Generating animal and tool names: An fMRI study of effective connectivity

Paolo Vitali[a,b,*], Jubin Abutalebi[c], Marco Tettamanti[a], James Rowe[d], Paola Scifo[a], Ferruccio Fazio[a,e,f], Stefano F. Cappa[a,c,e], Daniela Perani[a,c,e]

[a] *Scientific Institute San Raffaele, Milan, Italy*
[b] *Université de Montréal and Institut Universitaire de Gériatrie de Montréal, Que., Canada*
[c] *Vita Salute San Raffaele University, Milan, Italy & Interdisciplinary Center for Cognitive Studies, University of Potsdam, Potsdam, Germany*
[d] *Wellcome Department of Imaging Neuroscience, London, UK*
[e] *Institute of Bioimaging and Molecular Physiology-CNR, Milan, Italy*
[f] *Università di Milano-Bicocca, Milan, Italy*

Abstract

The present fMRI study of semantic fluency for animal and tool names provides further evidence for category-specific brain activations, and reports task-related changes in effective connectivity among defined cerebral regions. Two partially segregated systems of functional integration were highlighted: the tool condition was associated with an enhancement of connectivity within left hemispheric regions, including the inferior prefrontal and premotor cortex, the inferior parietal lobule and the temporo-occipital junction; the animal condition was associated with greater coupling among left visual associative regions. These category-specific functional differences extend the evidence for anatomical specialization to lexical search tasks, and provide for the first time evidence of category-specific patterns of functional integration in word-retrieval.
© 2004 Elsevier Inc. All rights reserved.

Keywords: fMRI; Neuroimaging; Effective connectivity; Functional integration; Psychophysiological interaction; Semantic memory; Semantic fluency; Semantic categories; Living and non-living; Tools and animals

1. Introduction

Disorders of identification and/or naming, which display selectivity for a specific category of entities, such as animals or people, have been repeatedly described in patients with brain damage, and may be expected to contribute to the understanding of the organization of conceptual knowledge and of its neurological substrate.

At the cognitive level of analysis, several models have attempted to account for category-specific disorders (see Caramazza & Shelton, 1998; Forde & Humphreys, 1999;

Tyler & Moss, 2001 for extensive reviews). Broadly summarising, there are two classes of models.

The "reductionist" class of interpretations proposes that category-specific impairments emerge because of the peculiar processing demands of, respectively, living and non-living entities. The multiple-semantic systems hypothesis (Warrington & McCarthy, 1987; Warrington & Shallice, 1984) and its computational variant (Farah & McClelland, 1991) are both based on the hypothesis that the identification of living and non-living entities depends on specific features, referring to perceptual/visual aspects (e.g., "has small ears"), or to functional properties (e.g., "can cut paper"). Perceptual/visual features are considered to play a crucial role for the representation of living entities, whereas functional-associative features

---
* Corresponding author. Fax: +39 02 21717558.
E-mail address: vitali.paolo@hsr.it (P. Vitali).

are more important in the representation of non-living entities. According to one of the most popular versions of this view, category specific impairments then emerge when the visual, or, respectively, the verbal semantic system are selectively affected (McCarthy & Warrington, 1988; Warrington & Shallice, 1984). It has also been suggested that perceptual features are particularly vulnerable to the effects of brain damage, thus explaining why deficits for living entities are more frequently observed.

An alternative reductionist account has been proposed by Tyler and Moss (2001), on the basis of a connectionist model of conceptual structure. These authors propose a unitary, distributed system, in which concepts are defined in terms of properties with different degrees of intercorrelation. The specific prediction of this model is that severity of brain damage is a major determinant of category specificity. Mild disorders should be associated with living impairments, while non-living impairments should be observed only with diffuse, severe damage. Additional predictions include the presence of graded effects, and interaction with task demands, with more severe impairment in tasks associated with the retrieval of distinctive, rather than shared, features (Tyler & Moss, 2001).

According to the second class of interpretations, category-specific semantic disorders reflect a genuine segregation of knowledge pertaining to different entities. Caramazza and Shelton have proposed a 'domain-specific knowledge' hypothesis, essentially based on the theory that evolutionary pressures have resulted in specialized mechanism for perceptually and conceptually distinguishing living and non-living entities, leading to a 'separated' categorical organization of the corresponding knowledge in the brain (1998). A selective dysfunction of one of these domain-specific knowledge systems might result in a selective category-specific impairment.

At the neurological level, it has been proposed, on the basis of lesion location evidence, that category-specific disorders might be associated with different lesion sites in the brain. As underscored by Gainotti (2000), the models discussed above are associated with a different set of predictions about the underlying neurological substrates. In particular, the sensory-functional account predicts that damage to high-order visual processing areas should be associated with an impairment of living entities. Models based on feature intercorrelations emphasize the importance of the extent of brain damage. On the other hand, the domain-specific hypothesis suggests a link between damage to evolutionary salient categories and limbic area involvement. Patients with bilateral inferomedial temporal lobe damage secondary to herpes simplex virus encephalitis often show a significant impairment for living entities. In Gainotti's detailed review (2000), bilateral damage to the antero-mesial and inferior temporal lobes was consistently associated with semantic impairments for living entities, whereas a selective lexical disorder for the plant category was found in patients with unilateral damage to the left infero-mesial temporo-occipital areas. Tranel, Damasio, and Damasio (1997) found that defective knowledge about animals was associated with medial occipito-temporal lesions, more extensive on the right. In the case of impaired performance for non-living entities, the most frequently described lesions were in the left hemisphere, usually involving the perisylvian areas (Saffran & Schwartz, 1994).

A more direct method to investigate the correlates of categorical semantic knowledge has been provided in recent years by functional neuroimaging in normal subjects. Perani et al. (1995) using a visual picture-matching task, have shown for the first time different locations of brain activation according to the semantic category (animals vs. tools). Animal identification was associated with activations in the inferior temporo-occipital areas, bilaterally. On the other hand, the identification of non-living entities engaged the activation of a predominantly left hemispheric network involving the left dorsolateral frontal cortex, and the left middle temporal gyrus (Perani et al., 1995, 1999). Soon afterwards, activations in separate locations were observed during naming of pictures of animals and tools. In particular, greater activation for non-living entities than for living entities was found in left temporal or temporo-parietal areas (Damasio, Grabowski, Tranel, Hitchwa, & Damasio, 1996; Martin, Wiggs, Ungerleider, & Huxby, 1996) and also in a left inferior frontal area (Grabowski, Damasio, & Damasio, 1998; Martin et al., 1996). In general, these category-specific effects appear to represent differential profiles of activation, rather than all-or-none activation differences. It has been suggested that they reflect the retrieval of category-specific features and attributes (Chao, Weisberg, & Martin, 2002). In particular, the activation in the left inferior frontal gyrus and middle temporal gyrus repeatedly observed for tools is considered to reflect the retrieval of action knowledge related to tool motion and/or manipulation (Beauchamp, Lee, Haxby, & Martin, 2002; Martin et al., 1996; Perani et al., 1995; Phillips, Noppeney, Humphreys, & Price, 2002).

There is also evidence that the type of task interacts with semantic category effects in determining the pattern of brain activation. Most of the studies summarized above involved matching or naming of picture stimuli. Word generation in response to a semantic cue (semantic verbal fluency) is a widely used task in brain imaging research, which can be expected to be sensitive to semantic variables. While the anterior part of the left inferior prefrontal cortex seems to be related to the executive/strategic requirements of lexical search, the comparison of phonological with semantic fluency indicated that the latter task is more dependent from the left temporal regions (Paulesu et al., 1997). Similar results have been reported, contrasting semantic with phonological decision, by Gold and Buckner (2002). In a PET study

contrasting the generation of names of natural kinds with man-made objects (Mummery, Patterson, Hodges, & Wise, 1996), bilateral anteromedial temporal right parietal activations were associated with the former task, left posterior temporal for the latter.

