyrus (pMTG), bilateral inferior temporal gyri, left middle temporal gyrus, and left premotor region (Damasio et al., 1996; Martin et al., 1996). The relative contribution of the various areas may vary depending on the type of task used (Tyler and Moss, 2001). [For recent reviews of the neuroimaging and neuropsychological evidence on category-specificity see Martin (2007) and Mahon and Caramazza (2009), respectively].

The view that object knowledge is distributed over a number of cortical areas gives rise to the fundamental question of how these areas are bound together into effective domain-specific cortical (–subcortical) networks. A plausible answer is that this function is carried out by long-distance subcortical connections (e.g., Mahon et al., 2009; Riesenhuber,

\* Corresponding author. Fax: +39 0264483706.

E-mail addresses: [costanza.papagno@unimib.it](mailto:costanza.papagno@unimib.it) (C. Papagno), [caramazz@fas.harvard.edu](mailto:caramazz@fas.harvard.edu) (A. Caramazza).

**Table 1**  
Clinical and demographic data of the 38 patients who participated in the study.

| Lesion site           | Gender         | Histology        | Age (years) | Education (years) |
|-----------------------|----------------|------------------|-------------|-------------------|
| <i>Right temporal</i> |                |                  |             |                   |
| N <sup>a</sup> = 2    | F <sup>b</sup> | LGG <sup>c</sup> | 29.5        | 16.5              |
| N = 1                 | M <sup>d</sup> | LGG              | 39          | 16                |
| <i>Left temporal</i>  |                |                  |             |                   |
| N = 5                 | F              | LGG              | 47.6        | 10.4              |
| N = 3                 | M              | LGG              | 34.3        | 13.6              |
| N = 3                 | F              | HGG <sup>e</sup> | 39          | 11.3              |
| N = 4                 | M              | HGG              | 48.25       | 15.5              |
| <i>Left frontal</i>   |                |                  |             |                   |
| N = 4                 | F              | LGG              | 41.25       | 13                |
| N = 5                 | M              | LGG              | 47.6        | 11.6              |
| N = 3                 | F              | HGG              | 41.3        | 13                |
| N = 3                 | M              | HGG              | 55.3        | 9.6               |
| <i>Right parietal</i> |                |                  |             |                   |
| N = 2                 | M              | LGG              | 49          | 8                 |
| <i>Left parietal</i>  |                |                  |             |                   |
| N = 1                 | F              | LGG              | 36          | 11                |
| N = 2                 | M              | LGG              | 53.5        | 8                 |

<sup>a</sup> N = number of patients.<sup>b</sup> F = female.<sup>c</sup> LGG = low grade glioma.<sup>d</sup> M = male.<sup>e</sup> HGG = high grade glioma.

2007; Thomas et al., 2009). However, there is a total absence of human neurophysiological data on this subject. In the present study, we used intraoperative direct cortical and subcortical stimulation to investigate the animate and inanimate domain-specific cortical networks and their associated subcortical connecting fibers in patients undergoing the removal of gliomas. This technique allows for localization of extremely small (<1 cm<sup>2</sup>) brain areas (Ojemann et al., 1989). During brain surgery for tumor resection it is common clinical practice to awaken patients in order to assess the functional role of restricted brain regions, so that the surgeon can maximize the extent of the exeresis without provoking cognitive impairment, particularly of language. Patients may be asked to perform a picture naming task while the surgeon temporarily inactivates restricted regions around the tumor by means of electrical stimulation. If the patient is unable to produce a response or produces an incorrect one, such as a semantic or phonemic paraphasia, the surgeon refrains from removing the stimulated region. By cumulating performance over the areas stimulated and across subjects, a map can be constructed of the functional role of different brain regions. This neurophysiological procedure allows us to assess the contribution of both cortical and subcortical structures in naming animate and inanimate objects.

Yet, because the brains of these surgical patients are likely to have reorganized as a consequence of their slowly growing tumors, the functional maps constructed in this way may differ from those obtained

**Table 2**  
Pre-surgical neuropsychological evaluation.

|                         | Left temporal LGG  | Left temporal HGG | Left frontal LGG | Left frontal HGG | Left parietal LGG | Right parietal LGG |
|-------------------------|--------------------|-------------------|------------------|------------------|-------------------|--------------------|
| Verbal LTM <sup>a</sup> | N <sup>b</sup> = 4 | N = 3             | N = 1            | N = 1            | N = 1             |                    |
| Visual LTM              | N = 5              |                   | N = 4            | N = 3            |                   | N = 1              |
| Verbal STM <sup>c</sup> | N = 1              |                   |                  |                  | N = 1             |                    |
| Famous face naming      | N = 4              | N = 3             | N = 3            |                  |                   |                    |
| Picture naming          | N = 2              | N = 3             | N = 1            |                  |                   |                    |

<sup>a</sup> LTM = long-term memory.<sup>b</sup> N = number of patients showing an impaired performance on the reported test.<sup>c</sup> STM = short-term memory.**Table 3**  
Post-surgical neuropsychological evaluation (3–7 days).

|                         | Left temporal LGG  | Left temporal HGG | Left frontal LGG | Left frontal HGG | Left parietal LGG | Right parietal LGG |
|-------------------------|--------------------|-------------------|------------------|------------------|-------------------|--------------------|
| Verbal LTM <sup>a</sup> | N <sup>b</sup> = 7 | N = 4             | N = 3            | N = 1            | N = 1             |                    |
| Visual LTM              | N = 2              | N = 2             | N = 2            |                  |                   |                    |
| Verbal STM <sup>c</sup> | N = 5              | N = 2             |                  | N = 2            | N = 2             |                    |
| Famous face naming      | N = 6              | N = 4             | N = 3            | N = 1            |                   |                    |
| Picture naming          | N = 4              | N = 2             | N = 1            |                  | N = 1             |                    |

<sup>a</sup> LTM = long-term memory.<sup>b</sup> N = number of patients showing an impaired performance on the reported test.<sup>c</sup> STM = short-term memory.

in healthy individuals using other methods (e.g., fMRI). By comparing the normal and reorganized cortical networks it may be possible to infer the constraints that operate on the process of reorganization itself. Although the brain's plasticity in response to sensory deprivation and other perturbations is well-established (Kujala et al., 2000; Neville and Bavelier, 2008; Thiel et al., 2001; Wong et al., 2009), and while the functional properties of the reorganized areas are under vigorous investigation (Kech et al., 2008), the factors that determine cortical reorganization remain poorly understood. One factor constraining such reorganization may be long-distance subcortical connectivity between relevant cortical regions.