The studies mentioned above have investigated the brain correlates of different semantic categories from the point of view of functional specialisation of different areas. A complementary approach is provided by the investigation of the effective connectivity among cerebral areas (functional integration: see Friston, 2002). Mechelli, Price, Noppeney, and Friston (2003) have recently reported the first attempt to explore the neural interactions that mediate the category effects in the left occipital and temporal cortex. Using the newly developed analytical technique Dynamic Causal Modeling (DCM), they have shown that the category effects of picture stimuli of houses, faces, and chairs in the occipital and temporal cortex were associated with greater connectivity from left early visual cortex, rather than from left superior/inferior parietal area. The authors have concluded that the depicted category effects could be mediated, at least partially, by bottom-up mechanisms. However, the nature of the experimental task (passive viewing of pictures and delayed match-to-sample task)—exalting the visual features of the stimuli—, and the restriction of the connectivity analysis to the posterior regions of the brain could not exclude top-down influences during semantic processing, especially from the left prefrontal regions, which may be involved in semantic retrieval (Noppeney & Price, 2002). In the present study, we have extended the analysis of the functional integration subserving category-specific effects to the retrieval of lexical items denoting entities of different semantic categories. We have used fMRI to investigate the brain functional correlates of animal and tool category fluencies, and we have subsequently performed a Structural Equation Modelling (SEM) analysis of fMRI time-series to evaluate the inter-regional covariance and the task-related changes in coupling among brain areas activated in the two semantic tasks. This was aimed to verify a possible modulation of the connection strengths between cerebral regions in semantic conditions requiring word retrieval. Additionally, a psychophysiological interaction analysis was carried out to further investigate the cortical interactions depending on the semantic context during semantic fluency.

2. Materials and methods

2.1. Subjects

The experimental subjects were 10 right-handed male volunteers, who gave written informed consent prior to the experiment. All subjects had no history of neurolog-

ical or psychiatric disorders. Right-handedness was verified using the Edinburgh Inventory (Oldfield, 1971). The experimental protocol has been approved by the local hospital Ethics Committee.

2.2. Experimental design

Blood oxygenation level measurements were collected in one single frame of 120 consecutive, T2* weighted fMRI multislice scans, during which subjects alternated for three times between a rest condition, where they were instructed to empty the mind and to avoid inner speech, and one of the following semantic verbal fluency conditions:

(a) Semantic verbal fluency, animal category: subjects were instructed to generate covertly as many common nouns belonging to the 'animal' category as possible, during all the task duration (30 s × 3 times).
(b) Semantic verbal fluency, tool category: subjects were instructed to generate covertly as many common nouns belonging to the 'tool' category as possible, during all the task duration (30 s × 3 times).

The block design was the following:

(a) Rest—Animals1—Rest—Animals2—Rest—Animals3.
(b) Rest—Tools1—Rest—Tools2—Rest—Tools3.

A total of 12 epochs, each epoch lasting 30 s and including 10 scans, were performed.

Subjects were trained in the different tasks before positioning on the magnet cradle. Instructions were then recalled by the examiner at the beginning of each task-epoch, by saying aloud a fixed cue (e.g. 'animals' for task A, 'tools' for task B). After total scan acquisition, subjects were asked to recall the list of words generated during each scan epoch and items were recorded by the examiner.

2.3. Scanning procedures

MRI scans were performed on a 1.5 T General Electric Signa Horizon System (GE, Milwaukee, WI, USA), equipped with Echo-speed gradient coils and amplifier hardware, using standard quadrature head-coil. Scout spin-echo sagittal scans were acquired to visualize the anterior and posterior commissures on a midline sagittal section and to facilitate data acquisition roughly along the bicommissural plane. Prior to fMRI data collection, a structural spin-echo data set matched to the fMRI images was acquired in order to facilitate subsequent stereotactic normalization with SPM software of the MRI images. Field homogeneity was adjusted by means of 'global shimming' for each subject.

The acquisition of the functional images was performed with Gradient Echo Echoplanar pulse sequence (TE = 60 ms, TR = 3000 ms). Nineteen 4 mm-thick slices volumes (FOV = 280 × 280 mm, matrix 64 × 64) were acquired. Acquisition occurred in a single scan of 120 volumes with a total acquisition time of 6′ 30″ (the first 30″ being discarded from the analysis to allow steady state magnetisation).

2.4. Data analysis

After image reconstruction, raw-data visualization and pre-processing were performed with ANALYZE 7.5 (BRU, Mayo Foundation, Rochester, MN, USA). All subsequent data analysis was performed in MAT-LAB 5.3 (Math Works, Natick, MA, USA) using Statistical Parametric Mapping software (SPM-99, Wellcome Department of Cognitive Neurology, London, UK).

The fMRI scans were subdivided into two groups according to the two experimental conditions and their corresponding rest and then each group was realigned separately; all scans were then normalized into the standard stereotactic space implemented in SPM-99 software (Montreal Neurological Institute template), to allow inter-subject data averaging and comparison across tasks. The normalization parameters were taken from the realigned functional images. At this stage the data matrix was interpolated to produce voxels of dimensions 2 × 2 × 4. After stereotactic normalization, the common stereotactic space for the experimental subjects covered planes from −20 to +56 mm according to the bicommissural plane.

All the stereotactically normalized scans were smoothed through a Gaussian filter of 10 × 10 × 10 mm to reduce anatomical differences among subjects and to improve signal to noise ratio. High-pass filtering was used to remove artefactual contribution to fMRI signal such as physiological noise from cardiac and respiratory cycles. Global differences in fMRI signal were co-varied out for all voxels.

2.5. SPM-99 statistical comparisons

We have used the implementation of the general linear model for fMRI data devised by Friston et al. (1995) for SPM-99. The experiment has been treated as a block design (types of fluency and rest). Comparisons of means have been made for all voxels by using the t statistic, thus generating statistical parametric maps of the t values SPM {t} that have been transformed to Z distribution maps. Simple main effects of the different fluencies (animals and tools) in comparison with their time-matched resting scans have been calculated. The threshold applied to the statistical maps was $p < .05$ (corrected for multiple comparisons). Additionally, differences between the two semantic fluencies have

been also calculated by the direct comparisons between conditions using the inclusive masking procedure in SPM-99. This eliminated voxels that were not significant at $p < .05$ in each contrast.

In the tools versus animals contrast, a hypothesis-driven analysis at the lowered statistical threshold of $p < .01$ (uncorrected) has been conducted in order to assess the involvement of premotor, inferior parietal and middle temporal regions.

Since only 10 subjects were involved in the study, it was not possible to contrast the size of the effects of interest in the standard SPM analysis against the variability of those effects over subjects (random effects approach). Consequently, a conjunction analysis of the individual effects of interest has been performed in order to verify if the activation in the areas we were most interested in was at least seen in all 10 subjects, even if inter-subject variance was not used as the denominator. This approach enables the generalisation of the results from subjects to the general population.

2.6. Structural equation modeling analysis

The influence one brain region has over another has been termed effective connectivity and it may be measured, among other tools, by SEM of fMRI data over time, within specified constraints based largely on consideration of anatomical connectivity of the brain. SEM is a statistical technique developed to represent and to estimate the causal relationships between quantitative variables (Bentler, 1988). SEM of fMRI time series estimates the effects of experimental manipulation on connectivity among brain regions within a specified anatomical model (Buchel & Friston, 1997).

The anatomical model we have identified for the estimation of effective connectivity included regions of interest (ROI) in the left hemisphere, representing the neural substrate involved in both semantic fluency tasks, as derived by simple main effects analysis in SPM-99 (see Tables 1–3): the dorsal lateral (Ba 45 and 46) and inferior frontal (Ba 47) cortex, the precentral gyrus (Ba 6), the inferior parietal cortex (Ba 40) and occipital and temporal visual associative regions (Ba 18, 19, and 37). To allow for task-related changes in coupling between brain regions, we have also included moderator variables that modulate how changing conditions alter the connectivity between two areas. We have attributed value "−1" to the "animal context" and value "+1" to the "tool context." The task covariates have been convolved by a canonical haemodynamic response function and multiplied by the activity (in terms of BOLD signal) in the source area to form the interaction or moderator variables. Residual variance for every variable within the model has been modelled by a reciprocal connection from each node to itself. Direct connections between variables within the model were unidirectional to ensure

Table 1
Location of regions of interest for SEM—coordinates and the F statistic for each region included in the structural equation model

Brain regions (Brodmann area)	X	Y	Z	F statistic
Precentral gyrus (Ba 6)	−28	2	52	13.63
Precentral gyrus (Ba 6)	−54	4	36	7.39
Inferior frontal gyrus (Ba 47)	−30	24	−4	12.23
Inferior frontal gyrus (Ba 45)	−48	28	16	9.03
Inferior frontal gyrus (Ba 46)	−44	32	12	8.60
Inferior parietal lobule (Ba 40)	−40	−60	44	5.38
Lateral fusiform gyrus (Ba 37)	−46	−56	−12	6.69
Medial fusiform gyrus (Ba 37)	−24	−48	−16	3.37
Temporo-occipital junction (Ba 37/19)	−42	−64	−8	9.56
Superior occipital gyrus (Ba 19)	−28	−80	24	5.75
Inferior occipital gyrus (Ba 18)	−32	−78	0	4.96

All regions were localized in the left hemisphere and were defined as 5 mm radius spheres. The maximum of each region was significant at $p < .001$ (uncorrected) in the group analysis SPM {F}. The principal component of the adjusted (for effects of interest) BOLD signal in every ROI was entered as a variable into the model for the analysis of effective connectivity. Noteworthy, these areas included voxels that showed the contrast effect in all subjects (as revealed by the conjunction analysis in SPM-99).

Table 2
Simple main effect: tools vs. rest—coordinates and the Z statistic for brain regions showing greater activity during the tool condition in comparison with rest

Brain regions—Brodmann area	X	Y	Z	Z-score
Left				
Precentral gyrus Ba 6	−28	2	52	11.9
	−54	4	36	10
Inferior/middle frontal gyrus Ba 46	−44	32	12	11.4
Middle frontal gyrus Ba 9/45	−52	16	32	11.3
Middle frontal gyrus Ba 9	−38	18	28	11
Middle frontal gyrus Ba 46/10	−30	46	4	7.3
Insula/inferior frontal gyrus Ba 47	−30	24	−4	13.3
Inferior frontal gyrus Ba 45	−48	28	16	11.5
Inferior frontal gyrus Ba 47	−48	16	−8	7.3
Inferior frontal gyrus Ba 44	−52	12	12	7.1
Insula	−32	8	12	4.8
Inferior parietal lobule Ba 40	−30	−46	44	7.7
Middle temporal gyrus Ba 21	−44	−54	0	4.27
Lateral fusiform gyrus Ba 37	−46	−56	−12	8.3
Temporo-occipital junction Ba 37/19	−42	−64	−8	8.2
Middle occipital gyrus Ba 19	−36	−68	−4	9.1
Cuneus Ba 19	−24	−76	36	13.3
Cingulate cortex Ba 32	−8	18	44	8.0
Hippocampus	−16	−18	−12	6.5
Thalamus	−16	−12	4	7.3
Caudate nucleus	−12	20	16	7.0
Right				
Precentral gyrus Ba 6	28	−8	32	5.0
Superior frontal gyrus Ba 6	18	0	52	6.6
Middle frontal gyrus Ba 46	40	36	16	7.2
Inferior frontal gyrus Ba 47	40	24	−12	6.4
Insula	30	20	8	6.2
Cingulate cortex 24	14	30	24	9.1
Caudate nucleus	0	16	4	6.1

The contrast has been thresholded at $p < .05$ (corrected for multiple comparisons).

robust estimates. Since the task required subjects to generate words to a rule, rather than perceiving words presented to subjects, we have preferred to model for top-down fronto-temporal and fronto-parietal connections of influence, rather than for bottom-up occipito-frontal and parieto-frontal connections, giving thus the prefrontal and premotor regions a major role in lexical retrieval.

The structural model has been implemented by Lisrel 8.51 (Student Edition) (Joreskog & Sorbom, 2001) using an iterative maximum likelihood algorithm (Higham,

Table 3
Simple main effect: animals vs. rest—coordinates and the Z statistic for brain regions showing greater activity during the animal condition in comparison with rest

Brain regions—Brodmann area	X	Y	Z	Z-score
Left				
Precentral gyrus Ba 6	−40	−6	32	9.3
	−28	0	48	8.9
Superior frontal gyrus Ba 8/6	12	22	44	6.3
Middle frontal gyrus Ba 9/45	−40	20	28	9.5
Insula/inferior frontal gyrus Ba 47	−30	22	−4	11.9
Inferior frontal gyrus Ba 47	−40	36	0	9.3
Inferior frontal gyrus Ba 44	−40	6	24	8.2
Medial fusiform gyrus Ba 18/37	−38	−66	−8	7.3
Medial fusiform gyrus Ba 37	−24	−48	−16	5.6
Superior occipital gyrus Ba 19	−28	−80	24	6.2
Superior occipital gyrus Ba 19/7	−28	−58	32	5.5
Inferior occipital gyrus Ba 18	−32	−78	0	7.6
Precuneus Ba 7	−22	−76	44	9.2
Precuneus Ba 31/7	−26	−42	44	5.9
Cingulate cortex Ba 32/24	−6	10	36	8
Thalamus	−6	−24	4	5.5
Caudate nucleus	−16	−6	20	5.9
Right				
Middle frontal gyrus Ba 10	36	44	24	6.8
Inferior frontal gyrus Ba 45	40	36	16	8.5
Inferior frontal gyrus Ba 47	42	30	−8	6.8
Insula/inferior frontal gyrus Ba 47	30	20	−8	6.2
Retrosplenial cortex Ba 31/18	26	−54	8	5
Lingual gyrus Ba 19	24	−52	4	5.5
Cingulate cortex Ba 24	12	22	28	8.5
Thalamus	22	−20	16	6
Caudate nucleus	22	14	8	6.6
Putamen	24	10	4	6.5

The contrast has been threshold at $p < .05$ (corrected for multiple comparisons).

1993) to estimate the covariance that best predict the observed variance–covariance structure of the empirical data. Statistical inferences about the path coefficients were based on the comparison of a free model with a model constrained to zero for the interaction variable. The difference in goodness of fit between free and constrained models was expressed as chi-squared (χ^2 difference test or likelihood ratio test, with degrees of freedom determined by the number of constraints, namely 1; Bollen, 1989). Under the null hypothesis, that one area has the same influence over another during the two semantic tasks, the free and constrained models do not differ in goodness of fit. If the models produced a significantly better fit when the interaction terms were not constrained to zero, then these pathways were considered to explain a greater quota of variance in the target variable. A significant task-dependent modulation of coupling between two cerebral regions indicated that the two areas have coherently increased or decreased their neural activity during task execution, but it is not possible to point out if this greater connectivity was a sign of an excitatory or an inhibitory influence, at synaptic level, of one area upon the other.

Path coefficients were identified for every connection in the structural model. The significance of path coeffi-cients for the interaction terms was tested at two stages, first at a group level (i.e., first level fixed effects analysis) and then between subjects (i.e., second level analysis); this means that, first, an analysis of the chi-squared dif-ference value has been conducted for the grouped data from all the subjects (χ^2 difference threshold = 3.84, $df = 1$, $p < .05$). Successively, since the group-level path coefficients may not reflect the underlying path coeffi-cients in the individual subjects, we have tested for the significance of path coefficients at the individual subject level (i.e. running the SEM model separately for each subject to get 10 values for each path). Finally, a second level two-tailed one-sample t-test has been performed using the 10 individual subject path coefficients to make inferences at the population level (i.e. verifying that the population mean path coefficient has a significant non-zero value).

2.7. Psychophysiological interaction analysis

The concept of the psychophysiological interaction (PPI) refers to the idea of explaining and predicting vari-ations of activity in one cortical area (target) in terms of an interaction between the influence of a distal area (source) and some experimental (task-related) parame-

ter. This approach can be related to effective connectivity as measured by SEM, but, in this latter case, both source and target areas are specified according to prior anatomical knowledge and theoretical considerations, and, additionally, the effects from many possible sources of input can be modelled. By contrast, in PPIs the modelled effects derive from only one region (source area) and cognitive covariates, revealing potentially multiple target areas from the analysis. An exhaustive description of the PPI analysis, as implemented in SPM-99, can be found in Buchel and Friston (1997).