Using intraoperative DES (Ojemann et al., 1989), we provide human neurophysiological evidence for the role of the subcortical connections in shaping cortical reorganization following perturbation of normal function.

## Materials and methods

### Participants

Thirty-eight patients, 20 male and 18 female 13 with high-grade (HGG, fast growth rate) and 25 with low-grade gliomas (LGG, slow growth rate) underwent awake surgery (see Table 1). They gave informed consent to have their language-cognitive areas studied by direct mapping and agreed to have the procedure video- and audio-recorded. All but five came for clinical observation because of epileptic seizures. Of these five, one had a left temporal LGG and presented with anomia for proper names, while three LGG patients and one HGG patient were diagnosed after head trauma or in the course of a general assessment. The pre-operative neurological examination was normal and none of the right temporal patients showed any deficit during the pre-surgical neuropsychological examination. Only minimal impairments were detected in a few patients in the other groups (see Table 2 for number of patients with neuropsychological deficits and for deficit type). Handedness was evaluated with the Edinburgh Handedness Inventory (Oldfield, 1971). Functional MR imaging (fMRI) was performed to assess language dominance by using a word generation task and a picture naming of objects. In the first task, patients were

**Table 4**  
Post-surgical neuropsychological evaluation (follow-up).

|                         | Left temporal LGG  | Left temporal HGG | Left frontal LGG | Left frontal HGG | Left parietal LGG | Right parietal LGG |
|-------------------------|--------------------|-------------------|------------------|------------------|-------------------|--------------------|
| Verbal LTM <sup>a</sup> | N <sup>b</sup> = 3 |                   | N = 1            |                  |                   |                    |
| Visual LTM              | N = 2              |                   |                  |                  |                   |                    |
| Verbal STM <sup>c</sup> | N = 2              |                   |                  |                  |                   | N = 1              |
| Famous face naming      | N = 3              |                   | N = 1            | N = 1            |                   |                    |
| Picture naming          | N = 2              |                   |                  |                  |                   |                    |

<sup>a</sup> LTM = long-term memory.<sup>b</sup> N = number of patients showing an impaired performance on the reported test.<sup>c</sup> STM = short-term memory.

**Table 5**  
Percentage of disruptions in nine right-handed patients with a left LGG.

|            | BA 22 | BA 21 | BA 45 | Supramarginal Gyrus |
|------------|-------|-------|-------|---------------------|
| Living     | 9.1%  | 100%  | 37.5% | 0                   |
| Non-living | 50%   | 0     | 0     | 87.5%               |

required to produce a verb in response to the presentation of an object picture (i.e. apple: to eat). For picture naming the same 82 items that were used during the neuropsychological examination were presented (see below). Only those patients presenting activation areas in the hemisphere where the tumor was located underwent awake surgery and were therefore included in the present study.

Tumor volume was calculated on T2-weighted MRI scans for LGG and on post-contrast T1-weighted MRI scans for HGG via a computerized system (Bello et al., 2008). Histology was classified according to the WHO (brain tumor classification).

Intraoperative electrical stimulation was well tolerated, and the patients reported no abnormal visual sensations.

Patients were first evaluated at 3–7 days after surgery (see Table 3 for post-surgery neuropsychological performance). Only one of them showed a selective semantic categorical deficit before and after surgery. Patients were re-evaluated three months later (see Table 4).

Four additional male right-handed patients (two left temporal LGG, one left parietal HGG and one left frontal HGG) were studied for subcortical mapping. In the two temporal LGG the tumor involved the anterior two-thirds of the middle and inferior temporal gyri; the left parietal HGG involved the supramarginal gyrus in its posterior part and the frontal HGG was situated in the posterior part of the inferior frontal gyrus.

#### Neuropsychological examination

Each patient was submitted to an extensive neuropsychological battery in the week before surgery. The standard evaluation included tests assessing nonverbal intelligence (Basso et al., 1987); verbal and visuospatial, short- and long-term memory [digit and Corsi span (Orsini et al., 1987), word list learning (Novelli et al., 1986a), supraspan learning (Capitani et al., 1991), Rey figure reproduction (Bertolani et al., 1993)]; selective (Attentional Matrices, Spinnler and Tognoni, 1987) and divided attention (Trail Making Test, Giovagnoli et al., 1996); orofacial, ideomotor and constructional apraxia (Spinnler and Tognoni, 1987), spatial cognition (Ronchi et al., 2009) and language. The following language tasks were performed: verbal fluency on phonological and semantic cue (Novelli et al., 1986b), famous face naming (50 items, Rizzo et al., 2002), picture naming of nouns (82 items) and verbs (50 items, Crepaldi et al., 2006), naming by description (38 items, Novelli et al., 1986b), pointing to picture (48 items), sentence comprehension [Token Test (De Renzi and Faglioni, 1978) and picture-to-sentence matching task, 80 items (Parisi and Pizzamiglio, 1970)], repetition of syllables, words, nonwords and sentences (Miceli et al., 1994). Stimuli for naming and comprehension were controlled for all relevant variables such as word frequency ( $p=0.1$ ), age of acquisition ( $p=0.25$ ), picture typicality ( $p=0.2$ ), image complexity ( $p=0.08$ ), semantic category, semantic relevance ( $p=0.92$ ), name agreement ( $p=0.18$ ), familiarity ( $p=0.62$ ), and length. The naming tasks (face, nouns and verbs) were repeated three times in different sessions to verify response consistency. For intraoperative testing we chose only items produced correctly three times out of three without abnormal delay. Among these stimuli, we selected 20 living and 20 non-living items, balanced for frequency, typicality and image complexity: each block of stimuli (living versus non-living) was presented at least three times to each patient during cortical mapping. Therefore, each patient was submitted to a specific, ad hoc intraoperative protocol designed according to his/her pre-surgical performance; also, each patient served as a control for his/her

own performance (verbs and faces were tested as well, but the results are not reported here). Stimuli consisted of colored drawings and were presented by computer.

#### Surgical procedure

Neuronavigation was available and loaded with volumetric T2 and post-gadolinium T1 imaging. During surgical removal of the tumor, the neuropsychologist presented blocks of items (living, non-living, faces, and verbs) counterbalanced across patients, and reported all the responses in the subsequent runs. The number of stimulated sites varied between 30 and 40 for each subject. Maximum individual current intensities ranged from 2 to 8 mA. Throughout the cortical and subcortical language mapping, the ECoG was continuously monitored to signal after discharge spikes, both to reduce the chances of evoking a seizure by continued stimulation at that current, and to avoid the chance that naming errors were caused by the propagated effects of the current. Only those sites whose stimulation induced a reproducible error at least three times were considered as cortical or subcortical *positive* sites and mapped with sterile numbered tickets. A digital picture of the surgical cavity was taken at the end of the resection. Motor responses were registered by means of a 24-channel EMG (ISIS Inomed) and were collected by pairs of subdermal hooked needle electrodes inserted into contralateral muscles from face to foot. Each pair of electrodes recorded two different muscles in the same body segment (i.e., a flexor and an extensor muscle in the forearm), in order to sample as many muscles as possible. Recording included lips, masseteris and cryothyroid. This allowed differentiating speech arrest due to muscle inhibition (stimulation of the negative motor area, see Lüders et al., 1988), motor block due to upper and lower face tonic activation, and anomia without muscle activation or inhibition.

The brain mapping procedure was video- and audio-recorded and reviewed postoperatively by two surgeons and two neuropsychologists in order to verify the stimulation sites and the corresponding response on picture presentation.

#### MR-DTI data acquisition and processing

Preoperative MR imaging was performed on a Philips Intera 3.0-T (Best, The Netherlands) system with a maximum field gradient strength of 80 mT/m. Five right-handed healthy volunteers were also studied (mean age 34 years, range 26–41). All controls were left hemisphere language dominant as determined by verbal fluency fMRI tasks. DTI data were acquired using a single-shot echo planar imaging (EPI) sequence (TR/TE 8986/80 ms) with parallel imaging (SENSE factor, R=2.5). Thirty-two diffusion gradient directions ( $b=1000$  s/mm<sup>2</sup>) and one image set without diffusion-weighting were obtained. A field of view measuring 240×240 mm<sup>2</sup> and a data matrix of 96×96 were used, leading to isotropic voxel dimensions (2.5×2.5×2.5 mm<sup>3</sup>). The data were interpolated in-plane to a matrix of 256×256 leading to voxel size of 0.94×0.94×2.5 mm<sup>3</sup>. Acquisition coverage extended from medulla oblongata to the brain vertex (56 slices, no gap). The sequence was repeated twice consecutively and data were averaged off-line to increase signal-to-noise ratio; DTI datasets were aligned offline to the echo-planar volume without diffusion weighing on a PC workstation using the AIR (Automatic Image Registration) software to correct artifacts due to rigid body movement during scan acquisition. 3D Fast

**Table 6**  
Percentage of disruptions for subcortical stimulations in two right-handed patients with a left temporal LGG.

|            | BA 21/BA 45 | BA 22/SG |
|------------|-------------|----------|
| Living     | 23.6%       | 0        |
| Non-living | 0           | 87.5%    |

Field Echo (FFE) T1-weighted imaging (TR 8 ms; TE 4 ms; image resolution equal to DTI) was performed for anatomic guidance.