To further investigate the task-related modulator effects on connectivity within the cerebral network activated by the two semantic tasks, we have performed a SPM PPI analysis in a number of source regions to test the hypothesis that the semantic context (indicated by "−1" for animals and "+1" for tools) was able to predict a significant component of the activity in target areas. We have used the interaction term (or modulator variable, as previously indicated) as a regressor or explanatory variable and tested for the significance of the regression using a conventional SPM $\{Z\}$ analysis. Resulting SPM $\{Z\}$ maps assemble all voxels showing a significant regression with the interaction term.

We have explored for a significant psychopsysiological interaction with the activity in three reference locations (source areas): (1) *left lateral fusiform gyrus*, (2) *left medial fusiform gyrus* and (3) *left Ba 45* (for coordinates, see Table 1).

3. Results

3.1. Functional specialisation

3.1.1. Simple main effects in comparison to baseline

The patterns of brain activation for each fluency task (tools, animals), compared to rest, are shown in Fig. 1 and Tables 2 and 3. The patterns of brain activation observed during tool and animal fluency are quite similar, and involve an extensive activation of ventrolateral and dorsolateral prefrontal cortex, with a left-side prevalence.

Bilateral activations in associative visual regions, cingulate cortex and subcortical structures have been also observed for both categories. On the other hand, the left inferior parietal lobule, middle temporal and lateral fusiform gyri, cuneus, and hippocampus were engaged only by tool fluency, whereas the left medial fusiform gyrus and precuneus, only by animal fluency.

3.1.2. Direct comparisons

The direct comparison, masked with the appropriate simple main effect (animal/tool fluency versus rest), failed to show significant differences in the case of animal fluency versus tool fluency. For tool fluency versus animal fluency, there were several areas of increased activation

with prevalence in the left hemisphere (Table 4). These include bilateral prefrontal and premotor regions, and, on the left, the superior and middle temporal gyri, the inferior parietal lobule, and the lateral fusiform gyrus.

3.2. Functional integration

3.2.1. Structural equation modelling analysis

The significant group-level estimates (from the first level analysis) of the path coefficients relative to the interaction variables, defining the task-related influence of the source areas upon the target areas, are reported in Fig. 2. The asterisk indicates those values which were significant also in the second level *t*-test analysis including individual path coefficients. We show separately the significant changes in connectivity between regions during the covert production of tool (part a) and animal (part b) names. These values indicate the modulation of the basic connectivity between two anatomical regions, by the semantic tasks, and they represent the increasing covariance between the two brain areas under the defined experimental condition with respect to the other; a positive covariance is interpretable in terms of a greater coupling.

During tool condition, the second level analysis revealed a task-related enhancement of the effective connectivity in the left hemisphere, between regions in the dorsolateral frontal cortex (Brodmann Area (Ba) 45 and Ba 47), the premotor areas (Ba 6), the inferior parietal lobule (Ba 40) and the temporo-occipital junction (Ba 37/19); a specific increase of covariance between the inferior frontal gyrus (Ba 45) and the superior occipital gyrus (Ba 19) has been also observed; a more anterior component of the inferior frontal gyrus (Ba 46) showed a specific increase of covariance with the lateral fusiform gyrus (Ba 37) and the temporo-occipital junction (see Fig. 2A).

During animal condition, the second level analysis failed to show significant modulations of the regional connectivity by the task within the defined anatomical model. However, the SEM model incorporating all data from all subjects (the first level fixed effects analysis) revealed a significant pattern of connectivity which was specifically circumscribed to the left visual associative regions (lateral and medial fusiform gyri, superior and inferior occipital gyri), with a task-related enhancement of path-strengths among these regions; in addition, a specific increase in connectivity between the inferior frontal gyrus (Ba 45) and both the medial fusiform and the inferior occipital gyri has been observed (see Fig. 2B).

3.2.2. Psychophysiological interaction analysis

We report the results relative to the left hemisphere only. For the *left inferior frontal gyrus (Ba 45)* no voxels in the left hemisphere showed significant regression at
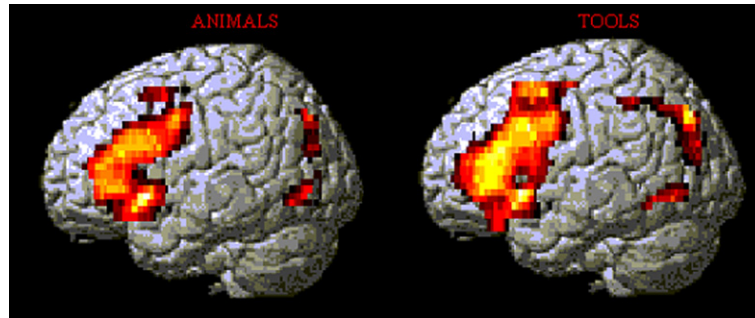
Fig. 1. Cortical areas illustrating simple main effects in the two semantic fluency tasks (see Tables 2 and 3 for stereotactic coordinates). For visual clarity the *t*-statistical maps corresponding to animal and tool fluency (corrected at *p* < .05) have been superimposed onto a rendering of a standardized MRI brain scan, as implemented in SPM-99.

Table 4
Direct comparison: tools vs. animals—coordinates and the *Z* statistic for brain regions showing greater activity during the tool condition in comparison with animals

Brain regions—Brodmann area	X	Y	Z	Z-score
Left				
Precentral gyrus Ba 6	−34	4	40	3.4
Superior frontal gyrus Ba 6 (pre-SMA)	−4	26	56	3.6
Middle frontal gyrus Ba 8	−10	30	48	3.8
Inferior frontal gyrus Ba 47	−46	34	−4	3.9
Inferior frontal gyrus Ba 45/46	−52	26	12	3.0
Inferior parietal lobule Ba 40	−40	−60	44	3.5
Superior temporal gyrus Ba 22	−50	0	8	3.3
Middle temporal gyrus Ba 21	−40	−62	0	3.1
Lateral fusiform gyrus Ba 37	−48	−56	−12	3.1
Superior occipital gyrus Ba 19	−36	−78	40	3.4
Precuneus Ba 7	−22	−76	40	3.4
Right				
Precentral gyrus Ba 6	30	−6	32	2.8
Superior frontal gyrus Ba 8/6	10	30	48	3.8
Middle frontal gyrus Ba 9	50	34	−12	3.9
Inferior frontal gyrus Ba 47	40	36	−8	4.5
Inferior parietal lobule Ba 39	30	−54	28	3.4
Middle temporal gyrus Ba 21	38	−52	8	2.9
Cingulate cortex Ba 31	22	−40	32	4.0
Cingulate cortex Ba 24/32	28	36	12	3.2
Cingulate cortex Ba 23	26	−26	28	2.8
Hippocampus	26	−30	−8	3.2

This contrast has been inclusively masked at *p* < .05 with the simple main effect: tools vs. rest, and thresholded at *p* < .01 (uncorrected).

the uncorrected threshold *p* < .001. However, significant regressions for animals and tools were present at a reduced threshold of *p* < .01 in cortical areas, which also showed an increased coupling with Ba 45 in the SEM analysis (see Table 5 and Figs. 3A and B).

For the *left lateral fusiform gyrus*, we found a significant regression with the activity in the left prefrontal and premotor cortex only during the retrieval of tool names. During animal condition, indeed, no voxels showed significant regression with activity in the left lateral fusiform gyrus (see Table 5 and Fig. 3C).

For the *left medial fusiform gyrus*, we found a significant regression in a number of voxels of the left temporal lobe and prefrontal areas only during animal condition (see Table 5 and Fig. 3D).