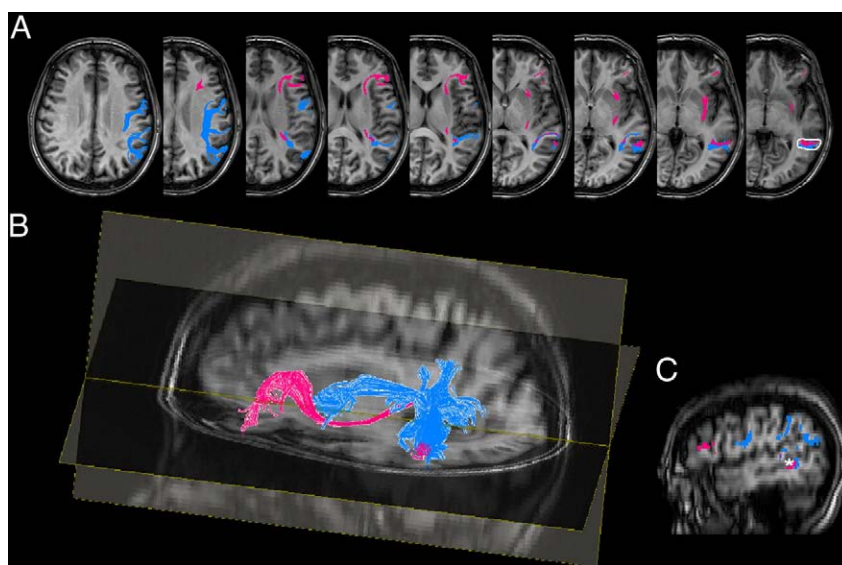
### Tractography

Deterministic tractography was performed in all patients, by using DTI Studio v2.4.01 software (Jiang H, Mori S, Radiology Department, Johns Hopkins University, Baltimore, MD, USA), obtaining main eigenvector and fractional anisotropy (FA) maps. Subcortical connections were reconstructed using the “fiber assignment by continuous tracking” (FACT) method (Mori et al., 1999). An FA threshold of 0.1 and a turning angle  $>55^\circ$  were used as criteria to start and stop tracking. Seed ROI were placed on an axial section in correspondence to the stimulation sites previously recorded on the neuronavigational system at the level of the subcortical white matter of BA 21 and BA45, and of BA 22 and BA40, allowing visualization of all the fibers connecting these areas. Probabilistic tractography was performed in five patients and five right-handed healthy volunteers. All scans were transferred to a Linux based Sun workstation; the DICOM files of each DTI acquisition were converted into a single multivolume ANALYZE 7.5 file, and were then corrected for eddy currents using the ‘eddy-correct’ algorithm implemented in FSL v4.1 (<http://www.fmrib.ox.ac.uk/fsl/>). After this co-registration step, the two  $b=0$  volumes of each subject were extracted and averaged. A multi-tensor model was fitted to the diffusion data using the FDT (FMRIB’s Diffusion Toolbox) v2.0 software tool (<http://www.fmrib.ox.ac.uk/fsl/fdt/>), and allowed modeling multiple fiber orientations per voxel (Behrens et al., 2007). Probabilistic tractography analysis was carried out using the method described by Behrens et al. (2003), extended to multiple fibers as implemented in the FDT software tool (Behrens et al., 2007). FDT repetitively samples from the distributions on voxel-wise principal diffusion directions, each time computing a streamline through these local samples to generate a probabilistic streamline or a sample from the distribution on the location of the true streamline. By taking many such samples FDT is able to build up the posterior distribution on the streamline location or the connectivity distribution. The program FSL view (<http://www.fmrib.ox.ac.uk/fsl/fslview/>) was used to visualize images and create masks. Seed masks for tractography were placed in correspondence to the stimulation sites previously recorded on the neuronavigational system. At a temporal level, the posterior part of the middle temporal gyrus (BA 21) and the middle part of superior

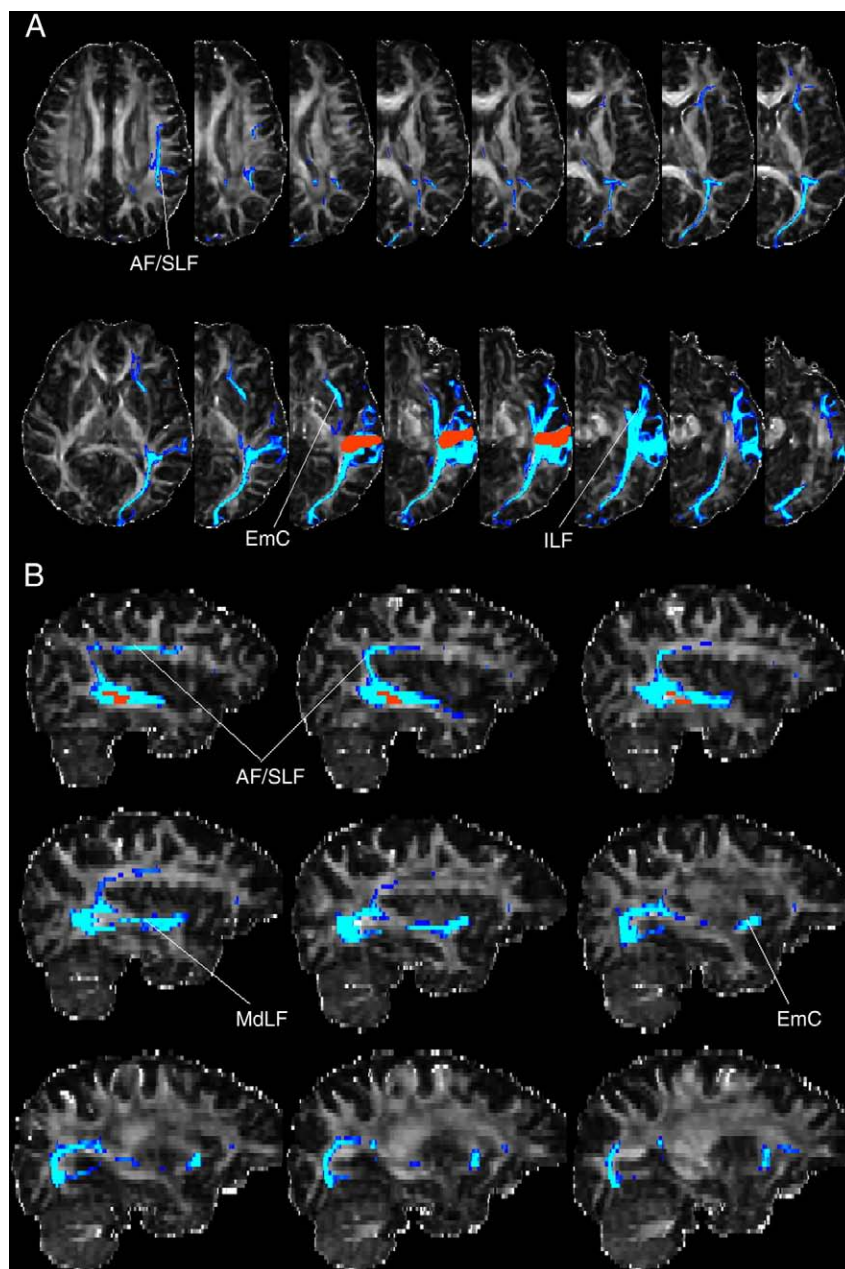
temporal gyrus (BA 22) were identified on  $b_0$  images and FA maps. At a frontal level, the pars opercularis and triangularis of the inferior frontal gyrus (F3op-BA44 and F3tri-BA45) was identified, as well as the supramarginal gyrus in the parietal lobe. For all these sites, seed masks were identified and positioned in the white matter from axial views; a rim of gray matter was included in the mask, in order to ensure contact of the cortical seed regions with white matter. An exclusion mask at the midline level on a sagittal plane was used to restrict the pathways to the hemisphere ipsilateral to the seed mask, so all streamlines from the seed region that intersected with the exclusion mask were discarded. Waypoints masks at the level of external-extreme capsule were also used, in order to include from the calculation of the connectivity distribution only tracts that pass through all these masks. The same masks were identified and positioned on control scans, to verify the presence of the described pathways also in healthy subjects.

### Statistical analyses

Due to surgical constraints, patients were stimulated a varying number of times at different sites, for either living or non-living objects or both. As a consequence, for each site the comparison between responses for living and non-living stimuli involved repeated observations of the patients, with occurrences of missing values. To test the effect of the type of stimuli (living versus non-living) on response interference we used a series of logistic regression models in which the presence of interference (normal response versus disrupted response) was the dependent variable and the type of stimuli was the independent variable. Due to the statistical dependency of responses and missing values, the logistic regression parameters and the associated inferential tests were obtained with GEE methodology (Zeger and Liang, 1986), implemented by the SAS system. In view of the limited number of patients and observations per patient, an exchangeable working correlation matrix was used to model the dependency of observations. Following the GEE methodology (Zeger and Liang, 1986), we employed the z-test to obtain inferential p-values. All p-values were evaluated as 2-tailed tests. Estimates were also obtained using an alternating logistic regression algorithm (Carey et al., 1993), obtained by specifying an exchangeable log odds ratio error structure. Results were practically identical to the ones reported in the text. The error pattern analysis was conducted by considering only the disrupted responses, regardless of



**Fig. 1.** Tractography reconstructions superimposed on axial T1-weighted images (A) and visualized in three-dimensional view (B) of two direct connections between BA 21 area and BA 45 and between BA 22 area and BA40 in left hemisphere: a pathway passing through the extreme capsule (magenta) and a pathway passing through the arcuate fasciculus (blue). Seed ROI for deterministic tractography at the level of stimulation area is shown in (A) (white line) and (C) (white asterisk). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)



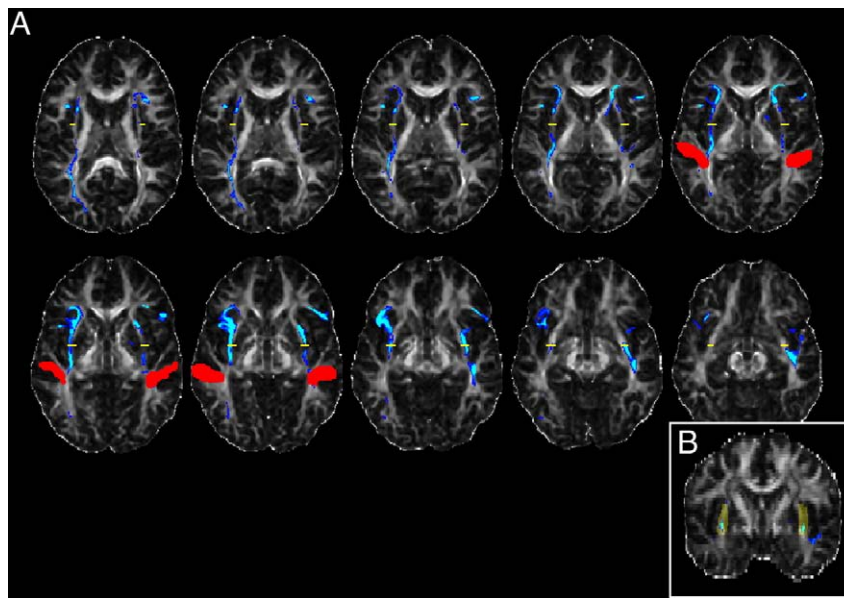
**Fig. 2.** Probabilistic tractography of connections starting from temporal seeding masks (A, red) in the same patient of Fig. 1, superimposed on axial (A) and sagittal (B) FA maps. Fibers from the posterior part of the middle temporal gyrus were collected from the middle longitudinal fascicle (MdLF) before entering into the AF/SLF system in the posterior superior temporal lobe. From there, fibers arch around the caudal end of the Sylvian fissure and continue in the white matter of the rostral parietal lobe to the premotor cortex. A composite fiber bundle of MdLF and SLF/AF fibers constitutes the dorsal pathway for language. Fibers from the middle temporal gyrus are also connected via a ventral pathway running through the extreme capsule (EmC); starting from the posterior part of the middle temporal gyrus, fibers join the MdLF in anterior direction and then continue into the EmC. After entering into the frontal lobe, the EmC splits into two branches, an inferior branch running in the white matter on the floor of the orbital cortex, and a superior branch running in the white matter of the inferior frontal gyrus, which terminates at the pars triangularis. The EmC is the ventral association pathway connecting the middle temporal lobe with the ventrolateral prefrontal cortex. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the stimulus type. Disrupted responses were classified either as anomia (non-responses and latencies) or paraphasia (phonemic and semantic paraphasias). Pure “motor” blocks were excluded from the analysis. The estimate and the inferential test for the odds of non-response/hesitation over paraphasias was obtained, for each site, using the GEE method. Subcortical data were collected for four male right-handed patients for the white matter corresponding to the cortical sites BA 45 and BA 21 (139 stimulations, 78 for living stimuli and 61 for non-living stimuli) and SG-BA 40 and BA 22 (123 stimulation, 41 for living stimuli and 82 for non-living stimuli). Because the number of stimulations across participants was highly unbalanced, and the cross-tabulation of type of stimuli and type of response (disrupted versus normal) presented zero

count cells (for the fiber tracts under the cortical sites BA 45 and BA 21 there was no disruption for non-living items), data for each tract were analyzed using a logistic regression with exact conditional test (Mehta and Patel, 1995) for determining the effect of type of stimuli on the probability of disruption. The exact p-value obtained refers to the null hypothesis that disruption probabilities were equal for living and non-living stimuli.