4. Discussion

The generation of words according to a cue is a complex task, which involves multiple cognitive processes, such as lexical search, lexical retrieval and speech production. A crucial aspect of the task is the type of cue priming the lexical search process. For example, in the case of initial letter (phonological) fluency, the characteristics of the search process, driven by the word form, are different from conditions in which a semantic cue is given (Martin, Wiggs, Lalonde, & Mack, 1994). Verbal fluency tasks have been extensively employed for language activation studies, and have been associated with a consistent pattern of activation, centred on the left lateral frontal cortex (Frith, Friston, Liddle, &
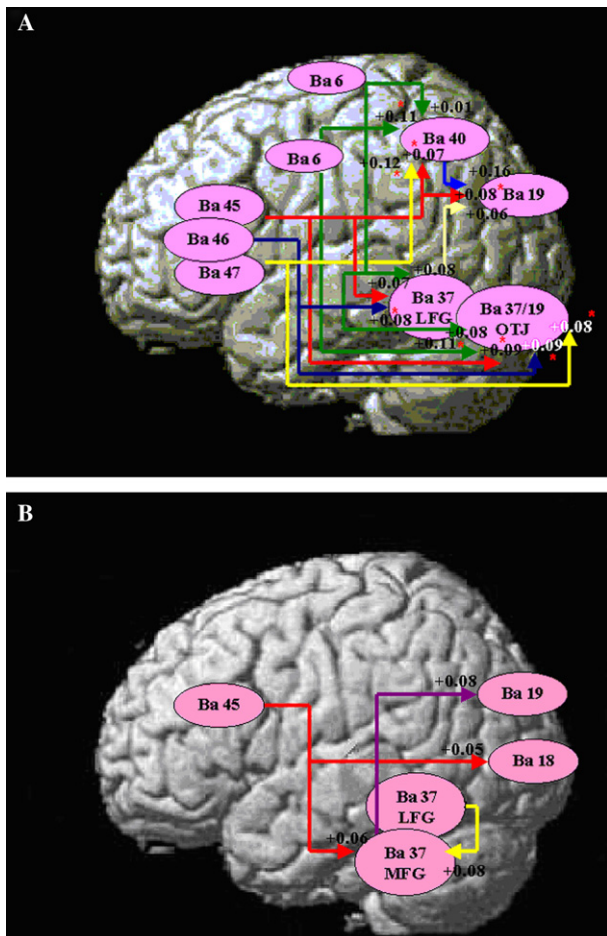
Fig. 2. Pattern of effective connectivity with modulation of path-strengths for tool (A) and animal (B) conditions. Modulations of effective connectivity between regions are illustrated with arrow lines of different colours. The medial fusiform gyrus is reported for illustration's sake on the lateral surface of the brain. Red asterisks indicate path-strength modulations significant also in the second level analysis (see text for details). Legend: Ba, Brodmann area; MFG, medial fusiform gyrus; LFG, lateral fusiform gyrus; OTJ, occipito-temporal junction.

Frackowiak, 1991; Petersen, Fox, Posner, Mintun, & Raichle, 1988; Poline et al., 1996). Further studies have attempted to delineate the specific features of brain activation according to the type of generation task. Anatomo-functional differences have been reported between phonemic verbal fluency (initial letter fluency) and semantic verbal fluency within the left frontal lobe (Mummery et al., 1996; Paulesu et al., 1997). Indeed, phonemic fluency has been reported to engage the left inferior frontal gyrus extensively, including the posterior frontal operculum (Ba 44). On the other hand, during semantic fluency there was a discrete activation of more anterior frontal regions (Ba 45 and 46).

The present study confirms that a common activation of the left inferior frontal gyrus (Ba 45) is associated with both living and non-living fluency, providing further evidence that this area is involved in lexical retrieval based on meaning. A large number of neuroimaging studies, using a range of different tasks, have implicated the left inferior frontal gyrus in the retrieval of semantic knowledge (Damasio et al., 1996; Martin, Huxby, Lalonde, Wiggs, & Ungerleider, 1995; Perani et al., 1995; Petersen et al., 1988; Vandenberghe, Price, Wise, Joseph's, & Frackowiak, 1996; Wiggs, Weisberg, & Martin, 1999). Activation in similar and adjacent locations, including Ba 9 and 10, have been observed in association with working memory tasks (Owen, Milner, Petrides, & Evans, 1996; Petrides, Alivisatos, Evans, & Meyer, 1988), in particular with verbal working memory (Smith, Jonides, & Koeppe, 1996). This may suggest an association with some aspects of working memory, specific to the fluency task. One of these aspects may be presented by the fact that during a fluency task, words generated one-by-one must be held in mind, in order to avoid their repetition (since the subjects of fluency studies are usually invited to not repeat the words generated).

The activation of lateral and medial occipital regions suggests the involvement of a visualization strategy during the semantic tasks. These regions have been found to be activated during tasks involving encoding of episodic memory (Fletcher et al., 1995) and in tasks requiring mental imagery (Kosslyn et al., 1994). Fletcher, Shallice, Frith, Frackowiak, and Dolan (1996) have proposed that the cuneus/retrosplenial regions participate in imagery processes elicited to aid episodic retrieval. Specifically, they have argued that these brain areas are required for inspecting visual images. This framework posits that retrieval of concepts depends on the reconstruction of images or actions pertaining to characteristics and properties of entities.

The left temporo-parietal region has been shown to be involved in semantic tasks (Vandenberghe et al., 1996), together with other areas in the inferior temporal lobe: the lack of activations in the latter region in the present study is probably due to technical limitations, related to a signal reduction in functional magnetic resonance images of that area.

A significant activation of subcortical structures (thalamus, caudate nucleus) was also present. Thalamic activation has been already reported during noun and verb retrieval (Warburton et al., 1996) and picture naming (Martin et al., 1995; Price et al., 1996). A possible role of the thalamus in the selection process for the items to be generated in verbal fluency tasks has been suggested on the basis of lesion studies in aphasic patients (Vallar, Cappa, & Wallesch, 1992).

In agreement with several studies, category-related differences in brain activation were also observed. In particular, the direct comparisons between fluency tasks have showed a more extensive activation in the left frontal region with the generation of tool names, indicating that a differential degree of frontal activity is related to the retrieval of words denoting entities in different

Table 5
Psychophysiological interaction analysis—coordinates and the *Z* statistic for target regions displaying significant task-related regressions with the activity in the three locations of interest (source areas)

| Source areas	Target areas (Brodmann area)	X	Y	Z	Z-score
Left lateral fusiform gyrus (Ba 37)					
Tools	Left inferior frontal gyrus (Ba 45)	−42	36	4	3.97
	Left middle frontal gyrus (Ba 9/6)	−54	14	36	3.91
Animals	—	—	—	—	—
Left medial fusiform gyrus (Ba 37)					
Tools	—	—	—	—	—
Animals	Left superior temporal gyrus (Ba 22)	−62	−4	8	5.82
	Left superior temporal gyrus (Ba 22)	−60	−2	0	5.82
	Left middle temporal gyrus (Ba 21)	−38	−34	4	5.18
	Left inferior frontal gyrus (Ba 47)	−38	26	−4	4.46
	Left cuneus	−10	−70	20	4.22
	Left middle frontal gyrus (Ba 46)	−46	42	20	4.17
Left inferior frontal gyrus (Ba 45)					
Tools	Left inferior parietal lobule (Ba 40)	−38	−46	48	3.00
	Left lateral fusiform gyrus (Ba 37)	−48	−56	−12	2.67
Animals	Left lingual gyrus (Ba 19)	−12	−70	−12	3.65
	Left lingual gyrus (Ba 19)	−28	−48	−4	3.11
	Left medial fusiform gyrus (Ba 37)	−24	−28	−10	2.59
	Left superior temporal gyrus (Ba 21)	−52	4	−8	3.11
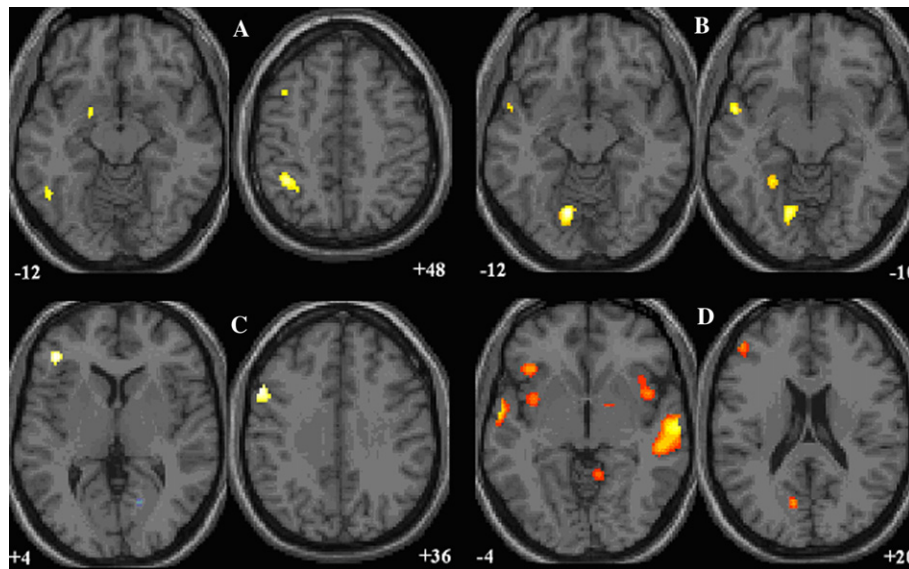
Fig. 3. Brain regions which show significant task-related SPM psychophysiological interaction with the activity in three locations of interest, defined by a 5 mm radius sphere: left Ba 45 (A tool condition; B animal condition), left lateral fusiform gyrus (C tool condition), and left medial fusiform gyrus (D animal condition). The source areas' coordinates are the same as in the SEM analysis (see Table 1). The statistical images are thresholded at *p*-level = .001 (uncorrected) for C and D and *p*-level = .01 (uncorrected) for A and B, and superimposed onto a single-subject T1* weighted normalized brain template, as implemented in SPM-99.