## Results and discussion

Across all patients, 931 cortical sites were stimulated during a naming task; of these sites, 253 led to non-response, hesitation, or



**Fig. 3.** Probabilistic tractography in a control subject, superimposed on axial (A) FA maps, showing bilateral ventral BA 21–BA 45 connections. A waypoint mask placed at the level of external-extreme capsule (B, yellow area, coronal view) was used so that only ventral temporo-frontal tracts would be included from calculation of the connectivity distribution. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

phonemic or semantic paraphasias (see Appendix A). DES delivered to the posterior part of BA 21 and BA 45 led to greater difficulty in naming living objects ( $p = 0.035$  and  $p = 0.028$ , respectively), while DES applied over the posterior third of the supramarginal gyrus (BA 40) led to greater difficulty for non-living things ( $p = 0.036$ ). DES over the anterior part of BA 22 almost reached significance ( $p = 0.065$ ) with a disruption probability of 0.08 for living items but 0.39 for non-living items. The results were unchanged when only right-handed, left language-dominant patients were considered (see Appendix B). The areas associated with category-specific naming difficulties revealed by DES in this study are different from those typically associated with the processing of animate and inanimate objects shown by other neuropsychological and neuroimaging methods, although this dissociation has not been consistently and unequivocally demonstrated in the human brain [see (Gainotti, 2000) for a review]. In addition, reorganization presumably varies between individuals given their different tumor location and the rate of growth. Therefore, we selected right-handed patients with the same type of lesion, namely an oligodendroglioma type II (LGG) with a similar location in the left hemisphere. Nine patients with these characteristics were found: the tumor involved the anterior and middle portion of the second and third temporal gyri in five patients; the posterior part of the inferior frontal gyrus in two; and the supramarginal gyrus (BA 40) in the remaining two. In the five temporal patient's stimulation over the anterior part of BA 22 produced 9.1% of disruption on living categories and 50% of disruptions for non-living items. On the contrary, stimulation of BA 21 produced 100% of disruption for living and 0 for non-living items. In the case of frontal lesions, DES applied over BA 45 caused 37.5% of errors for living things and no errors for non-living items. In parietal patients, DES over the posterior part of the supramarginal gyrus produced 87.5% of errors (more specifically, semantic paraphasias) for non-living items and no disruption for living things (see Table 5). The limited number of cases prevents any further statistical analysis, but confirms the trend observed with the whole sample.

After identifying relevant cortical sites of dissociation, we stimulated subcortical sites in order to further investigate whether the cortical areas differentially involved in lexical retrieval of living and non-living things are part of distinct networks that are connected by subcortical fibers. During surgery, we used a neuronavigational system and

preoperative MR scans to record the location of each subcortical site at each phase of resection. At the subcortical white matter level of BA 45 and BA 21 no disruption was found for non-living items, while there were 27.3% errors for living items (exact  $p < 0.001$ ); for subcortical sites at the level of BA 39/40 and BA 22, naming of non-living objects was severely impaired (41.5%) relative to living objects (9.7%; exact  $p < 0.001$ ). When we considered separately the two right-handed patients with a left temporal LGG, we observed the same trend (see Table 6).

To substantiate this finding, we used diffusion tensor deterministic tractography in the five temporal patients. We used two-point regions-of-interest (ROI) approach and defined ROIs around areas of white matter that all the fibers of each tract must pass through in order to reach their cortical or subcortical endpoints (Catani et al., 2002; Jones, 2008). Seed ROIs for tractography were placed on pre-operative scans of stimulation sites at the subcortical white matter level of BA 21 and BA 45, as well as the anterior part of BA 22 and BA 40. Using this approach, we detected two different connection pathways (see Fig. 1).

The first pathway between BA 21 and BA 45 moved (by convention since tractography cannot distinguish the direction of connections) from the posterior part of the middle temporal gyrus medially and anteriorly towards the external and extreme capsules where it descended into a first tract and then continued upwards, arching around the anterior gyri of the insula and moving downward into the white matter of the frontal operculum towards BA 45. The second course of streamlines connecting the anterior part of BA 22 to BA 39/40 was more variable; it moved medially and posteriorly from the superior temporal gyrus and running upwards and laterally to the temporo-parietal junction into the white matter of the inferior parietal lobule. These fibers appeared to be part of the indirect tract of the arcuate fasciculus.

To confirm data obtained with deterministic tractography, we used diffusion tensor probabilistic tractography. Seed masks for tractography were placed on pre-operative scans of the five patients in correspondence with the stimulation sites previously recorded on the neuronavigational system (see Fig. 2).

For the living objects, seeding masks were identified and positioned in the posterior part of the middle temporal gyrus (BA 21), and termination masks were placed in the pars opercularis (BA 44) and triangularis (BA 45) of the inferior frontal gyrus.

Long-distance association fibers connecting these sites were identified as part of a dorsal route along the arcuate fasciculus/superior longitudinal fasciculus system (AF/SLF) and a ventral pathway moving from the posterior part of the middle temporal gyrus medially and anteriorly towards the extreme capsule (EmC), from which fibers continue towards BA 44/45. This ventral pathway connecting the middle temporal gyrus with the ventrolateral prefrontal cortex receives fibers from two temporal association tracts: the middle longitudinal fasciculus (MdLF) and the inferior longitudinal fasciculus (ILF). These projections followed a pathway which is consistent with that of the extreme capsule system, originally shown in the macaque monkey by *Petrides and Pandya (1988)* and recently described by tractography in the human brain (*Frey et al., 2008; Saur et al., 2008*).

In the case of the sites whose stimulation disrupted non-living things, seeding masks were identified and positioned in the middle part of the superior temporal gyrus (BA 22), and termination masks were placed in the supramarginal gyrus (BA 40). Association fibers connecting these stimulation sites were more variable, moving upwards from the superior temporal gyrus to the temporo-parietal junction into the white matter of the inferior parietal lobule. Extensive white matter connections from the inferior parietal lobe to the superior temporal lobe in the left hemisphere of the human brain were also found by *Catani et al. (2005)*.