conceptual categories (Grabowski et al., 1998). It might be hypothesized that the more extensive involvement of the prefrontal and premotor cortex observed in our study for the non-living condition may be based on the recruitment of neural structures processing action-based information (see below). Besides the differences in frontal activity, other areas were selectively engaged by tool fluency. These include left temporal and parietal regions (Ba 21 and 40), and the left lateral fusiform gyrus.

On the other hand, no significant difference was observed in the reverse comparison. The lack of specific activations related to animals in the case of a lexical retrieval task is in agreement with the hypothesis that some of the differences reported in the literature up to now may reflect increased demands on structural differentiation in the case of animals, and may thus be apparent only when the task involves pictorial stimuli.

The effective connectivity analysis offers an additional perspective to the investigation of the patterns of cerebral specialisation for different semantic categories. The present investigation represents the first attempt to characterize the neural interactions mediating category effects when performing a lexical retrieval task. The results from SEMs provide first evidence for the existence of selective patterns of functional integration related to different semantic categories. The left frontal regions present a specific enhanced pattern of connectivity with left parietal and temporo-occipital areas during the tool condition, suggesting their implication in the neural processes subserving the retrieval of words designating man-made objects. It is noteworthy that brain activity within the same frontal areas has been also reported for tasks which were not explicitly verbal, such as object identification tasks (Martin et al., 1996; Perani et al., 1995), or the observation of meaningful actions and grasping of real objects (Decety et al., 1997; Rizzolatti et al., 1996), suggesting that these areas play a crucial role in action-based semantic information. Considering that most of the words generated in the non-living fluency task were represented by manipulable tools, one may deduce that this task should activate action-based neural circuits for their semantic processing. Indeed, Warrington and McCarthy (1987) theorized that there might even be finer-grained distinctions among representations for non-living entities that reflect the relative "importance of somatosensory information and information derived from actions. For small manipulable objects, the information derived from fine distal arm movements, is highly salient but clearly much less so for large man-made objects." The observed pattern of connectivity among prefrontal and premotor areas, parietal and temporo-occipital regions for tool fluency may reflect the anatomical connections existing between these brain areas, as revealed by neurophysiological studies on animals (Oram & Perrett, 1996), and is consistent with data from both the monkey literature (Perrett, 1989; Sakata, Taira, Murata, & Mine, 1995) and neuroimaging studies (Rizzolatti et al., 1996; Rushworth et al., 2001) investigating the neural activity associated with the visuomotor processing of manipulable objects. The same functional network (a "visuomotor action network" as defined by Devlin et al., 2002), specialised for man-made items and action representations, is active when people process the meaning of graspable objects such as tools, and it could represent thus a second alternative route involved in the semantic elaboration of manipulable objects, in addition to the common semantic regions activated by all categories of items. The presence of two distinct neural systems responsible for tool processing could account for the more frequent occurrence of semantic impairments specific to the living category. Moreover, the enhanced connectivity between premotor and parietal cortex is supposed to reflect the

visuospatial control of planning goal-directed actions, that is normally activated by the processing of action-based information (Milner & Goodale, 1996), whereas the greater coupling with the left temporo-occipital junction (Ba 37/19) could be due to the storage of tool conceptual representations close to areas that are active when perceiving motion and using objects (Martin et al., 1996). These findings enhance and stress the role of action knowledge related to tool motion and/or manipulation during generation of tool names.

The pattern of effective connectivity during animal condition, even though less robust and consistent across subjects than that observed during tool condition, underlines the role of specific circuitry within the visual associative areas during the generation of animal names. The present results are compatible with the idea that perceptual visual features play a crucial role for the representation of living entities, in line with the proposal that category-specific impairments for living entities may reflect a disproportionate impairment of visual semantics (McCarthy & Warrington, 1988; Warrington & Shallice, 1984).

The application of the SEM technique to the analysis of fMRI data presents some advantages with respect to traditional methodological approaches to functional imaging; these include, obviously, observing patterns of functional linkage, rather than isolated cortical areas. Noteworthy, SEMs are governed by prior hypothesis about anatomical networks, and test the null hypothesis of psychophysiological interaction (i.e., regional coupling changes between task-related contexts) within this model. The model is validated by prior knowledge of anatomical connections (human or monkey) and the participation of regions (forming observed variables) during performance of tasks (from SPM analysis) and from knowledge of the experimental conditions. SEM is therefore a powerful technique to test specific hypotheses about the interactions between brain regions of interest. It is evident that the model has many limitations. In particular, the fact that researcher has to predetermine the potentially linked areas could bias observation away from unexpected results. With respect to this, PPI analysis in SPM is different from SEM in that it is more explorative, free from anatomical constraints. Strictly speaking, SEM moderator terms represent psychophysiological interactions in SPM analysis (SPM-PPIs), as defined by Friston et al. (1997). However, in this paper, we draw a distinction between SEM and the SPM-style implementation of PPIs within design matrices. SEM and SPM-PPIs are complementary approaches to the study of effective connectivity. For simple two-node models without moderators, they are formally similar and, despite the different approaches to optimize solutions for path coefficients (SEM) and β parameters estimates (SPM-type PPIs), the results are pretty much the same. However, in the

case of more complex models the two approaches differ, and it is legitimate to use both in a single study to assess the presence of possible differences in task-related functional integration patterns.

The SPM analysis of PPIs demonstrated category-related patterns of connectivity (in terms of significant regressions) with the three source regions relevant in the analysis (left Ba 45, left lateral fusiform gyrus and left medial fusiform gyrus, see Fig. 3).

The left inferior frontal gyrus (Ba 45) was specifically connected with a left parieto-temporal network (including lateral fusiform gyrus) during tool condition, and with the left temporo-occipital visual associative areas (including medial fusiform gyrus) during animal condition. These results are comparable with those obtained from the SEM analysis and support the hypothesis that two partially separated anatomo-functional pathways process semantic information during the retrieval of tool and animal names.

In addition, the lateral and medial part of the fusiform gyrus displayed selective activity depending on the task context, with the former being specifically activated only during production of tools names, the latter only during animal fluency. These results suggest the existence of regional and functional specificity of activity within the fusiform gyrus.