To verify the presence of the described pathways in healthy subjects, the temporal and frontal masks (BA 21 and BA44/45) for the pathways subserving naming of living items and the temporal and parietal masks (BA 22 and BA 40) for the pathways subserving naming of non-living entities were also identified and positioned on five control scans (see *Fig. 3*). Crucially, two distinct connection pathways between BA 21 and BA 45 with the same dorsal and ventral course previously described were identified in all subjects, confirming the existence of the two probable connections also in healthy controls. In all subjects the BA 45/BA 21 connection was found bilaterally. For the pathways subserving naming of non-living entities, the most probable connections between BA 22 and BA 40 were part of the indirect branch of the arcuate fasciculus.

## Conclusions

The results reported here provide the first direct evidence for the role of subcortical connections in defining the neural circuits involved in processing lexical-conceptual categories. We do not argue that these are the only circuits involved in such processing or that these pathways are exclusively involved in category-specific naming. For example, we collapsed across animal and plant life because of the small number of observations that could be made with each patient, even though it is known that these categories can be damaged independently of each other (*Crutch and Warrington, 2003; Samson and Pillon, 2003*) and presumably involve partially different neural circuits. Crucially, an important implication of the results reported here concerns the role of subcortical connectivity in shaping cortical reorganization following sustained perturbation of normal function. The domain-specific cortical networks identified through DES in these patients probably reflect the reorganization of cortical regions due to slowly evolving brain damage. Importantly, these new cortical regions are strategically located so as to be able to exploit subcortical tracts in order to recreate frontal–temporal–parietal domain-specific networks.

## Acknowledgments

We thank Joanna Willms for the editorial assistance. Preparation of this manuscript was supported in part by a grant from the Fondazione Cassa di Risparmio di Trento e Rovereto.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at doi:10.1016/j.neuroimage.2011.01.005.

## References

- Basso, A., Capitani, E., Laiacona, M., 1987. Raven's coloured progressive matrices: normative values on 305 normal adults controls. *Funct. Neurol.* 2, 189–194.
- Behrens, T., et al., 2003. Characterization and propagation of uncertainty in diffusion-weighted MR Imaging. *Magn. Reson. Med.* 50, 1077–1088.
- Behrens, T., Berg, H., Jbabdi, S., Rushworth, M., Woolrich, M., 2007. Probabilistic diffusion tractography with multiple fiber orientations: what can we gain? *Neuroimage* 34, 144–155.
- Bello, L., et al., 2008. Motor and language DTI fiber tracking combined with intraoperative subcortical mapping for surgical removal of gliomas. *Neuroimage* 39, 369–382.
- Bertolani, L., De Renzi, E., Faglioni, P., 1993. Test di memoria non verbale di impiego diagnostico in clinica: taratura su soggetti normali. *Arch. Psicol. Neurol. Psichiatr.* 54, 477–486.
- Capitani, E., Laiacona, M., Ciceri, E., 1991. Sex differences in spatial memory: a reanalysis of block tapping long-term memory according to the short-term memory level. *Ital. J. Neurol. Sci.* 12, 461–466.
- Capitani, E., Laiacona, M., Mahon, B., Caramazza, A., 2003. What are the facts of semantic category-specific deficits? A critical review of the clinical evidence. *Cogn. Neuropsychol.* 20, 213–261.
- Caramazza, A., Shelton, J., 1998. Domain-specific knowledge systems in the brain: the animate-inanimate distinction. *J. Cogn. Neurosci.* 10, 1–34.
- Carey, V., Zeger, S., Diggle, P., 1993. Modelling multivariate binary data with alternating logistic regressions. *Biometrika* 80, 517–526.
- Catani, M., Howard, R., Pajevic, S., Jones, D., 2002. Virtual in vivo interactive dissection of white matter fasciculi in the human brain. *Neuroimage* 17, 77–94.
- Catani, M., Jones, D., Ffichte, D., 2005. Perysilvian language networks of the human brain. *Ann. Neurol.* 57, 8–16.
- Crepaldi, D., et al., 2006. Noun/verb dissociation in aphasia: the role of imageability and functional locus of the lesion. *Neuropsychologia* 44, 73–89.
- Crutch, S., Warrington, E., 2003. The selective impairment of fruit and vegetable knowledge: a multiple processing channels account of fine-grain category specificity. *Cogn. Neuropsychol.* 20, 355–372.
- Damasio, H., Grabowski, T., Tranel, D., Hichwa, R., Damasio, A., 1996. A neural basis for lexical retrieval. *Nature* 380, 499–505.
- De Renzi, E., Faglioni, P., 1978. Normative data and screening power of a shortened version of the token test. *Cortex* 14, 41–49.
- Frey, S., Campbell, J., Pike, G., Petrides, M., 2008. Dissociating the human language pathways with high angular resolution diffusion fiber tractography. *J. Neurosci.* 28, 11435–11444.
- Gainotti, G., 2000. What the locus of brain lesion tells us about the nature of the cognitive defect underlying category-specific disorders: a review. *Cortex* 36, 539–559.
- Giovagnoli, A., et al., 1996. Trail making test: normative values from 287 normal adult controls. *Ital. Neurol. Sci.* 17, 305–309.
- Hillis, A., Caramazza, A., 1991. Category-specific naming and comprehension impairment: a double dissociation. *Brain* 114, 2081–2094.
- Jones, D., 2008. Studying connections in the living human brain with diffusion MRI. *Cortex* 44, 936–952.
- Kech, T., et al., 2008. Massive restructuring of neuronal circuits during functional reorganization of adult visual cortex. *Nat. Neurosci.* 11, 1162–1167.
- Kreiman, G., Koch, C., Fried, I., 2000. Category-specific visual responses of single neurons in the human medial temporal lobe. *Nat. Neurosci.* 3, 946–953.
- Kriegeskorte, N., et al., 2008. Matching categorical object representations in inferior temporal cortex of man and monkey. *Neuron* 60, 1126–1141.
- Kujala, T., Alho, K., Naatanen, R., 2000. Cross-modal reorganization of human cortical functions. *Trends Neurosci.* 23, 115–120.
- Lambon Ralph, M.A., Lowe, C., Rogers, T.T., 2007. Neural basis of category-specific semantic deficits for living things: evidence from semantic dementia, HSVE and a neural network model. *Brain* 130, 1127–1137.
- Lüders, H., Lesser, R.P., Dinner, D.S., Morris, H.H., Wyllie, E., Godoy, J., 1988. Localization of cortical function: new information from extraoperative monitoring of patients with epilepsy. *Epilepsia* 29, S56–S65.
- Mahon, B., Caramazza, A., 2009. Concepts and categories: a cognitive neuropsychological perspective. *Annu. Rev. Psychol.* 60, 27–51.
- Mahon, B., Anzellotti, S., Schwarzbach, J., Zampini, M., Caramazza, A., 2009. Category-specific organization in the human brain does not require visual experience. *Neuron* 63, 397–405.
- Martin, A., 2007. The representation of object concepts in the brain. *Annu. Rev. Psychol.* 58, 25–45.
- Martin, A., Wiggs, C., Ungerleider, L., Haxby, J., 1996. Neural correlates of category specific knowledge. *Nature* 379, 649–652.
- Mehta, C., Patel, N., 1995. Exact logistic regression: theory and examples. *Stat. Med.* 14, 2143–2160.
- Miceli, G., Capasso, R., Laudanna, A., Burani, C., 1994. Batteria per l'analisi dei deficit afasici. CEPSAG, Roma.
- Mori, S., Crain, B., Chacko, V., van Zijl, P., 1999. Three dimensional tracking of axonal projections in the brain by magnetic resonance imaging. *Ann. Neurol.* 45, 265–269.

- Neville, H., Bavelier, D., 2008. Human brain plasticity: evidence from sensory deprivation and altered language experience. *Prog. Brain Res.* 138, 177–188.
- Novelli, G., et al., 1986a. Tre test clinici di memoria a lungo termine verbale: Taratura su soggetti normali (Three clinical tests of verbal long-term memory: standardization on normal subjects). *Arch. Psicol. Neurol. Psichiatr.* 47, 278–295.
- Novelli, G., et al., 1986b. Tre test clinici di ricerca e produzione lessicale: Taratura su soggetti normali (Three clinical tests of lexical search and production: standardization on normal subjects). *Arch. Psicol. Neurol. Psichiatr.* 47, 477–505.
- Ojemann, G., Ojemann, J., Lettich, E., Berger, M., 1989. Cortical language localization in left, dominant hemisphere: an electrical stimulation mapping investigation in 117 patients. *Neurosurgery* 71, 316–326.
- Oldfield, R., 1971. The assessment and analysis of handedness: the Edinburgh inventory. *Neuropsychologia* 9, 97–113.
- Orsini, A., et al., 1987. Verbal and spatial immediate memory span: normative data from 1355 adults and 1112 children. *Ital. J. Neurol. Sci.* 8, 539–548.
- Parisi, D., Pizzamiglio, L., 1970. Syntactic comprehension in aphasia. *Cortex* 6, 204–215.
- Petrides, M., Pandya, D., 1988. Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *J. Comp. Neurol.* 273, 52–66.
- Quiroga, R., Reddy, L., Kreiman, G., Koch, C., Fried, I., 2005. Invariant visual representation by single neurons in the human brain. *Nature* 435, 1102–1107.
- Riesenhuber, M., 2007. Appearance isn't everything: news on object representation in cortex. *Neuron* 55, 341–344.
- Rizzo, S., Venneri, A., Papagno, C., 2002. Famous face recognition and naming test: a normative study. *Neurol. Sci.* 23, 153–159.
- Rogers, T., Hocking, J., Mechelli, A., Patterson, K., Price, C., 2005. Fusiform activation to animals is driven by the process, not the stimulus. *J. Cogn. Neurosci.* 17, 434–445.
- Ronchi, R., Posteraro, L., Fortis, P., Bricolo, E., Vallar, G., 2009. Perseveration in left spatial neglect; drawing and cancellation tasks. *Cortex* 45, 300–312.
- Samson, D., Pillon, A., 2003. A case of impaired knowledge for fruit and vegetables. *Cogn. Neuropsychol.* 20, 373–400.
- Sartori, G., Job, R., 1988. The oyster with four legs: a neuropsychological study on the interaction of visual and semantic information. *Cogn. Neuropsychol.* 5, 105–132.
- Saur, D., et al., 2008. Ventral and dorsal pathways for language. *Proc. Natl Acad. Sci. USA* 105, 18035–18040.
- Spinnler, H., Tognoni, G., 1987. Standardizzazione e taratura italiana di test neuropsicologici (Italian standardization of neuropsychological tests). *Ital. J. Neurol. Sci. (suppl. 8)*.
- Thiel, A., et al., 2001. Plasticity of language networks in patients with brain tumors: a positron emission tomography activation study. *Ann. Neurol.* 50, 620–629.
- Thomas, C., et al., 2009. Reduced structural connectivity in ventral visual cortex in congenital prosopagnosia. *Nat. Neurosci.* 12, 29–31.
- Tranel, D., Damasio, H., Damasio, A., 1997. A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia* 35, 1319–1327.
- Tyler, L., Moss, H., 2001. Towards a distributed account of conceptual knowledge. *Trends Cogn. Sci.* 5, 244–252.
- Warrington, E., Shallice, T., 1984. Category-specific semantic impairment. *Brain* 110, 1273–1296.
- Wong, S., et al., 2009. Cortical reorganization following anterior temporal lobectomy in patients with temporal lobe epilepsy. *Neurology* 63, 518–525.
- Zeger, S., Liang, K., 1986. Longitudinal data analysis using generalized linear models. *Biometrika* 73, 13–22.