The pattern of connectivity changes within the left fusiform region deserves particular consideration, as it appears to be in contrast with the results of a series of fMRI investigations by Martin and co-workers. These studies have indicated that activations associated with living entities (animals, faces) cluster in the more lateral aspects of the fusiform gyrus, while activations associated with man-made objects cluster in the more medial aspects (see Martin & Chao, 2001 for a review). The increased activation in the lateral fusiform has been shown to be stronger in the case of picture stimuli, and may reflect a larger demand for stimulus differentiation (Price, Noppeney, Phillips, & Devlin, 2003). The present, apparently discordant findings could be explained if we speculate that during the semantic fluency task the left inferior frontal gyrus operates a choice between different competing responses belonging to distinct semantic categories. Two different theories try to account for the role of the left inferior frontal gyrus in language production. The first claims that this area is especially involved in lexical and/or phonological retrieval during attentive verbal processing (Fiez et al., 1995; Posner, Petersen, Fox, & Raichle, 1988; Zatorre, Evans, Meyer, & Gjedde, 1992), whereas the second proposes that it may not be implicated in retrieval per se but in the selection of relevant responses and suppression of alternative competing responses (Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997). Our study supports this second view. Indeed, while an activation of the left inferior frontal gyrus is present in both fluency tasks, the SPM-PPI analysis,

and to a lesser degree the SEM analysis, indicate that this area increases its connectivity with the lateral part of the fusiform gyrus during tool name production, and with its medial part during animal name production. If the left inferior frontal gyrus mediates a choice between competing responses belonging to distinct semantic categories during the semantic fluency tasks, it may do so by inhibiting the brain areas subserving the opposite semantic category's concepts. This inhibitory function may result in a stronger coupling between the prefrontal region itself and the area specialised for the opposite category.

The study has a number of limits, which should be taken into consideration. In the first place, we are fully aware that the definition of a "resting" state is equivocal, as indicated by studies which have shown extensive activations in the comparison of "baseline" with the active task. These activations have been considered to reflect spontaneous conceptual processing (Binder et al., 1999). We consider however highly unlikely that the differences between the two versions of the semantically driven language task could be attributed to random fluctuations in the baseline conceptual activity. Second, task performance was covert, thus not allowing a direct control of the subjects' behaviour during the scan. This is particularly problematic when studying patients, rather than highly educated normal subjects. Additional supporting evidence that the subjects were actually performing the task is the fact that the post-hoc assessment and interview failed to show an imbalance in word production among conditions, and that the main effect of word finding is highly comparable to what has been described in previous PET experiments in which overt verbal fluency was adopted (e.g., Mummery et al., 1996). Finally, the selection of a male-only subject group may prevent the extension of the findings to the female population, given the possible existence of gender-related differences in brain activation during language tasks (Shaywitz et al., 1995; but see Frost et al., 1999).

In conclusion, the present findings provide further evidence for the existence of semantic-category related differences in brain activation, not only involving functional segregation, but also functional integration. Over and above, the results demonstrate for the first time that these differences are also maintained during lexical search tasks based on meaning. Finally, the SPM, SEM, and PPI approaches together appear to emphasize the importance of different types of information processing, rather than of ontological categories, in the determination of topographical differences in the pattern of brain activation and integration.

liocco, by the 5th FW EEC project "Connectivity in language, Rehabilitation in stroke in Europe" (LSDE), and by the Italy/Quebec scientific and technological cooperation.

References

Beauchamp, M. S., Lee, K. E., Haxby, J. V., & Martin, A. (2002). Parallel visual motion processing streams for manipulable objects and human movements. *Neuron, 34*, 149–159.

Bentler, P. M. (1988). Causal modelling via structural equation systems. In J. R. Nesselroade & R. B. Cattell (Eds.), *Handbook of multivariate experimental psychology* (2nd ed., pp. 317–335). New York: Plenum.

Binder, J. R., Frost, J. A., Hammeke, T. A., Bellgowan, P. S., Rao, S. M., & Cox, R. W. (1999). Conceptual processing during the conscious resting state. A functional MRI study. *Journal of Cognitive Neuroscience, 11*, 80–95.

Bollen, K. A. (1989). A new incremental fit index for general structural models. *Sociological Methods and Research, 17*, 303–316.

Buchel, C., & Friston, K. J. (1997). Modulation of connectivity in visual pathways by attention: Cortical interactions evaluated with structural equation modelling and fMRI. *Cerebral Cortex, 7*, 768–778.

Caramazza, A., & Shelton, J. R. (1998). Domain specific knowledge systems in the brain: The animate–inanimate distinction. *Journal of Cognitive Neuroscience, 10*, 1–34.

Chao, L. L., Weisberg, J., & Martin, A. (2002). Experience-dependent modulation of category-related cortical activity. *Cerebral Cortex, 12*, 545–551.

Damasio, H., Grabowski, T. J., Tranel, D., Hitchwa, R. D., & Damasio, A. R. (1996). A neural basis for lexical retrieval. *Nature, 380*, 499–505.

Decety, J., Grèzes, J., Costes, N., Perani, D., Jeannerod, M., Procyk, E., et al. (1997). Brain activity during observation of actions. Influence of action content and subjects strategy. *Brain, 120*, 1763–1777.

Devlin, J. T., Moore, C. J., Mummery, C. J., Gorno-Tempini, M. L., Phillips, J. A., Noppeney, U., et al. (2002). Anatomic constraints on cognitive theories of category specificity. *NeuroImage, 15*, 675–685.

Farah, M. J., & McClelland, J. L. (1991). A computational model of semantic memory impairment: Modality specificity and emergent category specificity. *Psychological Review, 120*, 339–357.

Fiez, J. A., Raichle, M. E., Miezin, F. M., Petersen, S. E., Tallal, P., & Katz, W. F. (1995). PET studies of auditory and phonological processing: Effects of stimulus characteristics and task demands. *Journal of Cognitive Neuroscience, 7*, 357–375.

Fletcher, P. C., Frith, C. D., Baker, S. C., Shallice, T., Frackowiak, R. S. J., & Dolan, R. J. (1995). The minds eye: Precuneus activation in memory-related imagery. *NeuroImage, 2*, 195–200.

Fletcher, P. C., Shallice, T., Frith, C. D., Frackowiak, R. S. J., & Dolan, R. J. (1996). Imagery and semantic cueing in episodic memory: The influence of imagery and semantic cueing. *Brain, 119*, 1587–1596.

Forde, E. M. E., & Humphreys, G. M. (1999). Category-specific recognition impairments: A review of important case studies and influential theories. *Aphasiology, 13*, 169–193.

Friston, K. J., Holmes, A. P., Worsley, K. J., Poline, J. B., Frith, C. D., & Frackowiak, R. S. J. (1995). Statistical parametric maps in functional imaging: A general linear approach. *Human Brain Mapping, 2*, 189–210.

Friston, K. J., Buechel, C., Fink, G. R., Morris, J., Rolls, E., & Dolan, R. J. (1997). Psychophysiological and modulatory interactions in neuroimaging. *Neuroimage, 6*, 218–229.

Friston, K. J. (2002). Functional integration and inference in the brain. *Progress in Neurobiology, 68*, 113–143, Review.

Frith, C. D., Friston, K. J., Liddle, P. F., & Frackowiak, R. S. J. (1991). A PET study of word finding. *Neuropsychologia, 29*, 1137–1148.

Frost, J. A., Binder, J. R., Springer, J. A., Hammeke, T. A., Bellgowan, P. S., Rao, S. M., et al. (1999). Language processing is strongly left lateralized in both sexes. Evidence from functional MRI. *Brain, 122*, 199–208.

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, Review.

Gold, B. T., & Buckner, R. L. (2002). Common prefrontal regions coactivate with dissociable posterior regions during controlled semantic and phonological tasks. *Neuron, 35*, 803–812.

Grabowski, T. J., Damasio, H., & Damasio, A. R. (1998). Premotor and prefrontal correlates of category-related lexical retrieval. *NeuroImage, 7*, 232–243.

Higham, N. J. (1993). Optimization by direct search in matrix computations. *SIAM Journal of Matrix Analysis and Application, 14*, 317–333.

Joreskog, K., Sorbom, D., 2001. Lisrel 8.51 Student Edition. Scientific Software International.

Kosslyn, S. M., Alpert, N. M., Thompson, W. L., Chabris, C. F., Rauch, S. L., & Anderson, A. K. (1994). Identifying objects seen from different viewpoints. A PET investigation. *Brain, 117*, 1055–1071.

Martin, A., & Chao, L. L. (2001). Semantic memory and the brain: Structure and processes. *Current Opinion in Neurobiology, 11*, 194–201, Review.

Martin, A., Huxby, J. V., Lalonde, F. M., Wiggs, C. L., & Ungerleider, L. G. (1995). Discrete cortical regions associated with knowledge of color and knowledge of action. *Science, 270*, 102–105.

Martin, A., Wiggs, C. L., Lalonde, F., & Mack, C. (1994). Word retrieval to letter and semantic cues: A double dissociation in normal subjects using interference tasks. *Neuropsychologia, 32*, 1487–1494.

Martin, A., Wiggs, C. L., Ungerleider, L. G., & Huxby, J. V. (1996). Neural correlates of category-specific knowledge. *Nature, 379*, 649–652.

McCarthy, R., & Warrington, E. K. (1988). Evidence for modality specific meaning systems in the brain. *Nature, 334*, 428–430.

Mechelli, A., Price, C. J., Noppeney, U., & Friston, K. J. (2003). A dynamic causal modeling study on category effects: Bottom-up or top-down mediation?. *Journal of Cognitive Neuroscience, 15*, 925–934.

Milner, A. D., & Goodale, M. A. (1996). *The visual brain in action*. Oxford: Oxford University Press.

Mummery, C. J., Patterson, K., Hodges, J. R., & Wise, R. J. S. (1996). Generating a 'tiger' as an animal name or a word beginning with T: Differences in brain activations. *Proceedings of the Royal Society of London, Series B, 263*, 989–995.

Noppeney, U., & Price, C. J. (2002). A PET study of stimulus- and task-induced semantic processing. *Neuroimage, 15*, 927–935.

Oldfield, R. C. (1971). The assessment and analysis of handedness: The Edinburgh Inventory. *Neuropsychologia, 9*, 97–113.

Oram, M. W., & Perrett, D. I. (1996). Integration of form and motion in the anterior superior temporal polysensory area (STPa) of the macaque monkey. *Journal of Neurophysiology, 76*, 109–129.

Owen, A. M., Milner, B., Petrides, M., & Evans, A. C. (1996). Memory for object features versus object location: A positron emission tomography study of encoding and retrieval processes. *Proceedings of the National Academy of Sciences of USA, 93*, 9212–9216.

Paulesu, E., Goldacre, B., Scifo, P., Cappa, S. F., Gilardi, M. C., Castiglioni, I., et al. (1997). Functional heterogeneity of left inferior frontal cortex as revealed by fMRI. *NeuroReport, 8*, 2011–2016.

Perani, D., Cappa, S. F., Bettinardi, V., Bressi, S., Gorno-Tempini, M. L., Matarrese, M., et al. (1995). Different neural networks for the recognition of biological and man-made entities. *NeuroReport, 6*, 1637–1641.

Perani, D., Schnur, T., Tettamanti, M., Gorno-Tempini, M. L., Cappa, S. F., & Fazio, F. (1999). Word and picture matching: A PET study of semantic category effects. *Neuropsychologia, 37*, 293–306.

Perrett, D. I. (1989). Frameworks of analysis for the neural representation of animate objects and actions. *Journal of Experimental Biology, 146*, 87–113.

Petersen, S. E., Fox, P. T., Posner, M. I., Mintun, M., & Raichle, M. E. (1988). Positron emission tomographic studies of single word processing. *Nature, 331*, 585–589.

Petrides, M., Alivisatos, B., Evans, A. C., & Meyer, E. (1988). Dissociation of human mid-dorsolateral from posterior dorsolateral frontal cortex in memory processing. *Proceedings of the National Academy of Sciences of USA, 90*, 873–877.

Phillips, J. A., Noppeney, U., Humphreys, G. W., & Price, C. J. (2002). Can segregation within the semantic system account for category-specific deficits?. *Brain, 125*, 2067–2080.

Poline, J. B. et al. (Multi-Center Study) 1996. Reproducibility of PET activation studies: Lessons from a multi centre European experiment. *NeuroImage* 4, 34–54.

Posner, M. I., Petersen, S. E., Fox, P. T., & Raichle, M. E. (1988). Localization of cognitive operations in the human brain. *Science, 240*, 1627–1631.

Price, C. J., Moore, C. J., Humphreys, G. W., Frackowiak, R. S. J., & Friston, K. J. (1996). The neural regions sustaining object recognition and naming. *Proceedings of the Royal Society of London, Series B, 263*, 1501–1507.

Price, C. J., Noppeney, U., Phillips, J., & Devlin, J. T. (2003). How is the fusiform gyrus related to category-specificity? Cognitive Neuropsychology*, 20*, 561–574.

Rizzolatti, G., Fadiga, L., Matelli, M., Bettinardi, V., Paulesu, E., Perani, D., et al. (1996). Localization of grasp representations in humans by PET: Observation versus execution. *Experimental Brain Research, 111*, 246–252.

Rushworth, M. F. S., Krams, M., & Passingham, R. E. (2001). The attentional role of the left parietal cortex: The distinct lateralization and localization of motor attention in the human brain. *Journal of Cognitive Neuroscience, 13*, 698–710.

Saffran, E. M., & Schwartz, M. F. (1994). Of cabbages and things: Semantic memory from a neuropsychological perspective – a tutorial review. In C. Umiltà & M. Moscovitch (Eds.), *Attention and Performance XV*. Hove-London: Lawrence Erlbaum.

Sakata, H., Taira, M., Murata, A., & Mine, S. (1995). Neural mechanisms of visual guidance of hand action in the parietal cortex of the monkey. *Cerebral Cortex, 5*, 429–438.

Shaywitz, B. A., Shaywitz, S. E., Pugh, K. R., Constable, R. T., Skudlarski, P., Fulbright, R. K., et al. (1995). Sex differences in the functional organization of the brain for language. *Nature, 373*, 607–609.

Smith, E. E., Jonides, J., & Koeppe, R. A. (1996). Dissociating verbal and spatial working memory using PET. *Cerebral Cortex, 6*, 11–20.

Thompson-Schill, S. L., D'Esposito, M., Aguirre, G. K., & Farah, M. J. (1997). Role of left inferior prefrontal cortex in retrieval of semantic knowledge: A re-evaluation. *Proceedings of the National Academy of Sciences of USA, 94*, 14692–14797.

Tranel, D., Damasio, H., & Damasio, A. R. (1997). A neural basis for the retrieval of conceptual knowledge. *Neuropsychologia, 35*, 1319–1327.

Tyler, L. K., & Moss, H. E. (2001). Towards a distributed account of conceptual knowledge. *Trends in Cognitive Science, 5*, 244–252.

Vallar, G., Cappa, S. F., & Wallesch, C. W. (1992). *Neuropsychological disorders associated with subcortical lesions*. Oxford: Oxford University Press.

Vandenberghe, R., Price, C., Wise, R. S. J., Joseph's, O., & Frackowiak, R. S. J. (1996). Functional anatomy of a common semantic system for words and pictures. *Nature, 383*, 254–256.

Warburton, E., Wise, R. J., Price, C. J., Weiller, C., Hadar, U., Ramsay, S., et al. (1996). Noun and verb retrieval by normal subjects. Studies with PET. *Brain, 119*, 159–179, Review.

Warrington, E. K., & McCarthy, R. (1987). Categories of knowledge: Further fractionations and an attempted integration. *Brain, 110*, 1273–1296.

Warrington, E. K., & Shallice, T. (1984). Category-specific semantic impairment. *Brain, 107*, 829–854.

Wiggs, C. L., Weisberg, J., & Martin, A. (1999). Neural correlates of semantic and episodic memory retrieval. *Neuropsychologia, 37*, 103–118.

Zatorre, R. J., Evans, A. C., Meyer, E., & Gjedde, A. (1992). Lateralization of phonetic and pitch discrimination in speech processing. *Science, 256*, 846–849.